# Propanil

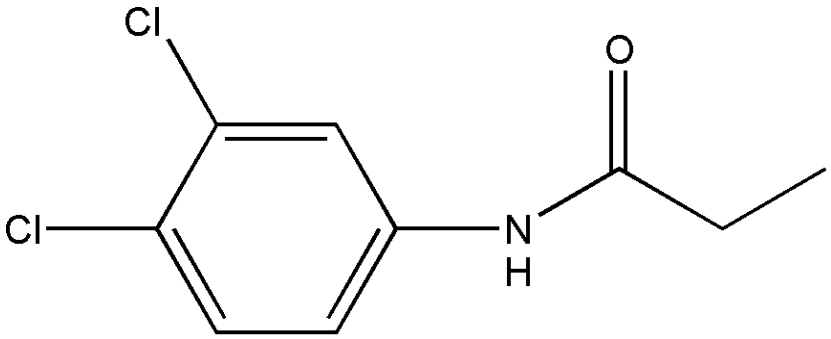
# (N-(3,4-dichlorophenyl)propanamide)

# Risk Characterization Document

## Occupational and Bystander Exposures

## Residential Bystanders: Spray drift, Dietary and Aggregate Exposures

## Workers: Occupational, Dietary and Aggregate Exposures

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# Table of Contents

**LIST OF TABLES**

## LIST OF FIGURES

## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| 2,4-D | 2,4-Dichlorophenoxyacetic acid |
| 3,4-DCA | 3,4-dichloroaniline |
| ABS | Absolute |
| A | Acre |
| AI | Active Ingredient |
| ALC | Approximate Lethal Concentration |
| ALT | Alanine Aminotransferase |
| AP | Alkaline Phosphatase |
| AR | Androgen Receptor |
| ASC | Antibody Secreting Cells |
| AST | Aspartate Aminotransferase |
| BDPA | Birth Defect Prevention Act of 1984 |
| BEAD | Biological and Economical Analysis Division |
| BLQ | Below Limit of Quantification for Analytical Method |
| BMD/BMR | Benchmark Dose or Response |
| BMDS | Benchmark Dose Software |
| BSM | Bensulfuron-Methyl |
| CALPIP | California Pesticide Information Portal |
| CALPIQ | California Pesticide Illness Query |
| CDC | Center for Disease Control |
| CDFA | California Department of Food and Agriculture |
| Cmax | Amount of [$^{14}$C] Specimen with the Greatest Amount of Same |
| CNS | Central Nervous System |
| CP | Cyclophosphamide |
| CYP | Cytochrome P450 |
| DEEM® | Dietary Exposure Analysis Model |
| DPR | Department of Pesticide Regulation |
| EC | European Commission |
| ECB | European Chemical Bureau |
| ED50 | Biological Potency |
| EFSA | European Food Safety Authority |
| ENEL | Estimated No Effect Level |
| EUDG | European Union Directorate General |
| FDA | Food and Drug Administration |
| F or f | Female |
| FIFRA | Federal Insecticide, Fungicide, and Rodenticide Act |
| FQPA | Food Quality Protection Act |
| GD | Gestation Day |
| HIARC | Hazard Identification Assessment Review Committee |
| Hb/metHb | Hemoglobin or Methemoglobin |
| Hct | Hematocrit |
| HSM | Halosulfuron Methyl |
| IFN | Interferon |
| HTS | High Throughput Screening Assays |
| IARC | International Agency for Research on Cancer |
| IDS | Incident Data System |
| IP | Intraperitoneal Exposure Route |
| IV | Intravenous Exposure Route |
| Kd | Disassociation Constant |
| $LC_{50}$ or $LD_{50}$ | Median Lethal Concentration or Dose |
| LD | Lactation Day |
| LO(A)EL | Lowest Observed (Adverse) Effect Level |
| MA | Metabolic Activation |
| MARC | Metabolism Assessment Review Committee |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Corpuscular Volume |

## LIST OF ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| M or m | Male |
| MMAD | Mass Median Aerodynamic Particle Diameters |
| MOA | Mode of Action |
| MOE | Margin of Exposure |
| MRL | Maximum Residue Level |
| MTD | Maximum Tolerated Dose |
| NA | Not Applicable |
| NCBI | National Center for Biotechnology Information |
| NCCT | National Center for Computational Toxicology |
| ND | Non-Detect |
| NIOSH | National Institute for Occupational Safety and Health |
| NO(A)EL | No Observed (Adverse) Effect Level |
| NRC | National Research Council |
| NTP | National Toxicology Program |
| OPP | Office of Pesticide Programs |
| PCV | Packed Cell Volume |
| PND | Postnatal Day |
| PO | Per Oral |
| POD | Point of Departure |
| ppb/ppm | Parts per Billion or Million |
| PPE | Personal Protective Equipment |
| RACB | Reproductive Assessment by Continuous Breeding |
| RAH | Rohm and Haas Company |
| RBC | Red Blood Cells |
| RCD | Risk Characterization Document |
| RE | Reticuloendothelial |
| REL | Relative |
| RelBd/Br | Relative To Body/Brain |
| Rfd | Reference Dose |
| ROS | Reactive Oxygen Species |
| RPF | Relative Potency Factor |
| RSC | Royal Society of Chemistry |
| SB950 | Senate Bill 950 (see BDPA) |
| SENSOR | Sentinel Event Notification System for Occupational Risk-Pesticides |
| SOS1 | Son of Sevenless |
| SOT | Society for Toxicology |
| T90 | Time of Specimen Collection Corresponding to Excretion of ≥ 90% of the Total Applied [$^{14}$C] |
| TiPARP | TCDD-inducible poly(ADP-ribose) polymerase |
| Tmax | Time of Specimen Collection Corresponding to Specimen with the Greatest Amount of Applied [$^{14}$C] |
| ToxCast | Toxicity Forecaster |
| UF($_{DB}$) | Uncertainty Factor (Database) |
| USA | United States of America |
| USDA ARS | United States Department of Agriculture Agricultural Research Service |
| US EPA | United States Environmental Protection Agency |
| USGPO | US Government Publishing Office |
| WBC | White Blood Cells |
| WHO | World Health Organization |

# I Executive Summary

This purpose of this Risk Characterization Document (RCD) is to evaluate the risks to human health resulting from occupational, spray drift, dietary, and aggregate exposures to propanil. Propanil was given a high-priority status for risk assessment due to adverse effects observed in chronic toxicity studies in dogs and mice (hematologic toxicity), results from oncogenicity studies in rats (testicular and liver tumors) and mice (lymphoma), and concerns relating to drift from application sites. DPR initiated its risk assessment on propanil in 2012.

## A) Introduction

Propanil is a broad-spectrum, contact, post-emergence herbicide that is applied as a broadcast spray by ground/aerial equipment. It is one of the most widely used herbicides for rice production and is currently ranked within the top 20 agricultural pesticides used in the US when assessed as pounds of active ingredient (AI) applied. The only currently approved use for propanil in California is for the protection of rice crops from annual/biennial/perennial broadleaf weeds and grasses and aquatic weeds. This risk characterization document (RCD) addresses the potential for human health effects arising from exposure to propanil in the food and drinking water, from occupational activities, and from residential bystander exposure to spray-drift. Aggregate risk was also evaluated for workers and residential bystanders.

Propanil acts as an herbicide by inhibiting photosynthesis in target species through direct action on photosystem II. The selective herbicidal activity of propanil is attributed to the activity and distribution of aryl acylamidase. Crops with high aryl acylamidase activities (i.e., rice, turf grass and wheat) tolerate propanil while weeds lacking this activity are killed. Mammals also metabolize propanil through the aryl acylamidase hydrolysis of the parent molecule. The resulting metabolite, 3,4-dichloroaniline (3,4-DCA), plays a central role in the mode of action (MOA) for propanil's hematologic toxicity that is initiated primarily by the oxidation of hemoglobin (Hb) to methemoglobinemia (metHb).

The US Environmental Protection Agency (US EPA) considers propanil to have "low acute toxicity" based on the following classifications: oral ($LD_{50}$ = 1080 mg/kg; category III); dermal ($LD_{50}$ > 2000 mg/kg; category IV), inhalation ($LC_{50}$ = 6.1 mg/L; category IV); primary skin irritation (category IV); primary eye irritation (II). US EPA established 0.009 mg/kg/day as the oral, chronic reference dose (RfD), which is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no observed adverse effect level (NOAEL), a lowest observed adverse effect level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used" (USEPA, 2011). The RfD is considered to be the maximum, safe, daily exposure level. The Agency also placed propanil into the category of chemicals with "suggestive evidence of carcinogenic potential by all routes of exposure but not sufficient to assess human carcinogenic potential" based, in part, on the lack of evidence for mutagenicity. US EPA issued the Registration Eligibility Decision (RED) for propanil in 2003, and included an evaluation of the human risks from occupational and aggregate exposures (i.e., combined dietary and drinking water) to propanil. The main conclusion from these assessments was that, while the aggregate exposure in the US population would not present unreasonable risk, the risk stemming from occupational exposures was high even when personal protective equipment and contemporary methods of

risk reduction were used. US EPA specified risk reduction measures to support the continued use of propanil in the RED. Select original mitigation measures were revised in the 2006 amendment to the RED based on review of public comments and additional data submitted by the Propanil Task Force.

Since its introduction in California, incidents where propanil drift unintentionally damaged the foliage and fruit of stone fruit trees have been reported. As a result of these incidents, propanil use was limited to defined use areas. Propanil was given a high-priority status for risk assessment by the California Department of Pesticide Regulation (DPR) due to adverse effects observed in chronic toxicity studies in dogs and mice (hematologic toxicity), results from oncogenicity studies in rats (testicular and liver tumors) and mice (lymphoma), and concerns relating to spray drift from application sites. DPR initiated a comprehensive human health risk assessment in 2012. The same year, DPR also identified propanil as a potential ground water contaminant based on data requirements established by the Pesticide Contamination and Prevention Act (PCPA) of 1985.

Propanil has slight solubility, low volatility, and moderate mobility under standard conditions for its application and therefore has some potential for ground water leaching. On the other hand, propanil has a low potential for bioconcentration in aquatic organisms. Propanil is stable to aqueous hydrolysis but susceptible to photolysis in aqueous and soil environments. Diverse photodegradant species have been reported that include small, water soluble compounds and insoluble adducts of humic acid. Aerobic, microbial degradation of propanil is initially rapid in soil and water, resulting in diverse degradant species including 3,3',4,4'-tetrachloroazobenzene (TCAB) and 3,4-DCA. Following the initial rapid degradation phase in soil, 3,4-DCA becomes covalently bound to the organic soil fraction with a mineralization phase extending for years. In rice, propanil is rapidly transported and metabolized by hydrolysis and by subsequent oxidative and conjugative pathways to diverse metabolic species including 3,4-DCA and $CO_2$. A substantial fraction of the propanil-derived rice metabolite load is complexed with lignin. Furthermore, a high constituent aryl acylamidase activity ensures that residual propanil in harvested rice grains from plants that have survived to maturity is likely to be entirely in the form of species derived from 3,4-DCA.

## B) Toxicological Profile

### 1) Pharmacokinetics

Both oral absorption and elimination of propanil were approximately 100% with minimal retention in the rat. The primary route of elimination was urine consistent with a high degree of oxidative metabolism and conjugation. Inter and intra-species differences in metHb formation, methemoglobinemia and hemolytic anemia may be due to differences in absorption, acylamidase activity, oxidative metabolism, and/or metHb reductase activity. In 3 humans, elimination half-lives were 0.9, 2.7, and 0.9 hours for propanil and 3.8, 4.4, and 2.8 hours for 3,4-DCA. The average human elimination half-life for propanil was 3.2 hours while the average elimination half-life for 3,4-DCA could not be calculated due to the variability of the data. Some individual human elimination profiles suggested that the formation of 3,4-DCA by acylamidase hydrolysis may be a more rapid process than elimination when 3,4-DCA concentrations are high. In general, observed human propanil bioconversion was variable, some of which may have been due to genetic polymorphisms related to esterase activity, bioavailability, and/or the saturability of the N-hydroxylation reaction.

### 2) Acute Toxicity

An acute, oral lethal dose for humans is estimated to be over 1 g/kg/day. Acute signs of propanil poisoning include nausea, vomiting, diarrhea, tachycardia, dizziness, central nervous system depression, cyanosis (with reddish-brown blood at collection), hypotension, hyperventilation requiring intubation, ischemia, seizures and coma. The severity of the poisoning generally correlated with the measured levels of metHb. In studies of the acute oral, inhalation, and dermal toxicity of propanil in rats and rabbits, the signs of propanil intoxication included mortality, piloerection, reduced food consumption, and reduced fecal volume, red-stained eyes and muzzle, restlessness, hunched posture, labored respiration, ruffled fur, chromodacryorrhea, eyelid adhesion, and red or discolored anatomical features (adrenal glands, kidney cortico-medullary junction, stomach areas, intestinal contents, urinary bladder contents, lungs, discolored liver). Oral median lethal doses ($LD_{50}$) ranged from 779 to 1384 mg/kg. Additionally, propanil was a mild or slight skin irritant and a moderate eye irritant in the rabbit. It was not a skin sensitizer in the guinea pig.

### 3) Subchronic Toxicity

Signs of propanil intoxication in subchronic studies using rat, mouse, dog and rabbit included increased mortality, cyanosis, lethargy, piloerection, lacrimation with ocular discharge, decreased defecation, mucoid feces with red material, decreases in body weight, body weight gain, and food consumption, changes in hematologic parameters, macro and microscopic signs of organ toxicity in the lungs, spleen, kidneys, liver, ovaries, and testes, and changes in blood chemistry and urinalysis parameters. Cyanosis, lethargy, changes in hematology and serum biochemistry, and splenic pathology were consistent with metHb formation and hemolytic anemia.

### 4) Reproductive Toxicity

In studies of the reproductive toxicity of propanil in rats, parental toxicity was characterized by decreased body weight and body weight gain and signs of toxicity to the spleen (e.g., increased weight and hemosiderin deposition). The effects of propanil on reproduction were characterized by decreased sperm and primordial follicle counts. Weanling pups exposed to propanil during and after pregnancy had reduced body weight, increased testes and liver weights and delayed completion of balanopreputial separation and vaginal perforation.

### 5) Developmental Toxicity

No developmental effects were attributed to treatment with propanil in either rats or rabbits in standardized developmental toxicity studies. However, as noted in the previous section, pups exposed to propanil indirectly throughout gestation and lactation were adversely impacted.

### 6) Genotoxicity

Results from limited genotoxicity tests based on FIFRA guideline and non-guideline studies were largely negative, including assays for gene mutation, DNA damage (induction of unscheduled DNA synthesis), mitotic recombination, and chromosomal aberration). Positive results were observed in an *in vitro* assay for DNA damage in repair-deficient bacteria with no metabolic activation, and in an *in vivo* somatic mutation and recombination test (Drosophila wing spot assay). On the other hand, 3,4-DCA was capable

of genotoxic effects including chromosomal aberrations, sister-chromatid exchanges , mitotic spindle disruptions, and aneuploidy under assay conditions although the mechanistic details for the above effects have not been described. Taken together, there is limited evidence for propanil-induced genotoxic activity, which may be mediated by one or more of its metabolites.

#### 7) Chronic Toxicity

The signs of chronic propanil intoxication in rats, mice and dogs included decreases in body weight gain, changes in hematologic parameters, increased organ weights (spleen, kidney, liver, ovaries, and testes), increased macro and microscopic organ pathologies (liver, spleen, lungs, ovary, uterus), changes in serum chemistry, and changes in urinalysis parameters. Changes to hematologic parameters and observed signs of splenic pathology were consistent with effects related to metHb formation and hemolytic anemia. Three tumor types were significantly increased with propanil treatment: testicular interstitial tumors (rat), hepatocellular adenomas (rat and mouse), and lymphoma (mouse). While the latter tumors may have been driven by genotoxicity, evidence suggested that testicular interstitial tumors in male rats resulted from the mediated disruption of endocrine signaling.

#### 8) Immunotoxicity

The signs of propanil immunotoxicity included increased splenic antibody production (i.e., IgM).

#### 9) Oncogenicity

There is evidence that chronic dietary propanil treatment may be oncogenic in the rat and mouse at dose levels that are relevant to low-dose extrapolation. There is also evidence for a genotoxic mode of action mediated by one or more related metabolites. However, based on an analysis of tumor data from the rat and mouse in the propanil database, none of the tumors that were considered to have arisen from a putative genotoxic MOA had data that was sufficient for low-dose, linear extrapolation. Benign testicular interstitial tumors in the male rat likely resulted from propanil-mediated disruption of androgen signaling leading to increased pituitary luteinizing hormone-releasing hormone or luteinizing hormone secretion; a threshold effect with probable neoplastic consequences in target tissues. Considered together, points of departure based on endocrine effects from laboratory animal studies are expected to be protective against those oncogenic effects mediated by the proposed endocrine MOA for the testicular tumors.

## C) Risk Assessment

#### 1) Hazard Identification

A summary of all critical points of departure (POD) for propanil has been provided below (Summary Table 1):

**Summary Table 1. Summary of Critical PODs for Propanil**

| Exposure Route and Duration | Critical Endpoint and Study | PODs[a] (mg/kg/day) | RfDs[c] (mg/kg/day) |
|---|---|---|---|
| Acute/All Routes | Increased metHB levels (m) (Day 5; rat) | $BMDL_{1SD}$[b]= 14.1 | 0.05 UFtotal = 300[c] |
| Subchronic/ All Routes | Increased metHb levels (m) (week 13; rat) | $BMDL_{1SD}$[b]= 5 | 0.02 UFtotal = 300[c] |
| Chronic/All Routes | Hemosiderosis of spleen (m) (total; rat) | $BMDL_{10}$[b] = 1.5 | 0.005 UFtotal = 300[c] |

[a]As defined by US EPA (2012), a point of departure (POD) is the dose-response point that marks the starting point for low-dose extrapolation, and generally corresponds to a select, estimated, low-level of response. In this Risk Characterization Document (RCD), the critical PODs for propanil are based on hematologic toxicity and are defined as an increased methemoglobin (metHB) level by one standard deviation compared to control levels or as a 10% increased incidence of hemosiderosis in the spleen.
[b]Benchmark Dose Lower Confidence Limit (BMDL): a value representing a 95% lower bound of the BMD and a point of departure (POD) for the observed effect; subscripts indicates an effect threshold based on data for concurrent controls (1SD = 1 standard deviation; 10 = 10% extra risk).
[c]Reference Dose (RfD): For propanil, the total uncertainty factors (UFtotal) used here are 10x for interspecies sensitivity and 10x for intraspecies variability and 3x for potentially enhanced sensitivity to metHb formation in infants and subpopulations with hereditary enzymatic deficiencies.
(Total UF = 300): RfD = (PoD ÷ UF of 300).

## 2) Exposure Assessment

### *(i) Dietary and Drinking Water Exposure*

Acute, dietary exposures to propanil residues in food and water were estimated using a mixed deterministic and probabilistic approach. The dietary exposure from rice was calculated using a distribution of consumption rates and a single residue value (point estimate). The exposure from drinking water was calculated using distributions of consumption rates and residue levels. The anticipated residue levels used for rice and water were from field trials and DPR surface water monitoring, respectively. Estimates for residues in ruminant, poultry, and crayfish products were from feeding studies. This analysis produced propanil exposures that ranged from 0.36 to1.75 µg/kg/day and from 0.67 to 3.24 µg/kg/day for the 95$^{th}$ and 99$^{th}$ percentiles, respectively. The population subgroups with the highest exposures at the 95$^{th}$ and 99$^{th}$ percentiles were "Non-Nursing Infants" and "All Infants", respectively. Rice was the main contributor to the total dietary exposure (food and drinking water) of these subpopulations (84% and 80%, respectively).

The chronic, dietary exposure to propanil residues in food and water was also estimated using a deterministic approach. The average anticipated residue levels used came from rice field trials and DPR surface water monitoring. Estimates for residues in ruminant, poultry, and crayfish products were from feeding studies. A California percent crop treated (PCT) factor of 75% was also applied. Estimated chronic propanil exposures ranged from 0.11 (adults 50-99 years) to 0.44 (non-nursing infants) µg/kg/day.

### *(ii) Occupational and Residential Bystander Exposure*

Occupational and residential bystander exposure assessments for propanil were prepared as a separate document. The occupational exposure assessment report includes estimates for acute, seasonal, annual, and lifetime exposures for herbicide handler and field worker scenarios as well as a complete description of the methods used (e.g., input data, formulae, assumptions, etc.).

### *(iii) Aggregate Exposure*

Exposures were not aggregated. Rather, an aggregate margin of exposure (MOE) approach was used.

### 3) Risk Characterization and Appraisal

An MOE of 300 assumes that humans are 10-times more sensitive to a toxicant's action than the laboratory animals used to obtain the critical end-point data and that sensitivity within the human population varies as much as 10-fold. An additional UF of 3 was imposed to protect infants and adults with hereditary enzymatic deficiencies that can lead to enhanced sensitivity to xenobiotic-mediated metHb formation. As such, a target MOE of 300 was used for propanil based on consideration of the weight-of-evidence for the critical PODs used, their corresponding MOAs, and their relationships to other end-points of concern.

### *(i) Dietary and Drinking Water Risk*

#### i(a) Acute

A refined acute mixed deterministic and probabilistic analysis using the critical acute POD of 14.1 mg/kg/day resulted in MOEs of 8040 to 39339, 4351 to 21140, and 1922 to 10520 at the 95$^{th}$, 99$^{th}$ and 99.9$^{th}$ percentiles, respectively. These exceeded the acute target MOE of 300.

#### i(b) Chronic

A refined, deterministic analysis using the critical chronic POD of 1.5 mg/kg/day resulted in MOEs that ranged from 3446 to 13945. These exceeded the acute target MOE of 300.

### *(ii) Occupational Risk*

#### ii(a) Acute/Short-Term Risk

Acute MOEs for herbicide handler and field worker scenarios used the critical acute POD of 14.1 mg/kg/day. Herbicide handler scenarios had acute MOEs ranging from 1 to 15 and lower than the target (300). The handler job category with the lowest MOE was the mixer/loader for aerial applications. In addition, acute MOEs for scouting (15) and weeding (233) were lower than the target (300).

#### ii(b) Seasonal and Annual Risk

Seasonal and annual MOEs for herbicide handler and field worker scenarios used the critical subchronic and chronic PODs of 5 and 1.5 mg/kg/day, respectively. All of the seasonal MOEs (1 to 74) and annual MOEs (2 to 133) for herbicide handler/applicator scenarios were lower than the target MOE of 300. As above, the handler job category with the lowest seasonal and annual MOE was the mixer/loader (M/L) for aerial applications. The seasonal MOEs for scouting (11) and weeding (173) and the annual MOE for scouting (20) were also lower than the target (300).

### *(iii) Residential Bystander Risk*

#### iii(a) Residential Bystander Risk from Aerial Applications

The acute oral POD (14.1 mg/kg/day) was used to calculate all MOE values. Adult dermal MOEs exceeded the target of 300 for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 and 25 feet, respectively. Adult inhalation MOEs exceeded the target for all aerial application scenarios. Child dermal MOEs exceeded the target of 300 for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 feet. Child inhalation and oral MOEs exceeded the target at downwind distances greater than 50 feet for all aerial application scenarios.

#### iii(b) Residential Bystander Risk from Ground Boom Applications

The MOEs for short-term daily exposure to propanil for residential bystanders from ground boom application drift scenarios were calculated using the acute POD (14.1 mg/kg/day). All adult and child dermal, inhalation, and oral MOEs exceeded the target of 300. The lowest MOEs were for dermal exposure in adults (25 feet/MOE = 572) and children (25 feet/MOE = 390). These MOEs exceeded the short-term target MOE of 300.

### *(iv) Aggregate Risk*

Aggregate MOEs were calculated as the reciprocal of the sum of reciprocals of MOEs for all scenarios. Workers: the risk from aggregate exposures was estimated for females of childbearing age (13 to 50 years old) herbicide handler/field worker that would be exposed to propanil through dermal and inhalation routes during working hours and to residues through the consumption of food and drinking water (oral route).

Residential Bystanders: the risk from aggregate exposures was estimated females of childbearing age (13 to 50 years old) and a child (1-2 years old) that would be exposed to residues through the consumption of food and drinking water (oral route) and to propanil spray-drift 0-1000 feet from the application site through inhalation, dermal contact, and, in the case of the child, ingestion of residues by object-to-mouth, hand-to-mouth, and incidental soil ingestion.

#### iv(a) Aggregate Risk for Workers

The aggregate MOEs for herbicide handlers and field workers ranged from 1 to 233 and were less than the target of 300 for all application scenarios. In all cases, the occupational MOE component was the majority contributor to exposure risk.

#### iv(b) Aggregate Risk for Residential Bystanders

The aggregate MOEs for adults (females of childbearing age, 13 to 50 years old) ranged from 67 to 6052 and exceeded the target (300) for fixed wing and rotary aerial scenarios at downwind distances greater than 50 and 25 feet, respectively and for ground boom scenarios at all distances. The aggregate MOEs for children (1 to 2 years old) ranged from 41 to 4123. MOEs exceeded the target (300) for all aerial applications at downwind distances greater than 50 feet and for all ground boom scenarios. In all cases, the relative contribution of spray drift MOE components decreased with increasing down-wind distance.

## D) Conclusions

A health risk assessment of propanil was conducted for residential bystanders and for agricultural workers. The general population was represented by the total US population and 12 population subgroups that included adults, women of child-bearing age, infants, and children. Workers included herbicide handlers and rice field workers. The following exposure scenarios were evaluated: (a) acute and chronic dietary; (b) acute/short-term, seasonal, annual, and lifetime, combined route (dermal and inhalation) occupational; (c) acute/short-term residential bystander, combined route (dermal, inhalation, and oral in children). Aggregate exposures risks that included dietary and residential bystander MOEs were also estimated for females of childbearing age (13 to 49 years old) and children (1-2 years old). Aggregate risks for workers included dietary and occupational MOEs. A target MOE of 300 was considered sufficiently protective against propanil's toxicity. The target of 300 includes an uncertainty factor of 10x for interspecies sensitivity, 10x for intraspecies variability, and 3x for the potential for enhanced sensitivity to metHb formation in and human subpopulations with hereditary enzymatic deficiencies including infants.

### 1) Dietary Risk

All acute MOEs were greater than 4382 at the 95th and 99th percentiles, respectively and all chronic MOEs were greater than 3446.

### 2) Occupational Risk

All acute and seasonal MOEs were less than 300 for all handler and field worker groups. Annual MOEs were below 300 for all handler/applicator groups and field scout groups.

### 3) Residential Bystander Risk

Adult dermal MOEs exceeded the target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 and 25 feet, respectively. All adult inhalation MOEs exceeded the target for all aerial application scenarios. Child dermal MOEs exceeded the target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 feet. Child inhalation MOEs exceeded the target for all aerial application scenarios.

All adult and child dermal, inhalation, and oral MOEs exceeded the target of 300 for ground boom application scenarios. The lowest MOEs observed were for dermal exposure in adults (0 feet/MOE = 576) and children (0 feet/MOE = 393).

### 4) Aggregate Risk

Workers: The aggregate MOEs for herbicide handlers and field workers were less than the target (300) for all application scenarios. In the above cases, the occupational MOE component was the majority contributor of exposure risk.

Residential Bystanders: The aggregate MOEs for adults (females of childbearing age, 13 to 50 years old) exceeded the target (300) for fixed wing and rotary aerial scenarios at downwind distances greater than 50 and 25 feet, respectively and for ground boom scenarios at all distances.The aggregate MOEs for children

(1 to 2 years old) exceeded the target (300) for all aerial and ground boom applications at downwind distances greater than 50 feet and all ground boom scenarios. In all of the above cases, the relative contribution of dietary MOE component increased with down-wind distance.

# II Introduction

## A) Chemical Identification

Propanil is a broad-spectrum, contact, post-emergence herbicide that is applied as a broadcast spray by ground/aerial equipment. It is one of the most widely used herbicides for rice production and is currently ranked within the top 20 agricultural pesticides used (as pounds of active ingredient (AI) in the US (Grube *et al.,* 2011). There are no currently approved residential uses for propanil in California or in the US as a whole. The only currently approved non-residential use in either region is for the protection of rice crops from annual/biennial/perennial broadleaf weeds and grasses and aquatic weeds (USEPA, 2003). In California, some propanil formulations also contain the herbicidal AIs bensulfuron methyl (BSM) and halosulfuron methyl (HSM) (NPIRS, 2012).

Propanil acts by inhibiting photosynthesis in target species through direct action on photosystem II. More specifically, it acts by binding to the D-1 quinone-binding protein thus disrupting electron transport that's normally facilitated by its bound ligand, plastoquinone (Fedtke, 1982; Greenhalgh and Roberts, 1986). The selective herbicidal activity of propanil is attributed to the activity and distribution of aryl acylamidase, an enzyme that catalyzes the hydrolysis of the propanil amide linkage creating two herbicidally-inactive metabolites: 3,4-dichloroaniline (3,4-DCA) and propionic acid (Hoagland *et al.*, 1974; Lamoureux and Frear, 1979). Crops with high aryl acylamidase activities (i.e., rice, turf grass and wheat) tolerate propanil while weeds lacking this activity are killed.

Mammals also metabolize propanil through the aryl acylamidase hydrolysis of the parent molecule (Williams and Jacobson, 1966; Singleton and Murphy, 1973; Chow and Murphy, 1975). The resulting metabolite, 3,4-DCA, has been shown to play a central role in the mode of action (MOA) for propanil's mammalian toxicity (Kiese, 1966; Kiese, 1970; Singleton and Murphy, 1973; Chow and Murphy, 1975; McMillan *et al.*, 1990a; McMillan *et al.*, 1990b; McMillan *et al.*, 1991a). Following the hydrolysis of the parent molecule's amide linkage, the primary amine of 3,4-DCA is susceptible to N-hydroxylation catalyzed by cytochrome P450. The resulting two metabolites are directly responsible for the oxidation of hemoglobin (Hb) to methemoglobin (metHb): N-hydroxy-3,4-DCA (N-OH-3,4-DCA) and 3,4-dichloronitrosobenzene (DCNB) (Kiese, 1966; Kiese, 1970; Singleton and Murphy, 1973; Chow and Murphy, 1975; McMillan *et al.*, 1990a; McMillan *et al.*, 1991a; McMillan *et al.*, 1991b). Because metHb has a greater affinity for oxygen, excess metHb production results in decreased levels of oxygen being delivered to tissues (methemoglobinemia) (Prchal and Gregg, 2005; Curran *et al.*, 2011). On the other hand, hemolytic anemia (i.e., hemolysis and/or reduced erythrocyte counts and hemoglobin levels) has been attributed to the oxidation of Hb sulfhydryl groups by reactive oxygen species (ROS) (i.e., $H_2O_2$, ·OH, etc.) that are secondary products of the *in situ* oxidation of Hb by N-OH-3,4-DCA (Ambrose *et al.*, 1972; McMillan *et al.*, 1991a; McMillan *et al.*, 1991b; Eddleston *et al.*, 2002; McMillan *et al.*, 2005).

Organ enlargement, hyperplasia, and hemosiderin deposition result from the splenic accumulation of scavenged erythrocytes that occurs with chronic hemolytic anemia (Bus and Popp, 1987). Hemosiderosis creates a local environment favorable to iron-catalyzed free radical reactions that cause cellular damage that includes lipid peroxidation, DNA strand breaks, and protein degradation (Bus and Popp, 1987). Propanil-mediated liver toxicity is also suggested based on the observations that the liver is a reservoir organ and is the primary site of aryl-acylamidase hydrolysis and subsequent oxidation reactions (Kiese, 1966; Kiese, 1970; Singleton and Murphy, 1973; Chow and Murphy, 1975; McMillan *et al.*, 1990a; McMillan *et al.*, 1991a; McMillan *et al.*, 1991b). Cellular damage associated with propanil's liver toxicity may be mediated by the direct oxidation of circulating cholesterol (Santillo *et al.*, 1995). Propanil and its metabolites have also been demonstrated to adversely affect components of both the innate and adaptive immune responses by suppression or enhancement depending on the exposure and the specific response being measured (Barnett and Gandy, 1989; Barnett *et al.*, 1992; Zhao *et al.*, 1995; Cuff *et al.*, 1996; Xie *et al.*, 1997a; Xie *et al.*, 1997b; Zhao *et al.*, 1998; Watson *et al.*, 2000; Frost *et al.*, 2001; de la Rosa *et al.*, 2003; Brundage *et al.*, 2004; de la Rosa *et al.*, 2005; Salazar *et al.*, 2005; Salazar *et al.*, 2006; Corsini *et al.*, 2007; Ustyugova *et al.*, 2007; Salazar *et al.*, 2008). Furthermore, there is evidence for endocrine system-mediated toxicity that is not mediated by the direct or indirect disruption of steroid hormone signaling at the levels of steroid receptor and steroid synthesis (Salazar *et al.*, 2006).

In humans, clinical signs of methemoglobinemia are proportional to the level of metHb and include: blue or grey skin pigmentation (cyanosis) and brown or chocolate colored blood (≤ 15 % metHb); headache, dyspnea, lightheadedness, syncope (fainting), weakness, confusion, palpitation, chest pain (25 to 50 % metHB); cardiovascular symptoms (e.g., abnormal cardiac rhythms, etc.), central nervous system symptoms (e.g., delirium, seizures, coma, etc.), metabolic symptoms (e.g., profound acidosis) (50 to 70% metHb) (Curran *et al.*, 2011; Lee, 2013). Clinical signs of hemolytic anemia include the following: intravascular hemolysis, cardiovascular symptoms related to anoxia (e.g., tachycardia, dyspnea, angina, etc.), weakness, symptoms related to hemosiderosis (e.g., bronze skin color, diabetes, etc.), dark urine (i.e., hemoglobinuria), jaundice and/or bilirubin gallstones, and splenic enlargement (Schick and Sacher, 2013). There is evidence for enhanced sensitivity to xenobiotic-mediated metHb formation in subpopulations that include infants and humans with hereditary enzymatic deficiencies (Kabra *et al.*, 1998; NAS, 2000; Knobeloch and Proctor, 2001).

Low levels of 3,3',4,4'-tetrachloroazobenzene (TCAB) (0.1-2900 ppm) and 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) (< 0.05 ppm) have been reported to be present in technical propanil and in finished propanil formulations as an artifact of manufacturing (Bunce *et al.*, 1979; Hill *et al.*, 1981; Di Muccio *et al.*, 1984; Singh and Bingley, 1991; van Birgelen *et al.*, 1999). TCAB and TCAOB are also created by soil microbes following propanil applications and their transport from the soil to the rice grain has been demonstrated under experimental conditions (Still, 1969; Still *et al.*, 1980; Pothuluri *et al.*, 1991). The presence of these contaminants is notable because TCAB and TCAOB are structural analogs of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and have dioxin-like modes of action primarily meditated by the aryl hydrocarbon receptor (AhR). The AhR is a ligand-dependent transcription factor with binding affinity for diverse endogenous and exogenous chemicals including TCDD, TCAB and TCAOB (Poland *et al.*, 1976; Hsia and Kreamer, 1979a; Kimbrough, 1980; Mensink and Strik, 1982; Hassoun *et al.*, 1984; Pothuluri *et al.*, 1991; Schneider *et al.*, 1995).

In the classical mode of AhR action, a high-affinity ligand traverses the plasma membrane of a target cell and binds to an AhR complex (AhR and chaperone proteins) in the cytoplasm. The ligand:AhR complex next undergoes a conformation change that facilitates its transport into the nuclear compartment. Once in the nucleus, the chaperone proteins are displaced by the AhR nuclear translocator (ARNT) (Denison *et al.*, 2011). The ligand:AhR:ARNT complex has a high binding affinity for a specific site on DNA known as a dioxin response element. The ligand:AhR:ARNT binding to the dioxin response element leads to increased transcription and expression of down-stream responsive genes.

The persistent, high-level expression of CYP1A1 or related CYPs mediated by AhR agonists leads to the increased metabolic conversion of endogenous and exogenous chemicals, the concomitant generation of ROS, and a local state of oxidative stress (Denison *et al.*, 2011). ROS are capable of damaging cellular macromolecules, activating intracellular kinase signaling pathways (i.e., c-Jun kinase, activator protein 1, nuclear factor-κB, nuclear factor erythroid 2-related factor 2, etc.), and altering gene expression and cellular responses. Cardiovascular ROS produced in the above scheme can cause endothelial dysfunction and hypertension. Alternatively, the AhR can induce the expression of TCDD-inducible poly(ADP-ribose) polymerase (TiPARP) that subsequently suppresses hepatic gluconeogenesis and induces wasting while the AhR-induced expression of son of sevenless (SOS1) leads to Ras-GTP mediated extracellular kinase activation and enhanced cell proliferation. Non-classical modes of AhR action follow the nuclear translocation of the receptor complex and include positive and negative modulation of estrogen, androgen, progestin, glucocorticoid, and thyroid hormone signaling (Denison *et al.*, 2011).

While the classical mode of action is considered to be essential for the major toxic effects mediated by AhR signaling, it is likely that non-classical modes of action will be found to play important roles as more information becomes available. Although TCAB and TCAOB have much lower potencies as AhR agonists than TCDD (Poland *et al.*, 1976), the general toxicities that have been directly attributed to AhR signal pathways and TCAB and/or TCAOB treatment include immunotoxicity, hematologic toxicity, hepatotoxicity, cardiotoxicity, male reproductive toxicity, dermal toxicity (including human chloracne), teratogenesis, endocrine disruption, genotoxicity and carcinogenesis (Hsia *et al.*, 1977; Hsia and Kreamer, 1979a; Hsia and Kreamer, 1979b; Morse *et al.*, 1979; Saint-Ruf *et al.*, 1979; Gilbert *et al.*, 1980; Kimbrough, 1980; Schrankel *et al.*, 1980; Hsia *et al.*, 1982; Schrankel *et al.*, 1982; D'Argy *et al.*, 1984; Hassoun *et al.*, 1984; Olson *et al.*, 1984; Bleavins *et al.*, 1985a; Bleavins *et al.*, 1985b; Hsia and Kreamer, 1985; Hassoun and Arif, 1988; Pothuluri *et al.*, 1991; van Birgelen, 1998a; van Birgelen, 1998b; van Birgelen *et al.*, 1999; Witt *et al.*, 2000; NTP, 2004; Ramot *et al.*, 2009; NTP, 2010; Singh *et al.*, 2010; Denison *et al.*, 2011; Ramot *et al.*, 2012; Bhusari *et al.*, 2014).

The transport of TCAB, and by inference TCAOB, from the soil to the rice grain has been demonstrated under experimental conditions, but there is insufficient evidence to conclude that the risk presented by dietary or occupational exposures to either of these compounds should be considered separately from the risk presented by corresponding exposures to propanil (Still, 1969; Still *et al.*, 1980).

A human health risk assessment for propanil was given a high-priority status for risk assessment due to adverse effects observed in chronic toxicity studies in dogs and mice (hematologic toxicity), oncogenicity studies in rats (testicular and liver tumors) and mice (lymphoma), and concerns relating to spray drift from application sites. This Risk Characterization Document (RCD) includes evaluations of potential

health risks from exposure to propanil residues in food and drinking water as well from occupational activities and ambient air. Aggregate exposures from combined exposure scenarios were also evaluated.

The studies evaluated in the toxicological profile included guideline studies submitted to fulfill data requirements for registration as well as those required under the California Birth Defect Prevention Act of 1984 (SB 950). Relevant reports published in the open literature (e.g., university research, etc.) and by other regulatory agencies (US EPA, National Toxicology Program (NTP), European Food Safety Authority (EFSA), European Commission (EC), etc.) were also included as part of a weight-of-evidence approach. Routine open-literature searches using the electronic databases at the National Center for Biotechnology Information (NCBI) (https://www.ncbi.nlm.nih.gov/pubmed) were performed and the RCD was updated as needed. The most recent NCBI search was conducted in June 2016.

## B) Regulatory History

### 1) General

Herbicide products formulated with propanil are registered in Australia, Cambodia, India, Madagascar, Philippines, Portugal, Tanzania, Uganda, Vietnam, the European Union (EU), and the USA.

### 2) US EPA

The first propanil-based herbicide formulations to be registered in the US were Rogue Herbicide and Stam F-34 by Monsanto Co. and Dow AgroSciences LLC, respectively. Both of the aforementioned products were registered in 1962 to control grasses and weeds in rice crops. Current manufacturers include Dow AgroSciences, LLC and RiceCo, LLC (USEPA, 2003).

Requirements for the re-registration of propanil were specified in the Propanil Reregistration Standard Guidance Document issued in 1987 with specified data call-ins issued subsequently (USEPA, 2003). US EPA issued a tolerance reassessment decision and a human health risk assessment in 2002 and accepted requests for the voluntary cancellation of propanil uses on small grains by technical registrants in 2003. The Registration Eligibility Decision (RED) for propanil was issued in 2003 (USEPA, 2003). The document included an evaluation of the human risks from occupational and aggregate exposures (i.e., combined dietary and occupational) to propanil. The main conclusion from these assessments was that, while the aggregate exposure in the US population would not present unreasonable risk, the risk stemming from occupational exposures was high even when personal protective equipment and contemporary methods of risk reduction were used. US EPA specified risk reduction measures necessary to support the continued use of propanil in the RED (USEPA, 2003). Select original mitigation measures were revised in the 2006 amendment to the RED based on its review of public comments and additional data submitted by the Propanil Task Force (USEPA, 2006).

### 3) California

Propanil was first registered in California in 1962 as Rogue Herbicide (Monsanto Co.) and Stam F-34 (Dow AgroSciences LLC) for the control of grasses and weeds in rice crops. Propanil-containing products are considered restricted-use herbicides; as such, they may only be purchased and used by licensed applicators. There are no approved residential uses for propanil.

Since its introduction, propanil use in California has unintentionally damaged the foliage and fruit of stone fruit trees (e.g., plums, peaches, etc.), cotton and vineyards adjacent to rice fields due to spray drift As a result of drift-related crop damage, propanil use was limited to defined use areas (DPR, 2002).

Although propanil is a Category III toxicant, it was given a high-priority status for risk assessment due to adverse effects observed in chronic toxicity studies in dogs and mice (hematologic toxicity), results from oncogenicity studies in rats (testicular and liver tumors) and mice (lymphoma), and concerns relating to drift from application sites (DPR, 2007). DPR initiated its risk assessment on propanil in 2012.

DPR identified propanil as a potential ground water contaminant based on data requirements established by the Pesticide Contamination and Prevention Act (PCPA) of 1985. 3,4-Dichloroaniline (3,4-DCA), a contaminant and degradate of several structurally-related herbicides (e.g., propanil, linuron, and diuron), was detected in water from 94 wells screened in California between 2004-2011 with concentrations ranging from 0.001-0.541 ppb (DPR, 2012a). The detected levels were found not to "pose a significant potential human health risk or a threat to public health" (DPR, 2012b).

## C) Product Formulations

Propanil is formulated as an emulsifiable liquid concentrate (16.6-58.0% AI), a water-dispersable or dry-flowable granule (59.6-81.0% AI), a soluble concentrate liquid (41.2-80.2% AI), or a flowable liquid concentrate (41.2% AI) (USEPA, 2003). Propanil is formulated alone or with the following AIs: bensulfuron-methyl (BSM) (0.32-0.62%), halosulfuron-methyl (HSM) (0.32-0.46%), clomazone (2.9%), quinclorac (2.0%), triethylamine triclopyr (3.8%), pendimethalin (11.25%) or thiobencarb (31%) (NPIRS, 2012). The only additional AIs currently used with propanil in California-registered formulations are BSM and HSM. As of 2016, there were three registrants for fourteen registered propanil products in California (DPR, 2016a). A complete list of the registrants and registered trade names for all active registration in California is provided below (Table 1).

**Table 1. Trade Names for Active California Propanil Registrations as of 2016**

| Registrant | Trade Names |
|---|---|
| Riceco LLC, Memphis, TN | Duet 60 DF[1], Duet 60 DF CA[1], Duet CA[2], RiceEdge 60 DF[3,] RiceShot 48 SF, Stam 80 EDF-CA, SuperWham! 80 DF-CA, SuperWham! CA, SuperWham! DF, Wham! 60 DF |
| Willowood LLC, Roseburg, OR | Willowood Propanil 4SC, Willowood Propanil 4SC (CA), Willowood Propanil 80CHS |
| Pronil, LLC, St. Joseph, MO | Propanil 4SC |

*Legend: (1) BSM 0.46%; (2) BSM 0.32%; (3) BSM 0.62%; (3) halosulfuron-methyl 0.46%.*

## D) California Usage

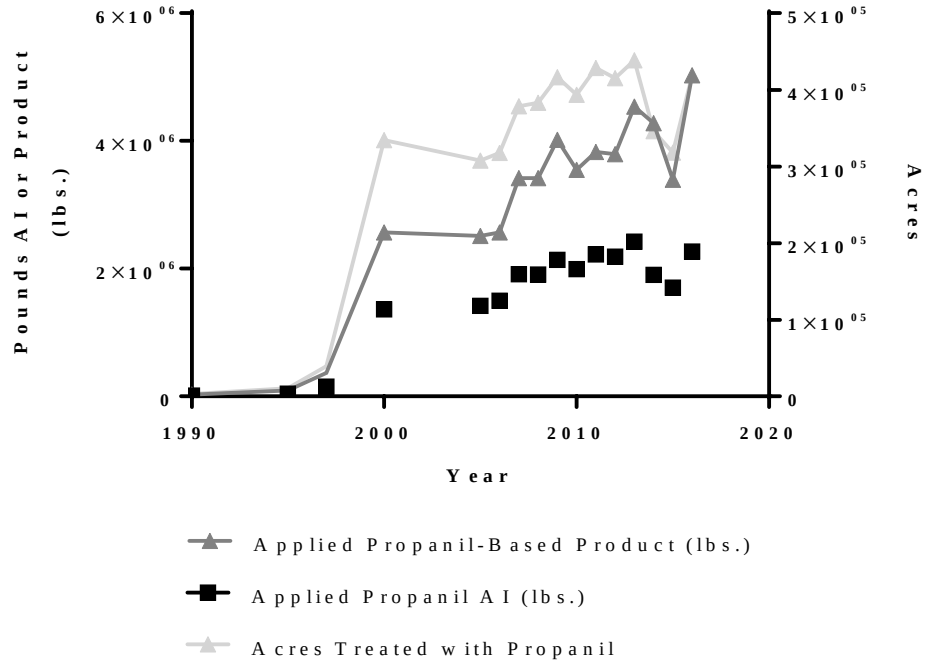
The use of propanil and propanil-based products on California rice crops has increased steadily since 1990 with the largest increases associated with the formation of an Expanded Use Area and the Butte County Study Area in 1997 (Table 2 and Figure 1) (DPR, 2017 ) (last access date: 10 Jan 19). The use of

propanil-based products peaked in 2016 when 5 million pounds of products, corresponding to 2.3 million pounds of AI, were used to treat 419,000 acres.

**Table 2. Summary of California Propanil Use Data**

| Year | Applied Propanil-Based Product (lbs.) | Applied Propanil AI (lbs.) | Acres Treated with Propanil |
|---|---|---|---|
| 1990 | 27215 | 11827 | 2947 |
| 1995 | 94357 | 40022 | 10550 |
| 1997 | 367754 | 154868 | 39392 |
| 2000 | 2566752 | 1361289 | 334249 |
| 2005 | 2511985 | 1418131 | 307675 |
| 2006 | 2568481 | 1497127 | 317521 |
| 2007 | 3419689 | 1910147 | 378512 |
| 2008 | 3416911 | 1906996 | 382998 |
| 2009 | 4018961 | 2139104 | 416346 |
| 2010 | 3547656 | 1993021 | 393401 |
| 2011 | 3825649 | 2222043 | 428345 |
| 2012 | 3793670 | 2188145 | 415329 |
| 2013 | 4535533 | 2422563 | 438515 |
| 2014 | 4275384 | 1901591 | 345985 |
| 2015 | 3391816 | 1702833 | 318105 |
| 2016 | 5029689 | 2269943 | 418789 |

**Figure 1. Summary Plot of California Propanil Use Data**



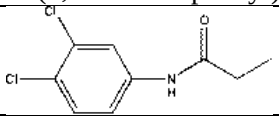
## E) Illness Reports

One propanil-related illness was reported by California Pesticide Illness Query (CalPIQ) between 1992 and 2015 for an applicator applying Cyhalofop Butyl, propanil, and Triclopyr herbicides in Sutter County, California (DPR, 2019) (last access: Jan 2019). The clinical signs were dizziness and nausea. One minor and two moderate severity incidents were reported involving propanil alone and with more than one AI including propanil, respectively, by the US EPA Office of Pesticide Programs (OPP) Incident Data System (IDS) between 2010 and 2014 (USEPA, 2015b). Ten incidents of low severity were reported involving propanil alone (1) and with more than one AI including propanil (9), respectively, by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) (USEPA, 2015b). USEPA OPP concluded that incident cases for propanil were of low severity and frequency and did not appear to be a concern at the time of the report but that continued monitoring was warranted.

## F) Environmental Fate

### 1) Physicochemical Properties

**Table 3. Physicochemical Properties of Propanil Herbicide**

| Parameter | Value(s) |
|---|---|
| Common Name | propanil |
| Synonyms | Partial List: Propanide, Grascide, Propanex |
| IUPAC Name | N-(3,4-dichlorophenyl)propanamide |
| Chemical Structure |  |
| Chemical Family | Acetanilide |
| DPR Chemical Code | 503 |
| CAS Registry Number | 709-98-8 |
| Empirical Formula | $C_9H_9Cl_2NO$ |
| Molecular Weight | 218.08 g/mole (O'Neil, 2001) |
| Appearance | Medium to dark grey crystalline solid (Tomlin, 2003) |
| Melting Point | 91-93° C (O'Neil, 2001) |
| Density | 1.41 g/cm$^3$ at 22° C (Tomlin, 2003) |
| Vapor Pressure | 9.08X10$^{-7}$ mm Hg (0.121 mPa) at 25° C; 9.0X10$^{-5}$ mm Hg (12 mPa) at 60° C (USDA, 2005) |
| Octanol/Water Partition Coefficient (log $K_{ow}$) | 3.07 (Tomlin, 2003) |
| Solubilities | Water (20° C): 0.130 g/L (slightly soluble); Isopropanol and Dichloromethane (20° C): > 200 g/L; Toluene (20° C): 50-100 g/L; Hexane (20° C): < 1 g/L; Benzene (25° C): 70 g/L; Acetone (25° C): 1700 g/L; Ethanol (25° C): 1100 g/L (Tomlin, 2003). |
| Henry's Law Constant | 1.7 x 10$^{-4}$ Pa m$^3$/mole (Tomlin, 2003) |
| Odor Threshold | Data not available. |
| Odor | Odorless (Tomlin, 2003) |
| Boiling Point | 351° C (Tomlin, 2003) |
| Flash Point | 100 ° C (Meister, 1992) |
| Corrosivity | Corrosive to polyethylene (Spencer, 1982); non-corrosive under normal use conditions (Hartley and Hamish, 1987) |
| Conversion Factors | 1 ppm = 8.90 mg/m$^3$<br>1 mg/m$^3$ = 0.11 ppm |

### 2) Summary

Propanil has low water solubility, low volatility, and moderate mobility under standard conditions for its application and therefore has the potential for ground water leaching. On the other hand, propanil has a low potential for bioconcentration in aquatic organisms. Propanil is stable to aqueous hydrolysis but susceptible to photolysis in aqueous and soil environments with half-lives ranging from 40 to 60 days and 18 to 21 days, respectively. Diverse photodegradant species have been reported that include small, water soluble compounds and insoluble adducts of humic acid. Aerobic microbial degradation of propanil is initially rapid in soil and in water and results in diverse degradant species including TCAB and 3,4-DCA. Following the initial rapid degradation phase in soil, 3,4-DCA becomes covalently bound to the organic soil fraction with a mineralization phase extending for years. In rice, propanil is rapidly transported and metabolized by hydrolysis and by subsequent oxidative and conjugative pathways to diverse metabolic species including 3,4-DCA and $CO_2$. A substantial fraction of the propanil-derived rice metabolite load is complexed with lignin. Furthermore, the high constituent acyl amidase activity in rice plants ensures that residual propanil in harvested rice grains from plants that have survived to maturity is likely to be entirely in the form of species derived from 3,4-DCA. TCAB and TCAOB are manufacturing artifacts and microbial degradants of propanil that can be applied directly to rice plants and/or be transported into foliage and grain from soil deposits. There are two DPR documents reviewing the environmental fate of propanil (DaSilva, 2016; Kanawi *et al.*, 2016).

### 3) Volatility

Propanil has a low intrinsic volatility under typical application conditions (USDA, 2005; Kanawi *et al.*, 2016). The likelihood of re-volatization (i.e., secondary drift) leading to post-application exposures that are relevant to human health is considered to be negligible (USEPA, 2014).

### 4) Hydrolysis

Propanil was stable in distilled water for over 4 months at 20° C at pH 6-9 (El-Dib and Aly, 1976). These data suggest that aqueous hydrolysis does not play a significant role in propanil degradation.

### 5) Photolysis

#### *(i) Vapor Phase*

The vapor phase half-life of propanil, through the photochemically-induced breakdown by hydroxyl radicals, was 4.2 days at 25 °C (Meylan and Howard, 1993).

#### *(ii) Aqueous Solution*

Following 34 days of irradiation in a photoreactor, 18% of propanil was unchanged in a 200 mg/L solution (Moilanen and Crosby, 1972) while 50% degradation was observed in a 100 mg/L solution after four (4) hours (Tanaka *et al.*, 1985). The following sunlight photolysis half-life values were reported for propanil: 60.3 days (lake water), 55.4 days (river water), 57.3 days (marine water), 40.3 days (ground water) and 44.1 days (distilled water) (Konstantinou *et al.*, 2001). The photodecomposition reactions reported for propanil in artificial light (310 nm) included: amide hydrolysis, substitution of ring chlorines

(H and OH), polymerization of hydroxylated rings (Menzie, 1974). Photodecomposition products reported for propanil in artificial and natural light included: 3'-hydroxy-4'-chloropropionanilide, 3'-chloro-4'hydroxypropionanilide, 3',4'-dihydroxypropionanilide, 3'-chloropropionanilide, 4'-chloropropionanilide, propionanilide, 3,4-DCA, 3-chloroaniline, propionic acid, propionamide, TCAB and a humic acid (Moilanen and Crosby, 1972; Tanaka *et al.*, 1985).

***(iii) Soil Surface***

The following photolysis half-lives were reported for propanil: 21.1 days (sandy clay loam), 19.9 days (clay loam) and 18.4 days (sandy loam) (Konstantinou *et al.*, 2001).

**6) Microbial Degradation**

***(i) Aerobic Degradation in Soil***

Data from grab-sample studies support a rapid biodegradation pathway with the conversion of propanil to 3,4-DCA and subsequently to TCAB (Bartha, 1971). In laboratory studies, 95% of applied propanil was degraded within 7 days when applied to diverse soils (clay, loam, heavy clay, and sandy loam) alone and in the presence of herbicides normally applied with propanil as tank or split-mix components (asulum, barban, bromoxynil, dicamba, 2-methyl-4-chlorophenoxyacetic acid (MCPA), 4-(4-chloro-2-methylphenoxy)butanoic acid (MCPB), metribuzin, and 2,4-Dichlorophenoxyacetic acid (2,4-D)) (Smith, 1984). Aerobic biodegradation products reported for propanil in soil included: 3,4-DCA, TCAB, azoxy-TCAB (TCAOB), 1,3-bis(3,4-dichlorophenyl)triazine, 4-(3,4-dichloroanilino)3,3',4'-trichloroazobenzene, 3,4-dichlorophenylhydroxylamine, nitroso-3,4-dichlorobenzene, coupled products of last two (2) compounds, and N-Formyl-3,4-dichloroaniline (Bartha and Pramer, 1970; Plimmer *et al.*, 1970; Kaufman *et al.*, 1972; Kearney and Plimmer, 1972; Pothuluri *et al.*, 1991). Despite the diversity of biodegradation products, it was reported that upon formation most of the 3,4-DCA becomes covalently bound to organic fraction in soil and that subsequent mineralization (i.e., conversion to $CO_2$) then proceeds slowly with times for 50% dissipation (DT 50) extending to several years (Hsu and Bartha, 1976).

***(ii) Soil Residue***

Soil samples (n = 99) were collected in rice fields in California, Arkansas, Louisiana, Mississippi, and Texas in the late summer of 1972 and tested for residual levels of TCAB (Carey *et al.*, 1980). Propanil was not detected in any samples while TCAB was detected in 6 of 99 samples (6.1%) with average concentrations that ranged from 0.01 to 0.05 ppm in positive samples. TCAB was detected in 5.3% of the 19 samples for California with an average concentration of 0.01 ppm in positive samples. In another study, low concentrations of TCAB (< 0.02 ppm) were detected in surface layer (0 to 10.1 cm) that decreased with increasing depth and time from last application (Kearney *et al.*, 1970). Based on the above, residual soil TCAB levels are likely to be low.

***(iii) Aerobic Degradation in Water***

Average biodegradation half-life values (17 and 154 hours) were calculated using study data from propanil applied to "amended" and "unamended" environmental waters (3 pond samples and 1 river

sample). The above results were consistent with rapid aerobic degradation (Paris and Rogers, 1986). Complete or near-complete degradation was observed for propanil applied to sea water (4 to 6 days) and non-sterile, distilled water (5 days) (Strekozov and Sokolov, 1979).

**7) Mobility in Soil and Water**

***(i) Soil***

Koc values range from 141 to 800 (silt loam) with the lowest mobility value corresponding to the silt loam soil type (Konstantinou *et al.*, 2001; USEPA, 2003; USDA, 2005). The above soil mobilities are classified as "moderate" (FAOUN, 2013).

***(ii) Water***

The Henry's Law constant (1.7 x $10^{-4}$ Pa $m^3$/mole) and vapor pressure (0.121 mPa (9.08X$10^{-7}$ mm Hg) at 25° C) reported for propanil are consistent with low volatility from water surfaces and moist or dry soil surfaces (Lyman *et al.*, 1990; USDA, 2005). Propanil has a low intrinsic volatility under typical application conditions. The solubility for propanil in water (20° C) is 0.130 g/L and is considered to be slight. Therefore, the predominant forms of propanil for all exposure routes are as a solid particulate, a solid particulate suspension in solvent, and a dilute solution. These findings suggest a potential for ground water leaching.

**8) Bioconcentration**

The bioconcentration factor (BCF) reported for propanil in whole-fish (fat-head minnows) was 1.6 where 1.8% of the tissue-localized [$^{14}$C]-propanil was extractable as parent (Call *et al.*, 1983). These data are consistent with a low potential for bioconcentration in aquatic organisms (Franke *et al.*, 1994).

**9) Plant Metabolism and Residues**

***(i) Plant Metabolism***

Propanoyl-labeled [$^{14}$C]-propanil applied to plant models of resistance (rice) and susceptibility (pea) was translocated throughout both plant models. Metabolism rapidly resulted in mineralization to [$^{14}$C]-$CO_2$ (Still, 1968a). Phenyl-labeled [$^{14}$C]-propanil applied to rice plants resulted in the following metabolite species (Figure 2): 3,4-DCA, sugar conjugates of 3,4-DCA (glucose, fructose, or xylose), and 3,4-dichloroacetanilide (Still, 1968b; Yih *et al.*, 1968b; Yih *et al.*, 1968a). Thirty-four percent (34%) of applied [$^{14}$C]-propanil was derived from 3,4-DCA and bound to lignin (Yih *et al.*, 1968b; RSC, 2008). Sugar conjugates accounted for 10% of metabolite at treatment Day +14 (Yih *et al.*, 1968b). Taken together, propanil is rapidly transported and metabolized by hydrolysis and by subsequent oxidation and conjugation to diverse metabolic species including 3,4-DCA and $CO_2$. A substantial fraction of the metabolite load is bound to lignin.

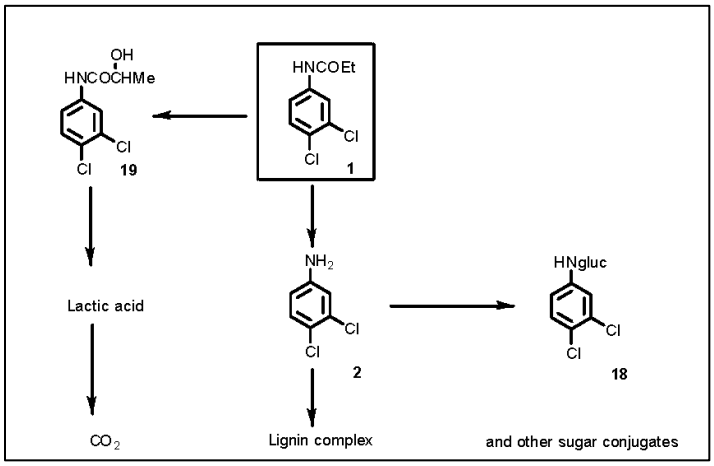
***(ii) Mechanism of Selectivity***

Propanil's herbicidal selectivity is attributed to the activity and distribution of the enzyme aryl acylamidase (Hoagland *et al.*, 1974; Lamoureux and Frear, 1979). Aryl acylamidase catalyzes the hydrolysis of the amide bond converting one equivalent of propanil into one equivalent each of 3,4-DCA and propionic acid. Both hydrolysis products no longer have the herbicidal activity of the propanil parent molecule. The susceptibility of a plant species to propanil's herbicidal action lies in its capacity to hydrolyze the propanilamide linkage. Application strategies for propanil formulations take advantage of the treated crop's high hydrolysis capacity relative to that for targeted weeds.

### *(iii) Plant Residues*

The high constituent acylamidase activity in rice ensures that residual propanil in harvested rice plants is likely to be primarily in the form of species derived from 3,4-DCA (Hoagland *et al.*, 1974; Lamoureux and Frear, 1979). Residual 3,4-DCA and derived species (TCAB, TCAOB, etc.) are primarily transported throughout the rice plant and to the rice grain following their release from the soil depot through microbial metabolism (Still *et al.*, 1980). Analytical methods that are used to verify residual levels in rice grains are able to quantify 3,4-DCA that has been released with base hydrolysis but do not provide data that can assigned to any single chemical species (Kinard, 2001). This also applies to 3,4-DCA derived from applied propanil, linuron, or diuron-based herbicides. It is not clear whether the residue analytical method routinely underestimates the levels of free 3,4-DCA, TCAB, or TCAOB present in the rice grain or released during food preparation and/or digestion.

**Figure 2. The metabolism of propanil in plants**




*Legend of Critical Metabolites: (2) 3,4-DCA, (18) sugar conjugates of 3,4-DCA (glucose, fructose, or xylose), and (19) 3,4-dichloroacetanilide* (Still, 1968b; Yih *et al.*, 1968b; Yih *et al.*, 1968a; RSC, 2008).

# III Toxicological Profile

## A) Metabolism and Pharmacokinetics

### 1) Overview

One open-literature clinical case reported on human oral absorption, distribution, metabolism, and excretion (ADME) for propanil. Human open literature studies are useful because they have clinical end-points specific to propanil's hematologic toxicity. DPR received six FIFRA registrant-submitted studies that encompassed the characterization of oral propanil ADME *in vivo*. Two studies each characterized oral propanil ADME in the rat, lactating goat, and laying hen. The general characteristics for the ADME of propanil in mammals are summarized below:

- propanil ADME was saturable.
- The oral absorption and elimination of propanil by oral or IV routes were approximately 100% with minimal retention.
- The primary route of elimination in urine was consistent with a high degree of oxidative metabolism and conjugation.
- Low levels of primary toxic metabolites (defined below) were recovered. This observation was likely because of their high reactivities/low stabilities *in situ* and the matrices that were sampled.
- Two parallel metabolic pathways (Pathways A and B) for propanil with similar capacities were identified. Pathway B is characterized by an aryl acylamidase-mediated hydrolysis step as a precursor to subsequent phase I and II metabolic reactions while pathway A is characterized by a lack of the former. Glucuronate conjugates of ring and propyl hydroxyl groups were observed for unhydrolyzed parent while acetyl and sulfyl conjugates of ring and propyl hydroxyl groups were observed when hydrolysis occurred further supporting a two-pathway model for propanil metabolism in the rat.
- Inter and intra-species differences in metHb formation, methemoglobinemia and hemolytic anemia may be due to differences in absorption, acylamidase activity, oxidative metabolism, and/or metHb reductase activity.

Metabolite species derived from propanil parent exposure can be placed in one of three distinct categories based on known pathways of hematologic toxicity as follows:

1. The exposures (as fractions of total parent exposure) to the "primary metabolites" N-OH-3,4-DCA and DCNB are considered to be critical exposures for subsequent evaluations because (a) they are the only currently identified parent-derived species that are capable of causing hematologic toxicity during the time period of exposure and (b) they appear to be terminal with regard to subsequent metabolic steps.
2. Metabolites with a primary amine resulting from the hydrolysis of the amide linkage and the formation of 3,4-DCA are considered "secondary metabolites" because they are one enzymatic step removed from full activation to a "primary metabolite".
3. "Tertiary metabolites" result from the conjugation of "secondary metabolite" species.

Taken together, the combined exposures to primary, secondary, and tertiary metabolite species represents an estimate of the maximum, potential, exposure pool of 3,4-DCA equivalents from which any individual, propanil-derived, toxicologically active molecules must arise.

### 2) Human Pharmacokinetics and ADME Studies

**Study Reference:** Roberts *et al.* (2009)
**Study Design:** An pharmacokinetic study was conducted as one part of a multi-center prospective cohort study of patients that were admitted with symptoms related to acute self-poisoning with propanil (n = 431; ages ranged from 18 to 54). Patients identified by clinical staff provided consent and histories of exposure upon admission. Patient symptoms were managed by administration of supplemental oxygen, intravenous fluids, and ventilatory and hemodynamic support per standards of care. Methemoglobinemia was managed as needed by administration of methylene blue (IV or per oral) and/or oral ascorbic acid (per oral), and exchange transfusions. Beginning at admission, serial blood samples were taken to confirm propanil exposure and to quantify circulating levels of propanil and 3,4-DCA in the patients by high performance liquid chromatography with ultraviolet detection (UV-HPLC).

*Acute Toxicity*
Thirty patients were disqualified based on their exposure to multiple active ingredients. Forty-two (42) patients died with the majority of deaths occurring before day 6 post-ingestion. Fatalities were more likely to have occurred in older patients with higher exposures to propanil and a depressed Glasgow Coma Score (GCS) as a measure of consciousness at admission. Minor poisoning was often recorded as asymptomatic or accompanied by mild symptoms that included nausea, vomiting, diarrhea, tachycardia, dizziness, and CNS depression with stable vital signs and no organ involvement. Symptoms of moderate to severe poisoning included cyanosis (with reddish-brown blood at collection), hypotension, hyperventilation requiring intubation, cardiac arrest or evidence of ischemia, sedation or coma, seizures, oliguria, and death. Average propanil concentrations in patients that with intoxication levels that were classified by the authors as minor, moderate, or severe including fatalities, had propanil concentrations of 1.3, 8.9, and 72.0 µM.

*Pharmacokinetics*
The authors suggested that the consistently higher concentrations observed for 3,4-DCA, versus propanil, could be due to a higher rate of clearance or volume of distribution for propanil or possibly flip-flop kinetics where the rate of elimination exceeds the rate of absorption (Yanez *et al.*, 2011). Elimination half-lives in 3 of the patients with the most data were 0.9, 2.7, and 0.9 hours for propanil and 3.8, 4.4, and 2.8 hours for 3,4-DCA. The average elimination half-life for propanil was 3.2 hours (95% confidence interval: 2.6 to 4.5 hours). The average elimination half-life for 3,4-DCA could not be calculated due to the variability of the data. Some individual elimination profiles suggested that the formation of 3,4-DCA by acylamidase hydrolysis may be a more rapid process than elimination when 3,4-DCA concentrations are high. In general, propanil bioconversion was variable which may have been due to genetic polymorphisms related to esterase activity, bioavailability, and/or the saturability of the N-hydroxylation reaction.

*Oral Absorption and Excretion*

Prior to 10 hours post-ingestion, the ratios of propanil to 3,4-DCA concentrations in blood samples were highly variable. The ratios were consistently 1 or less for subsequent time points. This was consistent with a continuing absorption phase for propanil followed by an elimination phase. The 3,4-DCA concentrations in the blood of surviving patients were negligible by 36 hours.

**Study Reference:** Pastorelli *et al.* (1998)
A high resolution gas chromatography with negative ion chemical ionization mass spectrometry with selected ion recording (HRGC-NICI-SIR) method was developed to isolate and quantify 3,4-DCA adducted to Hb (3,4-DCA-Hb) using blood from rats treated IP with propanil. The method was then used to quantify 3,4-DCA-Hb in the blood of 2 workers in Italy that were exposed to Stam (35% propanil) at weighing and dilution and following ground-level spray applications (5 hours per day). Blood and urine samples were taken from workers participating in the study prior to engaging in occupational activities leading to exposures, and 2 days and 4 months after ceasing those activities. A pre-existing gas chromatography-nitrogen-phosphorous detection (GC-NPD) was used to quantify 3,4-DCA in the workers urine. The workers were exposed to either 2 or 10 applications. All pre and post exposure blood specimens had detectable levels of 3,4-DCA-Hb and all post-exposure specimens had higher 3,4-DCA-Hb levels than their matched pre-exposure specimens. Urinary 3,4-DCA was only detectable within 2 days post-exposure. The levels of 3,4-DCA-Hb in blood were qualitatively correlated with levels of exposure. 3,4-DCA-Hb may be a more sensitive biomarker of exposure than urinary 3,4-DCA. 3,4-DCA is rapidly excreted within 6-10 hours after the last exposure so urine sample collection would need to occur very quickly to obtain useful information. On the other hand, 3,4-DCA-Hb levels are stable over a longer period of time and may provide information on cumulative exposures because its half-life is expected to be similar to that for the erythrocytes (120 days).

### 3) Animal Pharmacokinetic and ADME Studies

#### *(i) Oral and I.V. Routes*

**Study References:** Wu (1990a); (Wu, 1991)
**Study Design:** Two registrant-submitted studies were conducted to assess the absorption, distribution, metabolism, and excretion (ADME) of species derived from ring-labeled [$^{14}$C]propanil-parent. Five groups of male and female Sprague-Dawley rats, including concurrent controls, were dosed by oral gavage or intravenous routes. The IV and oral gavage groups were dosed with the following schemes (male/female): IV (0.55/0.64 mg/kg); single oral low dose (SOLD) (2.45/2.33 mg/kg); multiple oral low dose (MOLD) (2.36/2.44 mg/kg/day); single oral high dose (SOHD) (283.62/327.92 mg/kg). Timed urine, feces, and cages wash samples were taken as were post-mortem tissue and carcass samples. [$^{14}$C]$CO_2$ was not analyzed based on results for preliminary studies that indicated that exhalation did not represent a significant route of elimination. Endpoints included quantification of radioactivity as percentage of administered dose and the quantification and identification of metabolite species derived from parent in collected samples.

**Results:**
*Acute Toxicity*
Rats in the SOHD group showed frank toxic effects including: reduced activities, moribund appearance, swollen and watery eyes, reddish-brown urine, no feces collected for up to 36 hours post dosing. The

SOHD and SOLD/MOLD dose levels were approximately 30 and 0.2% of the oral $LD_{50}$ value (1080 mg/kg), respectively.

*Oral Absorption and Excretion*

The amount of propanil excreted as an absolute percent of the total applied [$^{14}$C] ranged from 78 to 90% for urine and 2 to 13% for feces. The total amount of propanil recovered as an absolute percent of the total propanil applied [$^{14}$C] ranged from 90 to 99%.The primary route of elimination was in urine consistent with a high degree of oxidative metabolism and conjugation. Based on the fractions of applied dose excreted in urine for per oral and IV dose groups, propanil had approximately 100% oral absorption. Furthermore, elimination was near complete with minimal retention in the tissues tested consistent with minimal covalent binding and/or incorporation.

*Pharmacokinetics*

The Tmax for urine (specimen collection time-point for with highest measured level) ranged from 4 to 8 hours for SOLD, MOLD, and IV routes and 24 to 36 hours for the SOHD route. Corresponding Cmax (highest measured level for a specimen) levels for urine ranged from 21 to 48% (SOLD, MOLD, and SOHD) and 47 to 67% (IV) absolute percent of the total applied [$^{14}$C]. The time for excretion of ≥ 90% of the total applied [$^{14}$C] (T90) ranged from 24 to 72 hours. The main sources variability for the average rates of oral absorption (based on the Tmax data) and urinary excretion for oral doses (based on the T90 data) were dose size and gender. Taken together, the oral absorption of propanil appeared to be rapid and saturable within the range of doses tested.

*Distribution*

The amount of propanil remaining unexcreted as an absolute percent of the total applied [$^{14}$C] ranged from 0.08 to 0.15% for tissues and 0.18 to 0.71% for the carcass. Propanil did not accumulate in rat tissues.

*Metabolism*

A scheme for metabolism in the rat is summarized in Figure 3. Species resulting from the oxidation of propanil's propyl moiety accounted for largest fraction of recovered radiocarbon (M3-7: 32-48%) while unmetabolized propanil parent accounted for < 1% of recovered radiocarbon in combined excreta. Species directly linked to propanil's hematologic toxicity (Primary "activated metabolites": 3,4-DCA and N-OH-3,4-DCA) accounted for 0.2 to 3% of recovered radiocarbon and the combined pool of primary, secondary, and tertiary metabolites for 16 to 38%. The majority of the Secondary metabolite radioactivity was in the form of [$^{14}$C] 3,4-dichloro-2-aminophenol-o-sulfamic acid (C4-2; M10) while the majority of the tertiary metabolite radioactivity was in the forms of [$^{14}$C] 4,5-dichloro-2-aminophenol-N-sulfamic acid (C4-1; M9) and [$^{14}$C] 4',5'-Dichloro-2'-O-sulfonic acid-acetanilide (A6d; M12). Taken together, two parallel metabolic pathways (Pathways A and B) for propanil with similar capacities were identified. Pathway B is characterized by an aryl acylamidase-mediated hydrolysis step as a precursor to subsequent phase I and II metabolic reactions while pathway A is characterized by a lack of the former. Glucuronate conjugates of ring and propyl hydroxyl groups were observed for unhydrolyzed parent while acetyl and sulfyl conjugates of ring and propyl hydroxyl groups were observed when hydrolysis occurred further supporting a two-pathway model for propanil metabolism in the rat.

**Study References:** Dawson (1990); Zdybak (1991)
**Study Design:** Two registrant-submitted studies were conducted to assess the absorption, distribution, metabolism, and excretion (ADME) of species derived from [$^{14}$C]propanil-parent in the goat. There were 2 groups of female goats, including a concurrent control. The test group (2 per group) was dosed by oral route for 5 days at treatment levels estimated to be > 10 times the theoretical real-world exposures through rice grains and hulls that may comprise 25% of livestock diet (79.5 mg [$^{14}$C]propanil/day for 5 days; 53 ppm; 1.5 mg/kg/day; or 1.542 mCi/day). Timed urine, feces, and milk samples were taken as were post-mortem tissue samples. Endpoints included quantification of radioactivity as percentage of administered dose and the quantification and identification of metabolite species derived from the parent in collected samples.

*Acute Toxicity*
There were no clinical observations that were attributed to treatment with propanil.

*Distribution: Fat, Milk, and Meat*
US EPA tolerances for goat milk, meat and meat-byproducts are 0.05, 0.10 and 1.0 ppm, respectively (USEPA, 2012b). The average study radiocarbon recovery was 0.8% in milk corresponding to 0.085 to 0.856 ppm. The highest propanil levels in milk were collected in the PM collection times. Based on the total radiocarbon recovery of 99.9 % for urine, feces, and milk, the estimated combined residual for all tissues is 0.1%. Residual propanil was distributed in liver (1.588-1.856 ppm), kidney (1.620-1.737 ppm), fat (0.169-0.278 ppm), leg muscle (0.068-0.091 ppm), and loin muscle (0.068-0.087 ppm).

*Metabolism*
Propanil was rapidly absorbed and eliminated in the goat and was found to be facile to metabolism by acyl amide hydrolysis, phase I oxidation of the side chain and/or the aromatic ring, and phase II conjugation. The authors concluded that propanil metabolism in the goat was similar to that of the rat with the exception of a major dimeric metabolite not found in the latter.

*Oral Absorption and Excretion*
The average study radiocarbon recovery was 99.9%: 87.4% in urine, 11.8% in feces, and 0.8% in milk. Radiocarbon levels for urine and feces reached steady-state after Day 1 in urine and feces with approximately complete elimination occurring in the interval between dose administrations (24 hours). Propanil was rapidly absorbed and eliminated in the goat.

**Study References:** Merricks (1990); Wu (1990b)
**Study Design:** Two registrant-submitted studies were conducted to assess the absorption, distribution, metabolism, and excretion (ADME) of species derived from [$^{14}$C]propanil-parent in the laying hen. There were 2 groups of laying hens, including a concurrent control. The test group (n = 30) was dosed by oral route at treatment levels estimated to be > 10 times the theoretical real-world exposures through rice grains and hulls that may comprise 20% of poultry diet (6.17 mg [$^{14}$C]propanil/day (51.42 ppm; 34.3 mg/kg/day) for days 1-7 and 6.62 mg [$^{14}$C]propanil/day (55.16 ppm; 36.8 mg/kg/day) for 8 days. Timed excreta and egg samples were taken as were post-mortem tissue samples. Endpoints included quantification of radioactivity as percentage of administered dose and the quantification and identification of metabolite species derived from parent in collected samples.

*Acute Toxicity*
There were no clinical observations that were attributed to treatment with propanil.

*Distribution: Fat, Eggs, and Meat*
US EPA tolerance for eggs is 0.30 ppm (USEPA, 2012b). Radiocarbon levels reached steady-state in laid eggs after day 7 (0.492 ppm). Propanil was extensively transported to eggs and distal tissue likely because of large administered dose but was not extensively incorporated into protein/carbohydrate/lipid macromolecules. Based on the total radiocarbon recovery of ~100 % for excreta, the estimated combined residual for all tissues was not significant.

*Metabolism*
Propanil was rapidly absorbed and eliminated in the laying hen and was found to be facile to metabolism by acyl amide hydrolysis, phase I oxidation of the side chain and/or the aromatic ring, and phase II conjugation. The authors concluded that propanil metabolism in the laying hen was similar to that of the rat with the exception of a major dimeric metabolite not found in the rat.

*Oral Absorption and Excretion*
The average study radiocarbon recovery was ~100 % in excreta. Complete elimination was achieved in excreta during the interval between dose administrations (24 hours) from day 2 to 8 and approximately 76% of final dose was eliminated within 8 hours of the final dose administration. Propanil was rapidly absorbed and eliminated in the laying hen.

**Figure 3. The metabolism of propanil in the rat**

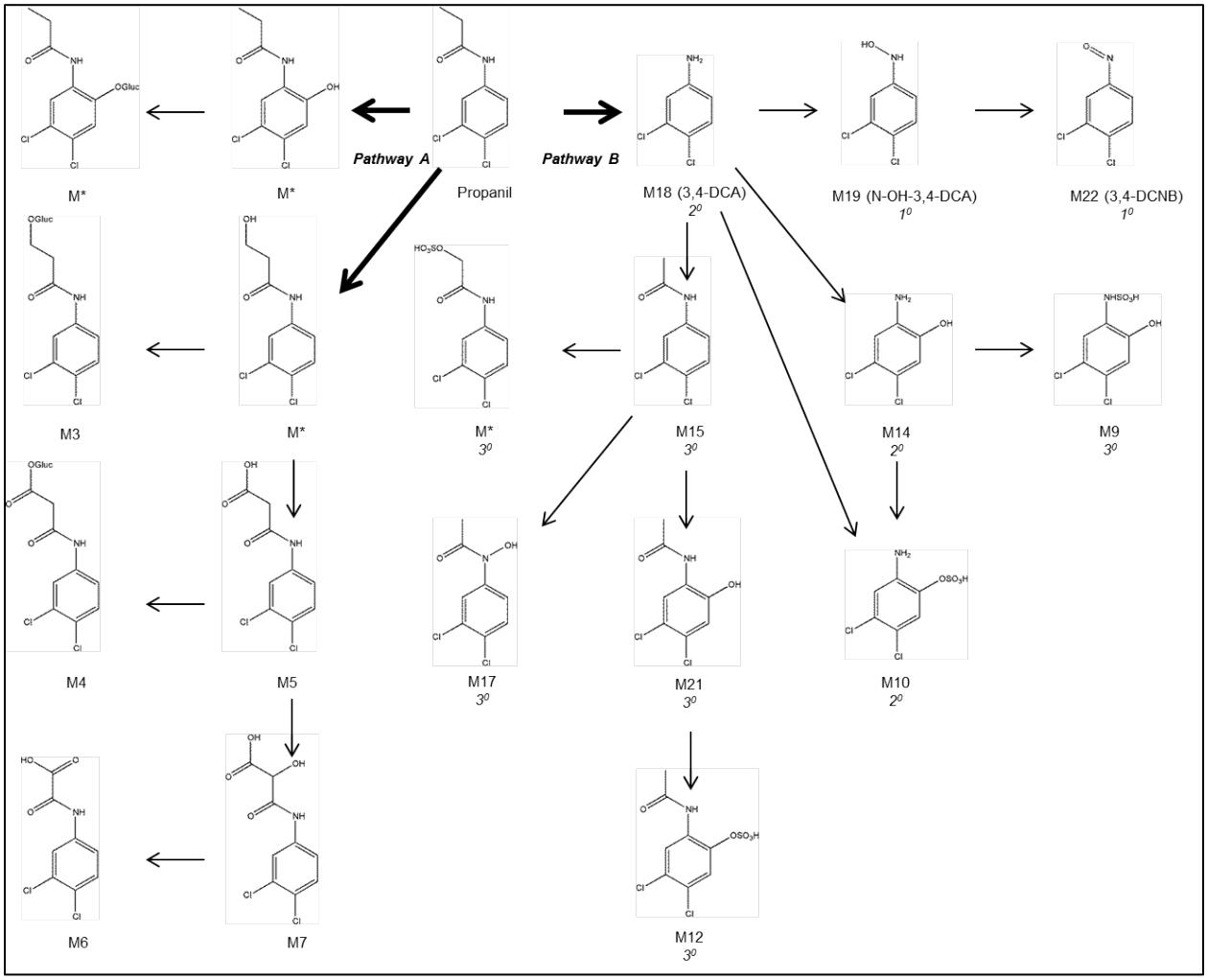



Figure Legend (Wu, 1991): *Bold arrows depict metabolic conversions of the propanil parent molecule while all other arrows depict metabolic conversions to metabolite species.$1^0$-$3^0$: Primary-Tertiary metabolites.*Proposed metabolite based on remainder of data.*

## B) ToxCast

### 1) Overview

In 2004, NTP proposed a strategic vision to transition toxicology testing from an observational science dependent on animal bioassays to a predictive science based on "target-specific, mechanism based, biological observations" (NTP 2004). US EPA created the National Center for Computational Toxicology (NCCT or CompTox) and commissioned the National Research Council (NRC) to present a long-range plan for the advancement of key scientific and technical aspects of toxicology testing within the current regulatory framework (National Research Council (U.S.). Committee on Toxicity Testing and Assessment of Environmental Agents., 2007; Stokstad, 2009). The Toxicity Forecaster (ToxCast) program was a product of NCCT research and based on the implementation of high-throughput screening (HTS) assays that were designed to provide *in vitro* information on molecular and cellular events that were considered

to be direct precursors to the toxic effects seen in in vivo bioassays (USEPA, 2013). Information obtained from these assays would initially be used in an iterative manner. That is, to obtain toxicologic information while simultaneously furthering the development and validation of key technologies needed to systematically move towards full implementation. The full implementation of this approach will be used to obtain toxicologic information on chemicals that can then be used for the prioritization of *in vivo* testing and eventually, for full characterization.

Approximately 700 HTS assays covering approximately 1000 end-points grouped into 300 signal pathways have been used to evaluate over 2000 chemicals in three phases (USEPA, 2013). Presently, DPR includes ToxCast data in the toxicity profile of its RCDs to add to the weight of evidence and, if possible, to gain additional insight into the nature of a chemical's toxicity that may be useful to define more accurate regulatory thresholds.

**2) Results**

ToxCast data for propanil was accessed in February 2017 through the US EPA iCSS ToxCast Dashboard version 2.0 (https://actor.epa.gov/dashboard2/) (USEPA, 2017). There were 711 results considered to be "Active" of which 79 were also considered to be true "hits". ToxCast data for propanil is summarized below in a plot of AC50 values (*in vitro* concentration with 50% activity for a given assay) for active assays and in a plot of active assays corresponding to specific "target families" of related endpoints (Figures 4 and 5).

Results showed that *in vitro*, propanil affected endpoints that were linked to xenobiotic metabolism, gene expression, and receptor binding. There were no assays in ToxCast testing platform that directly corresponded to hematologic toxicity. Cellular bioassays and biochemical assays that are able to quantify heme iron oxidation or a surrogate endpoint would be a useful addition to identify compounds with the potential for this MOA. A pattern of ToxCast active hits was identified indicating induction and inhibition of CYP enzymes, agonistic and antagonistic perturbations to the xenobiotic sensors pregnane x receptor (PXRE) and CAR (respectively), and perturbation to activator protein 1 (AP1) and nuclear factor-like 2 (NRF2) signaling pathways that may correspond to propanil's liver toxicity (e.g. pericholangitis, granulomatous inflammation, increased organ weight, and hepatocellular adenomas). Hits for AP1 and NRF2 assays suggest that propanil might generate intracellular reactive oxygen species (ROS). Effects that might also be correlated to hepatotoxicity include the BioSeek (BSK) BioMAP assay endpoints and cell cycle and cell morphology endpoints related to cytotoxicity, apoptosis, cell cycle arrest, and DNA damage (Houck *et al.*, 2009). Propanil was also shown to bind to the estrogen receptor (ER), AR, and thyroid hormone receptor (TR) and to dysregulate androstenedione (ANDR), testosterone (T), and 17-alpha-hydroxyprogesterone (OHPROG) synthesis. These endpoints may correspond to the observed *in vivo* reproductive, developmental, and oncogenic effects including decreased sperm and primordial follicle counts, delays for the completion of balanopreputial separation and vaginal perforation, testicular interstitial tumors. Propanil also had active hits of unknown toxicological significance corresponding to diverse endpoints in DNA binding, G protein-coupled receptor (GPCR), kinase, nuclear receptor, oxidoreductase, and transporter with higher relative potencies.

**Figure 4. Scaled AC50 values for "active" ToxCast end-points for propanil**

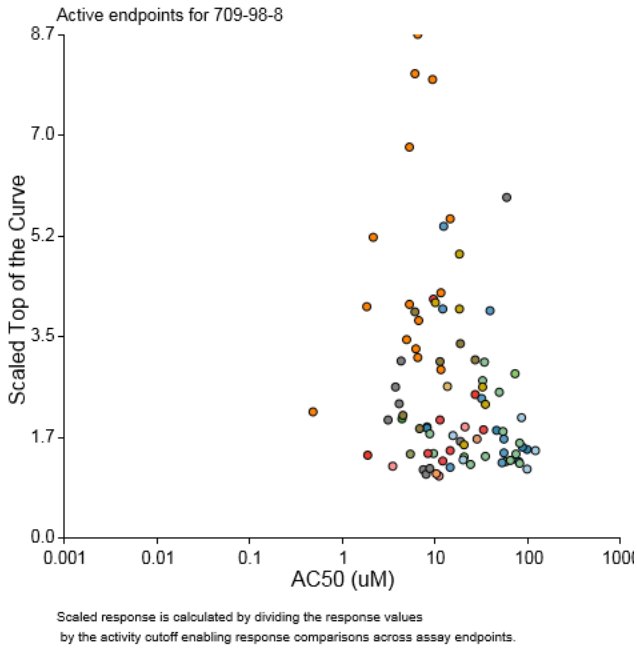
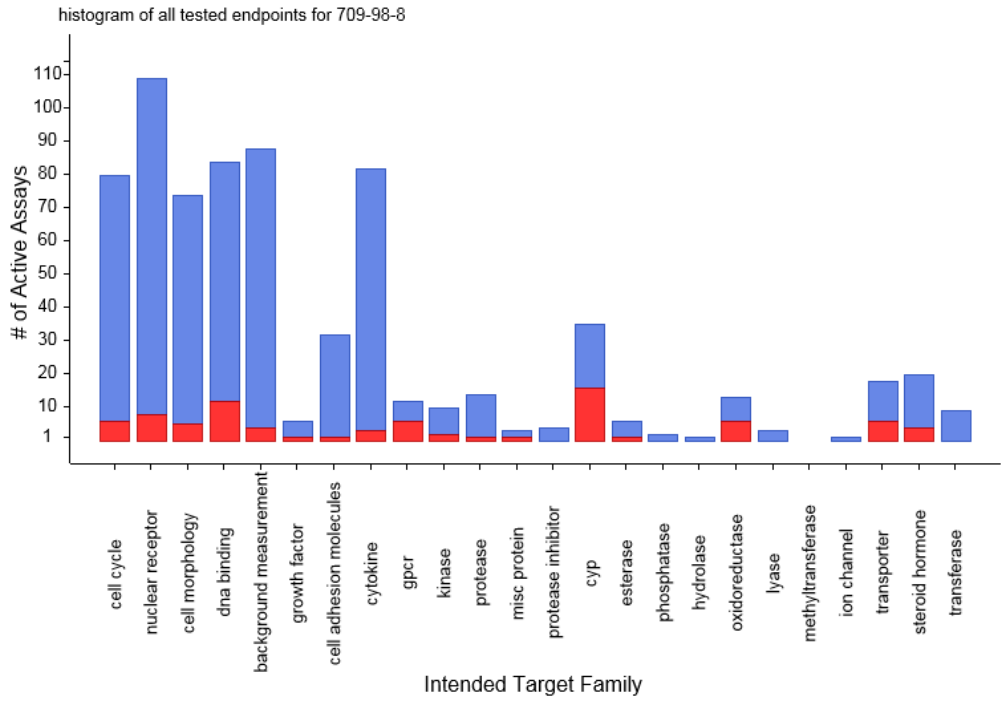



**Figure 5. "Active" ToxCast assay results for propanil sorted by target family**




Legend: red = "active"; blue = "inactive"

## C) Acute Toxicity

### 1) Summary

The data from the acute toxicity studies are used to establish the median lethal dose ($LD_{50}$) or lethal concentration ($LC_{50}$) values that are then used to determine the toxicity categories for the technical grade and formulations. Depending on the dose levels and toxicity of the test article in the animal model used, an acute NOEL (no observed effects level) or LOEL (lowest observed effects level) may be observed and subsequently used to define an acute threshold for non-carcinogenic effects for risk assessment. The acute toxicity databases for technical propanil and propanil formulations consist of registrant-submitted studies and studies reported in the open literature (Tables 5 and 6).

Human deaths from intentional ingestion of propanil were reported. Based on the results, an acute oral lethal dose can be estimated as over 1 g/kg/day. Initial clinical signs in fatalities included cyanosis, lactic acidosis, seizures, and unconsciousness, which are consistent with severe methemoglobinemia. The measured levels of metHb were 43-45% in 2 fatalities with death resulting from respiratory depression and cardiorespiratory arrest. Non-lethal acute signs included nausea, vomiting, diarrhea, tachycardia, dizziness, CNS depression, cyanosis (with reddish-brown blood at collection), hypotension, hyperventilation requiring intubation, ischemia, seizures and coma. The severity of the poisoning generally correlated with the measured levels of metHb. It has been reported that Hb adducts of 3,4-DCA are useful as biomarkers of cumulative propanil exposure in workers.

In studies of the acute oral, inhalation, and dermal toxicity of propanil in rats and rabbits, the signs of propanil intoxication included mortality, piloerection, reduced food consumption, reduced fecal volume, red-stained eyes and muzzle, restlessness, hunched posture, labored respiration, ruffled fur, chromodacryorrhea, eyelid adhesion, and red or discolored anatomical features (adrenal glands, kidney cortico-medullary junction, stomach areas, intestinal contents, urinary bladder contents, lungs, discolored liver). Additionally, propanil was a mild or slight skin irritant and a moderate eye irritant in the rabbit. Propanil was not a skin sensitizer in the guinea pig.

### 2) Acute Toxicity in Humans

#### *(i) Oral: Self-Poisoning*

Five open-literature studies were published describing the results of propanil self-poisoning in patients that were treated in hospitals in Sri Lanka and in Japan. An additional study was published describing a potential human biomarker for occupational and environmental propanil exposure. Study results are summarized below.

A prospective cohort study included 431 patients in Sri Lanka with propanil self-poisoning between 2002 and 2007 (Roberts *et al.*, 2009). Of these patients, 301 ingested propanil alone. This study was described in detail the Human Pharmacokinetics and ADME Studies section. The propanil formulations used in the poisoning were not specified, however propanil concentrations were measured in the blood at admission and varied between 0 and 128 µM. There were 42 deaths (a case fatality rate of 10.7%) occurring between 1.1 and 2.4 days post ingestion, despite treatment for methemoglobinemia with methylene blue.

The average propanil concentration at admission for these patents was 72.0 µM and the initial clinical signs were severe cyanosis, hypotension and acidosis. Based on the fatality rate, propanil was ranked as the second most lethal herbicide in Sri Lanka after paraquat.

The mean concentration of propanil in the 124 patients with moderate to severe poisoning was 8.9 µM and who exhibited symptoms varying from cyanosis (reddish-brown blood), hypotension, hyperventilation, coma, seizures, oliguria, cardiac arrest, and death. A total of 225 cases were characterized as minor based on average propanil blood concentrations of 1.3 µM and mild clinical signs including nausea, vomiting, diarrhea, tachycardia, dizziness, and CNS depression with stable vital signs and no organ involvement. The estimated elimination $t_{1/2}$ of propanil in humans was of 3.2 h.

Case reports were published for 5 patients with propanil self-poisoning in Sri Lanka (De Silva and Bodinayake, 1997). In all cases, the poisoning was from a 36% propanil formulation. The time between propanil ingestion and hospital admission was generally unknown. A 28 year-old man died within 36 hours of admission following ingestion of more than 200 mL propanil solution. The peak metHb level of 42.9% was measured 12 hours post admission. Severe poisoning signs (unconsciousness, cyanosis, irregular respiration and pulse, bradycardia) were characteristic for the peak metHb level. Assuming a default body weight for an adult of 71.8 kg, the acute oral lethal dose for humans is approximately 1 g/kg/day. Another patient (an 82 year old man) died within one week of admission of pneumonia following ingestion of 100 mL of propanil solution, which also contained unspecified amount of oxydiazone. This patient had lower metHb level (9.6%) at 48 hours post admission and milder clinical signs (drowsiness and cyanosis).

The other 3 patients (28-35 year old males) survived the ingestion of < 100 to 200 mL of a 36% propanil solution. The peak metHb levels for these patients ranged from 3.6 to 19.9%. The patients presented with signs of methemoglobinemia characteristic for these metHb levels (cyanosis drowsiness/stupor, headache, giddiness, and vertigo). Most of the patients had abnormal biochemistry results (high levels of bilirubin, blood urea, ALT activity, and AST activity, which may have been due to hemolytic anemia and liver toxicity.

A retrospective analysis was conducted using Sri Lanka's hospital records for 16 patients admitted for acute propanil intoxication between 1998 and 2002 (Eddleston *et al.*, 2002). Neither the ingestion times nor the exposure levels were known at admission and metHB levels were not measured. Symptoms of toxicity were typical for methemoglobinemia (confusion, reduced consciousness, cyanosis, and respiratory depression). Nine (9) patients died due to respiratory depression and cardiorespiratory arrest. A 16-week fetus died in utero though the mother survived. Methylene blue treatments were not available for this patient cohort.

In a case report from Japan, a 47-year old man was found dead 8 hours after ingesting approximately 9.7 mL of a formulation containing 25% propanil/5% carbaryl solution/70% organic solvent and/or emulsifier (Yamazaki *et al.*, 2001). Autopsy findings included pungent, greenish-brown gastric contents and fine foam in the throat, trachea, and esophagus. The highest levels of propanil and carbaryl were found in the gastric contents. The total amount of propanil in all specimens was 2.42 g with 1.75 g in the gastric fluids. Since carbaryl is a known inhibitor of the acylamidase activity of the cholinesterase enzyme, the co-

ingestion of propanil and carbaryl could possibly have resulted in a reduced conversion of propanil to 3,4-DCA and a reduced propanil toxicity compared with that for propanil alone. Severe methemoglobinemia was indicated by the blood metHb level of 45%. The death was attributed to propanil in the ingested solution based on anatomical findings consistent with anoxemia by CNS depression and methemoglobinemia, which likely led to respiratory and circulatory failure.

A 55-year old male patient in Sri Lanka admitted for acute propanil toxicity related to accidental ingestion was treated with methylene blue, blood transfusions, and hemodialysis and observed by the clinical staff (Kurukulasuriya *et al.*, 2003). The patient presented with an altered level of consciousness, cyanosis, and vomiting. Abnormal hematology results included reduced levels of Hb, and reduced red cell, platelet count, and white cell counts. Microscopic hematology revealed marked aberration in red cells (polychromasia, ghost cells, spherocytes, and nucleation, Heinz bodies), and white cells (neutrophil leukocytosis with left shift and toxic granulations). These observations were consistent with propanil-mediated oxidative hemolytic anemia. The patient was reported to have recovered by one month.

### 3) Acute Toxicity in Animals

#### *(i) Oral: Rat*

Two registrant-submitted studies and 1 open-literature study were conducted to assess the acute oral toxicity of technical propanil in the rat (Table 4) (Ambrose *et al.*, 1972; Naas, 1989b; Chang *et al.*, 1999c). Values for the oral $LD_{50}$ ranged from 779 (males) to 1384 mg/kg (combined), corresponding to toxicity category III. For comparison, eight (8) oral $LD_{50}$ values for propanil formulations (36 to 81% propanil) ranged from 500-1600 (males) to 5700 mg/kg (females), corresponding to toxicity categories III and IV (Tables 4 and 5).

#### *(ii) Oral: Dog*

One open-literature study was conducted to assess the acute oral toxicity of technical propanil in the dog (Table 4) (Ambrose *et al.*, 1972). The $LD_{50}$ value was 1217 mg/kg corresponding to toxicity category III. For comparison, the oral $LD_{50}$ value for a propanil formulation with 36% active ingredient was 1750 mg/kg (combined), also corresponding to toxicity category III (Table 4 and 5).

#### *(iii) Inhalation Rat*

One registrant-submitted study was conducted to assess the acute inhalation toxicity of technical propanil in the rat (Table 4) (Chang *et al.*, 1999a; Durando, 2010c). The mass median aerodynamic particle diameter (MMAD) for the study was 3.6 µm. The MMAD suggests that the primary deposition for the test article was in the bronchial and deep lung regions (< 5 µm) while the deposition for the subpopulations of larger particles (5 to 10 µm) was in the nasopharyngeal region (Raabe *et al.*, 1988; SOT, 1992; Pauluhn, 2003). The dose was 2.13 mg/L (341 mg/kg/day). There were no mortalities for the study so no value for the $LC_{50}$ could be calculated. For comparison, 8 $LC_{50}$ values for propanil formulations (43 and 80% propanil) ranged from 2.23 (combined) to 6.2 mg/L (combined) (357 to 992 mg/kg) corresponding to toxicity categories III and IV (Table 4 and 5).

### *(iv) Dermal: Rat*

One registrant-submitted study was conducted to assess the acute dermal toxicity of technical propanil in the rat (Table 4) (Durando, 2010a). The dose was 5000 mg/kg. There were no mortalities so no value for the $LD_{50}$ could be calculated. For comparison, 5 dermal $LD_{50}$ values for propanil formulations (43 to 81% propanil) ranged from > 2000 to > 5000 mg/kg (combined), corresponding to toxicity categories III and IV (Table 4 and 5).

### *(v) Dermal: Rabbit*

One registrant-submitted study was conducted to assess the acute dermal toxicity of technical propanil in the rabbit (Table 4) (Naas, 1989a). The dose was 2000 mg/kg. As with the rat study, there were no mortalities, so no value for the $LD_{50}$ could be calculated. For comparison, 2 dermal $LD_{50}$ values for propanil formulations (41 to 80% propanil) were > 2000 mg/kg (combined) corresponding to toxicity category III (Table 4 and 5).

### *(vi) Primary Dermal Irritation: Rabbit*

Two registrant-submitted studies were conducted to assess the primary dermal irritation toxicity of technical propanil in the rabbit (Table 4) (Naas, 1989c; Durando, 2010j). The dose for all studies was 0.5 g/site. The irritation scores for technical propanil ranged from non-irritating to slightly irritating. For comparison, 9 propanil formulations (36 to 81% propanil) were found to be slight to moderate irritants, with toxicity categories of III and IV (Table 4 and 5).

### *(vii) Dermal Sensitization: Guinea Pig and Rabbit*

Two registrant-submitted studies were conducted to assess the dermal sensitization toxicity of technical propanil in the guinea pig (Table 4) (Naas, 1989e; Durando, 2010g). The doses for all studies ranged from 25 to 80% (w/w). There were no mortalities for any study and all results indicated that propanil was not a sensitizer. For comparison, 6 of 8 propanil formulations (41 to 81% propanil) had positive results for sensitization in the rabbit (Table 4 and 5).

### *(viii) Eye Irritation: Rabbit*

Two registrant-submitted studies were conducted to assess the primary eye irritation toxicity of technical propanil in the rabbit (Table 4) (Naas, 1989d; Durando, 2010h). The dose for all studies was 0.1 g/eye. Irritation was observed in all eyes within 1 hour of instillation and cleared by Day 7. For comparison, 8 propanil formulations (41 to 85% propanil) were found to be minimally-irritating or to cause either reversible corneal opacity and/or iritis, corresponding to toxicity categories II through IV (Table 4 and 5).

**Table 4. Summary of Acute Toxicity Studies and Corresponding Results for Technical Propanil**

| Study Type | Species | Sex | Toxicity Category | Result (mg/kg or other) |
|---|---|---|---|---|
| Oral $LD_{50}$ | Rat | M | III | $LD_{50}$ = 779 to 1302[a] |
| Oral $LD_{50}$ | Rat | F | III | $LD_{50}$ = 907 to 960[a] |
| Oral $LD_{50}$ | Rat | Combined | III | $LD_{50}$ = 841 to 1384[a] |
| Oral $LD_{50}$ | Dog | Combined | III | $LD_{50}$ = 1217[b] |
| Dermal $LD_{50}$ | Rat | Combined | IV | $LD_{50}$ > 5000[c] |
| Dermal $LD_{50}$ | Rabbit | Combined | III | $LD_{50}$ > 2000[d] |
| Inhalation $LC_{50}$ (4-Hour, Whole Body) | Rat | Combined | III | $LC_{50}$ > 2.13 mg/L (341 mg/kg) (1) (MMAD: 3.6 µm)[e] |
| Eye Irritation | Rabbit | Combined | III | NA[f] |
| Dermal Irritation | Rabbit | Combined | IV | NA[g] |
| Dermal Sensitization | Guinea Pig | Combined | negative | NA[h] |

$LC_{50}/LD_{50}$: median lethal concentration/dose

MMAD: mass median aerodynamic particle diameter

NA: Not available.(1) Equivalent dosages were calculated by using the rat default breathing rate of 0.96 $m^3$/kg/day in the following equations: Dose (mg/kg/day) = Concentration (mg/L) x (1000 L/$m^3$) x (0.96$m^3$/ kg day) x (4hours/ 24 hours) (1 day exposure)

**References**

a Ambrose *et al*. (1972); Naas (1989b); Chang *et al.* (1999c); Ambrose *et al.* (1972); Naas (1989b); Chang *et al.*(1999c)

b Ambrose *et al.* (1972)

c Durando (2010a)

d Naas (1989a)

e Durando (2010c)

f Naas (1989d); Durando (2010h)

g Naas (1989c); Durando (2010j)

h Naas (1989e); Durando (2010g)

**Table 5. Summary of Acute Toxicity Studies and Corresponding Results for Propanil-Based Formulations**

| Study Type | Propanil Purity (%) | Species | Sex | Toxicity Category | Result (mg/kg or other) |
|---|---|---|---|---|---|
| Oral $LD_{50}$ | 36-81% | Rat | M | III, IV | $LD_{50}$ > 1500 to > 5000[a] |
| Oral $LD_{50}$ | 41-81% | Rat | F | III, IV | $LD_{50}$ = 500-1600 to 5700[a] |
| Oral $LD_{50}$ | 41-81% | Rat | Combined | III, IV | $LD_{50}$ = 1222.7 to > 5000[a] |
| Oral $LD_{50}$ | 36% | Dog | Combined | III | $LD_{50}$ = 1750[b] |
| Dermal $LD_{50}$ | 43-81% | Rat | Combined | III, IV | $LD_{50}$ > 2000 to > 5000[c] |
| Dermal $LD_{50}$ | 41-80% | Rabbit | Combined | III | $LD_{50}$ > 2000[d] |
| Inhalation $LC_{50}$ (4-Hour, Whole Body) | 80% | Rat | M | IV | $LC_{50}$ = 2.23 mg/L (357 mg/kg) (1)[e] |
| Inhalation $LC_{50}$ (4-Hour, Whole Body) | 80% | Rat | F | IV | $LC_{50}$ = 2.23 mg/L (357 mg/kg) (1)[e] |
| Inhalation $LC_{50}$ (4-Hour, Whole Body) | 43-80% | Rat | Combined | III, IV | $LC_{50}$ > 2.08 to 6.2 mg/L (> 333 to 992 mg/kg) (1) (MMAD: 2.8 to 7.11 µm)[e] |
| Eye Irritation | 41-85% | Rabbit | Combined | II-IV | NA[f] |
| Dermal Irritation | 36-81% | Rabbit | Combined | III, IV | NA[g] |
| Dermal Sensitization | 41-81% | Rabbit | Combined | Six (6) negative and two (2) positive results | NA[h] |

$LC_{50}/LD_{50}$: median lethal concentration/dose

MMAD: mass median aerodynamic particle diameter

NA: Not available.

(1) Equivalent dosages were calculated by using the rat default breathing rate of 0.96 $m^3$/kg/day in the following equations:

Dose (mg/kg/day) = Concentration (mg/L) x (1000 L/$m^3$) x (0.96$m^3$/ kg day) x (4hours/ 24 hours) (1 day exposure)

**References**

a Larson (1961b); Krajewski and Baldwin (1988b); Moore (1998c); Moore (1998d); Mallory (1999b); Mallory (2000b); Parno *et al.* (2000); Durando (2010e)

b Larson (1961a)

c Krajewski and Baldwin (1988a); Moore (1998b); Moore (1998a); Parno *et al.* (2001b); ECB (2006e); Durando (2010b)

d Mallory (1999a); Mallory (2000a)

e Fisher *et al.*(1985); Hagan (1989); Imamura (1989); Imamura *et al.*(1990); Dykstra (1991b); Wnorowski (1998a); Wnorowski (1998b); Bonnette (1999); Wilson (2000); Hilaski (2001); Durando (2010d)

f Krajewski and Baldwin (1988c); Krajewski and Baldwin (1990a); Moore (1998f); Moore, (1998g); Mallory (1999e); Mallory (2000e); Parno *et al.* (2001c); Durando (2010i)

g Krajewski and Baldwin (1988d); Krajewski and Baldwin (1990b); Moore (1998h); Moore (1998i); Mallory (1999d); Mallory (2000d); Parno *et al.* (2001d); Durando (2010k)

h Glaza (1989); Dykstra (1991a); Moore (1998e); Chang *et al.*(1999b); Mallory (1999c); Mallory (2000c); Parno *et al.* (2001a); Durando (2010f).

# D) Subchronic Toxicity

## 1) Summary

The subchronic toxicity database for propanil includes registrant-submitted studies (Table 9). Signs of propanil intoxication in subchronic studies included increased mortality, cyanosis, lethargy, piloerection, lacrimation with ocular discharge, decreased defecation, mucoid feces with red material, decreases in body weight, body weight gain, and food consumption, changes in hematologic parameters, macro and microscopic signs of organ toxicity in the lungs, spleen, kidneys, liver, ovaries, and testes, and changes in

biochemistry and urinalysis parameters. Cyanosis, lethargy, changes in hematology and serum biochemistry, and splenic pathology were consistent with metHb formation and hemolytic anemia.

**2) Subchronic Toxicity in Animals**

***(i) Oral: Rat***

**Study References:** Larson (1961e); Ambrose *et al.* (1972)
**Study Design:** The oral toxicity of propanil (technical grade, 97%) was evaluated in a registrant-submitted study using male and female albino rats (10 per dose group) for a period of 3 months. The dietary levels were 0, 0.010, 0.033, 0.10, 0.33, 1.0, and 5.0% corresponding to (m/f); 0/0, 5/4, 19/15, 54/46, 169/148, 490/491, and 2632/2268 mg/kg/day. Dose levels were not reported but rather were estimated using food intake and body weight data. (Note: Food intakes for 5% dose group were not reported and were based on averages for remaining dose levels by gender.)

**Results:** Complete mortality occurred in the high dose group between weeks 1 and 4. Mortalities also occurred in the 0.01% (1 male on week 6), 0.33% (1 female on week 12), and 1.0% (1 male on week 11) dose groups with no clear dose response for incidence or timing. Spleen weights relative to body weights increased in a dose-related manner in females (+6-146%) at all dose levels with statistical significance reached at ≥ 1.0%. Hematologic effects included dose-dependent decreases in Hb levels in males (-2 to -19%) at all dose levels. Necropsy results indicated that the spleen, kidneys, liver and testes were target organs. The NOEL was 0.033% (19/15 mg/kg/day) based on increased relative spleen weights (f), increased neutrophil counts (f), and decreased Hb levels (m) at 0.1% (54/46 mg/kg/day). Acute effects included dose-responsive decreases in body weight during week 1 in males (up to -56%) and females (up to -56%) at doses ≥ 0.33% (≥169/148 mg/kg/day). The results for the above study were also reported in the open literature. Information included in the open literature report was used to supplement data in the original report when possible.

**Study Reference:** Billington (1992)
**Study Design:** The oral toxicity of propanil (technical grade, 97.2 to 98.3%) was evaluated in a registrant-submitted study using male and female Crl:CD(SD)BR rats (5 per dose group) for a period of 13 weeks. The dietary levels were 0, 300, 1000, 2000, and 4000 ppm corresponding to (m/f): 0/0, 23/28, 76/93, 151/184, and 318/364 mg/kg/day.

**Results:** Changes to hematologic parameters with propanil treatment were observed at all dose levels (≥ 300 ppm) and included decreased Hct levels, decreased Hb levels, decreased RBC counts, and increased metHb levels (m: +2-77%; $p < 0.01$ at ≥ 2000 ppm). Absolute and relative spleen weights were also increased in a dose-dependent manner at all dose levels in females (absolute: +12-54%; $p < 0.05$ or 0.01 at ≥ 2000 ppm; relative: +20-110%). There were clear hematologic and necropsy results that indicated that the kidneys and liver were also adversely impacted in a manner that supported the formation of metHb as an important toxic pathway. The NOEL was 300 ppm (23/28 mg/kg/day) based on treatment-related effects including decreases in average bodyweight and food consumption (m and f) and statistically significant hematologic effects (f) observed at the 1000 ppm (76/93 mg/kg/day) dose level. Acute effects included dose-responsive decreases in body weight gain (m/f: up to -84/91%; $p < 0.01$) that

were observed during week 1 in parallel with increased values for food conversion (m/f: up to +229/780%) at doses ≥ 1000 ppm (76/93 mg/kg/day).

**Study Reference:** O'Neill (2002)
**Study Design:** The oral toxicity of propanil (technical grade, 99.3%) was evaluated in a registrant-submitted study using male and female Crl:CD®(SD)IGS BR rats (10 per dose group) for a period of 30 days. The dietary levels were 0, 300, 500, and 700 ppm, corresponding to (m/f): 0/0, 25/28, 41/41, 57/67 mg/kg/day. Test diet administration was suspended after day 17 and basal diet was administered to all groups for the remainder of the study.

**Results:** Select data are summarized in Table 6. Clinical observations made in the treated groups included the sporadic incidence of localized hair loss and scabs, chromodachyorhea, soft feces, or malaligned incisors. One (1) female died on day 7 of dose administration in the 300 ppm group. Increased metHb levels were observed at all treatment levels by day 1 (m: +50-100%; $p < 0.05$ at 700 ppm; f: +75-125%; $p < 0.01$ at 500 ppm). Significantly ($p < 0.01$) increased metHb levels were observed at all dose levels during days 5 (m/f: +67-200%/+117-450%), 7 (f: +125-400%), 14 (f: +175-538%), 21 (m: +40-120%), and 30 (f: +50-70%). Treatment was stopped on day 17 due to high levels of metHb. The LOEL was 300 ppm (25/28 mg/kg/day) based on increased metHb levels. Acute toxic effects observed during days 1 and 5 included increased levels of metHb.

**Table 6. Propanil-Induced Effects in a 30–day Subchronic Study with CD Rats**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)** | **0** | **300** | **500** | **700** | **0** | **300** | **500** | **700** |
| **Dose (mg/kg/day):** | **0** | **25** | **41** | **57** | **0** | **28** | **41** | **67** |
| **n:** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** |
| **Legend:** | **p < 0.05** | | | | **p < 0.01** | | | |
| **metHb Levels as Percentage (%) of Control and as (% Hb ± SD )** | | | | | | | | |
| **Day 1** | 0.6 ± 0.32% (100%) | 1 ± 0.69% (167%) | 0.9 ± 0.19% (150%) | 1.2 ± 0.28% (200%)[1] | 0.4 ± 0.29% (100%) | 0.7 ± 0.23% (175%) | 1 ± 0.46% (250%) | 0.9 ± 0.39% (225%) |
| **Day 5** | 0.6 ± 0.16% (100%) | 1 ± 0.27% (167%) | 1.4 ± 0.24% (233%) | 1.8 ± 0.27% (300%)[1] | 0.6 ± 0.2% (100%)[1] | 1.3 ± 0.35% (217%) | 2.3 ± 0.4% (383%) | 3.3 ± 0.52% (550%) |
| **Day 7** | 0.9 ± 0.47% (100%) | 1.2 ± 0.19% (133%) | 1.7 ± 0.43% (189%) | 2.2 ± 0.43% (244%)[1] | 0.8 ± 0.24% (100%) | 1.8 ± 0.12% (225%)[1] | 2.6 ± 0.57% (325%) | 4 ± 0.43% (500%) |
| **Day 14** | 0.9 ± 0.35% (100%) | 1.4 ± 0.35% (156%) | 2.1 ± 0.27% (233%) | 3.2 ± 0.76% (356%) | 0.8 ± 0.32% (100%) | 2.2 ± 0.24% (275%)[1] | 3.3 ± 0.36% (413%) | 5.1 ± 0.69% (638%) |
| **Day 21** | 1 ± 0.27% (100%) | 1.4 ± 0.36% (140%) | 1.7 ± 0.26% (170%) | 2.2 ± 0.22% (220%) | 1.2 ± 0.42% (100%) | 1.9 ± 0.18% (158%)[2] | 2.5 ± 0.34% (208%) | 3.1 ± 1.24% (258%) |
| **Day 30** | 0.8 ± 0.3% (100%) | 1.1 ± 0.67% (138%) | 1.2 ± 0.14% (150%) | 1.5 ± 0.13% (188%) | 1 ± 0.2% (100%) | 1.5 ± 0.24% (150%)[1] | 1.7 ± 0.23% (170%) | 1.5 ± 0.37% (150%) |

O'Neill (2002)
*Statistical analyses were performed using one way ANOVA and Dunnett's tests.*
*Legend*
[1] *n = 9*
[2] *n = 8*

### *(ii) Oral: Mouse*

**Study Reference:** McLaughlin (1983)
**Study Design:** The oral toxicity of propanil (STAM, 98%) was evaluated in a registrant-submitted study using male and female COBS-CD1 mice (10 per dose group) for a period of 3 months. The dietary levels were 0, 25, 200, 1600, 12800 ppm corresponding to (m/f): 0/0, 7/10, 49/78, 442/566, 5325/6467 mg/kg/day.

**Results:** Absolute and relative liver and spleen weights were increased at all dose levels (≥ 25 ppm) in females (liver (abs/rel): +7-20%/+5-38% (rel: $p < 0.01$ at ≥ 1600 ppm); spleen (abs/rel): +8-120% ($p < 0.01$ at ≥ 1600 ppm)/+9-154% ($p < 0.01$ at ≥ 1600 ppm)). Signs of liver toxicity included increased incidences of hepatocytic pleomorphism (m/f: ≥ 25/1600 ppm), pigmented Kupffer cells (m/f: ≥ 1600/≥12800 ppm), and total mixed function oxidase activity (m/f: ≥ 200/≥ 25 ppm). Furthermore, absolute and relative weights for the ovaries were decreased in females at the top dose level (12800 ppm) (abs/rel: -18-58% ($p < 0.01$)/-1-40% ($p < 0.05$)). DPR considers the signs of liver and spleen toxicity to be consistent with propanil's impact on primary reservoir organs subsequent to the hydrolysis of propanil and the 3,4-DCA mediated formation of metHb. The decreased ovary weights suggest propanil-induced follicular atresia. There were clear clinical signs and hematologic and necropsy results that indicated that implicated the spleen, kidneys, liver, ovaries, and testes as sites of toxicity and the formation of metHb as an important toxic pathway. The NOEL was 200 ppm (49/78 mg/kg/day) based on effects that include statistically significant increases to liver and spleen weights and incidences of liver lesions in the 1600 ppm (442/566 mg/kg/day) dose groups of both sexes.

**Study Reference:** Didonato and Cruszan (1979)
**Study Design:** The oral toxicity of propanil (STAM, 98%) was evaluated in a registrant-submitted study using male and female COBS-CD1 mice (5 per dose group) for a period of 2 weeks. The dietary levels were 0, 250, 1250, 6250, 31250 ppm, corresponding to (m/f): 0/0, 111/115, 571/589, 2949/2769, 15899/18799 mg/kg/day.

**Results:** Two mortalities (m/f: 1 on day 6/1 on day 11) occurred at the high dose level (31250 ppm). Food consumption was significantly increased in the males at 250 ppm (+20%; $p < 0.05$). Gross necropsy observations in treated groups included ovarian cyst(s) (f: 250 ppm), dark lungs (m: 31250 ppm), dark liver (m: 31250 ppm), blackish blood (m: 31250 ppm), blue skin (m: 31250 ppm), and thin uterine horns (f: 31250 ppm). A NOEL was not established. Acute effects observed during week 1 included significantly decreased bodyweights (m/f: -39/-30%; $p < 0.01$) at 31250 ppm (15899/18799 mg/kg/day) and decreased food consumption (f: up to -24%) at ≥ 1250 ppm (≥ 571/589 mg/kg/day).

**Study Reference:** Tompkins (1993b)
**Study Design:** The oral toxicity of propanil (technical grade, purity not reported) was evaluated in a registrant-submitted study using male and female COBS-CD1 mice (10 per dose group) for a period of 13 weeks. The dietary levels were 0, 400, 650, 900, 1150 ppm, corresponding to (m/f): 0/0, 71/98, 120/155, 166/238, 200/266 mg/kg/day.

**Results:** Select data are summarized in Table 7**.** MetHb levels were increased for both sexes in all treatment groups (≥ 400 ppm) (m/f: +1600-5333%/+1150-4500%; $p < 0.01$ at ≥ 650 ppm) while Hb and Hct levels were decreased in males. Signs of splenic toxicity at all dose levels (≥ 400 ppm) included increased absolute and relative organ weights (abs (m/f): +15-70%/+7-14%; rel (m/f): +15-69%/+4-16%) and increased incidences of splenic hemosiderin ($p < 0.05$ or 0.01 at ≥ 900 ppm). The LOEL was 400 ppm (71 mg/kg/day) based on treatment-related increases in metHb levels.

**Table 7. Propanil-Induced Effects in a 13-Week Subchronic with COBS-CD1 mice**

| Sex | Male | Male | Male | Male | Male | Female | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)** | **0** | **400** | **650** | **900** | **1150** | **0** | **400** | **650** | **900** | **1150** |
| **Dose (mg/kg/day):** | **0** | **71** | **120** | **166** | **200** | **0** | **98** | **155** | **238** | **266** |
| **n (hematology; metHb):** | **6** | **4** | **6** | **4** | **6** | **4** | **6** | **4** | **6** | **4** |
| **n (pathology):** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** |
| **Legend:** | **p < 0.05** | | | | | **p < 0.01** | | | | |
| **Hb Levels as Percentage (%) of Control and as g/dL ± SD** | | | | | | | | | | |
| **Week 13** | 14.6 ± 0.38 g/dL (100%) | 14.1 ± 0.38 g/dL (97%) | 13.8 ± 0.23 g/dL (95%) | 14 ± 0.76 g/dL (96%) | 13.7 ± 0.34 g/dL (94%) | 13.9 ± 0.52 g/dL (100%) | 14.6 ± 0.82 g/dL (105%) | 14.1 ± 0.59 g/dL (101%) | 14 ± 0.5 g/dL (101%) | 13.7 ± 0.41 g/dL (99%) |
| **Hct Levels as Percentage (%) of Control and as % ± SD** | | | | | | | | | | |
| **Week 13** | 50.2 ± 3.51% (100%) | 47.1 ± 1.57% (94%) | 46.5 ± 1.52% (93%) | 48.3 ± 3.51% (96%) | 44.5 ± 1.8% (89%) | 46.5 ± 3.19% (100%) | 51 ± 6.14% (110%) | 47.4 ± 0.79% (102%) | 46.5 ± 3.71% (100%) | 46.6 ± 3.55% (100%) |
| **metHb Levels as Percentage (%) of Control and as % ± SD[2]** | | | | | | | | | | |
| **Week 13** | 0.3 ± 0.39% (100%) | 5.1 ± 1.77% (1700%) | 10.8 ± 3.22% (3600%) | 11 ± 3.05% (3667%) | 16.3 ± 3.71% (5433%) | 0.2 ± 0.3% (100%) | 2.5 ± 1.29% (1250%) | 5.6 ± 1.73% (2800%) | 6.6 ± 1.3% (3300%) | 9.2 ± 4.35% (4600%) |
| **Abs Spleen Wt. as Percentage (%) of Control and as g** | | | | | | | | | | |
| **Week 13** | 0.074 ± 0.013 g (100%) | 0.085 ± 0.013 g (115%) | 0.099 ± 0.016 g (134%) | 0.126 ± 0.039 g (170%) | 0.123 ± 0.019 g (166%) | 0.11 ± 0.027 g (100%) | 0.118 ± 0.053 g (107%) | 0.122 ± 0.013 g (111%) | 0.125 ± 0.032 g (114%) | 0.139 ± 0.032 g (126%) |
| **Rel Spleen Wt. as Percentage (%) of Control and as %** | | | | | | | | | | |
| **Week 13** | 0.212 ± 0.038% (100%) | 0.243 ± 0.034% (115%) | 0.287 ± 0.039% (135%) | 0.358 ± 0.105% (169%) | 0.359 ± 0.053% (169%) | 0.387 ± 0.100% (100%) | 0.404 ± 0.176% (104%) | 0.421 ± 0.045% (109%) | 0.447 ± 0.090% (116%) | 0.483 ± 0.085% (125%) |
| **Spleen: Hemosiderin (incidences/total)[1]** | | | | | | | | | | |
| **Week 13** | 0/10 | 3/10 | 1/10 | 7/10 | 10/10*** | 4/10 | 6/10 | 7/10 | 9/10 | 10/10 |

Tompkins (1993b)

[1] Statistical analysis performed by DPR using STATOX: Fisher's Exact Test (*** $p < 0.001$)

[2] Statistical analysis performed by DPR using GraphPad Prism 7.00: 1-way ANOVA with Dunnett's post-test

### *(iii) Oral: Dog*

**Study References:** Larson (1961c); Ambrose *et al.* (1972)

**Study Design:** The oral toxicity of propanil (technical grade, 97%) was evaluated in a registrant-submitted study using male and female mongrel dogs (2 per group) for a period of 4 weeks. The dietary levels were 0, 0.2, 1, 5%, corresponding to (m/f): 0/0, 40/38, 72/65, 274/154 mg/kg/day. Dose levels were not reported but rather were instead estimated using reported dietary levels and food consumption data.

**Results:** Clinical signs in treated groups were not reported. Although dose-related decreases vs. controls were reported for the average body weight and body weight gain data during the dosing phase, in treated vs. control animals, the decreases were also observed during the pre-dose phase. Reduced food intake resulting from reduced food palatability is more likely to be the cause of the body weight gain reductions than overt systemic toxicity. There was insufficient information in the report with which to derive a reliable NOEL or LOEL. The results for the above study were also reported in the open literature. Information included in the open literature report was used to supplement data in the original report when possible.

**Study Reference:** Tompkins (1993a)
**Study Design:** The oral toxicity of propanil (technical grade, 97.2 to 98.3%) was evaluated in a registrant-submitted study using male and female outbred beagle dogs (2 per dose group) for a period of 8 weeks. The dietary levels were 0, 1600, 2800, 4000 ppm, corresponding to (m/f): 0/0, 57/44, 93/99, 114/81 mg/kg/day.

**Results:** Select data are summarized in Table 8**.** Propanil treatment resulted in changes to hematologic parameters at all dose levels (≥ 1600 ppm) including increased WBC counts, decreased RBC counts, increased reticulocyte counts, and increased metHb levels (week 4 (m/f): +194-259%; $p < 0.05$ or 0.01 at ≥ 1600 ppm /+333-442%; $p < 0.05$ or 0.01 at ≥ 1600 ppm; week 7 (m/f): +483-733% $p < 0.01$ at ≥ 1600 ppm /+1450-1600%). Splenic toxicity at all dose levels (≥ 1600 ppm) was indicated by increased organ weights (abs (f): +92-138%; rel (f): +72-192%). The above changes were consistent with the propanil-mediated formation of metHb and the subsequent onset of hemolytic anemia. Signs of liver toxicity at all dose levels (≥ 1600 ppm) included increased organ weights (abs (m/f): +20-29%/+6-23%; rel (m/f): +17-45%/19-62%) as well as increased circulating levels of bilirubin, cholesterol, and alkaline phosphatase (AP). Signs of kidney toxicity included increased levels of urea nitrogen and creatinine. Myeloid series hypercellularity was found in the bone marrow of all females in at dose levels ≥ 2800 ppm suggesting a possible pre-leukemic state to DPR The LOEL was 1600 ppm (57/44 mg/kg/day) for treatment-related increases in hematologic signs of methemoglobinemia (white, red and reticulocyte cell counts and metHb levels) and signs of spleen and liver toxicity (organ weight, metHb and white blood cell levels).

**Table 8. Propanil-Induced Effects in an 8-week Subchronic Study with Outbred Beagle Dogs**

| **Sex** | **Male** | **Male** | **Male** | **Male** | **Female** | **Female** | **Female** | **Female** |
|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)** | **0** | **1600** | **2800** | **4000** | **0** | **1600** | **2800** | **4000** |
| **Dose (mg/kg/day):** | **0** | **57** | **93** | **114** | **0** | **44** | **91** | **81** |
| **n:** | **2** | **2** | **2** | **2** | **2** | **2** | **2** | **2** |
| **Legend:** | **p < 0.05** | | | | **p < 0.01** | | | |
| **metHb Levels as Percentage (%) of Control and as (% Hb ± SD )** | | | | | | | | |
| **Week 7** | 0.6 ± 0.14% (100%) | 3.5 ± 0.14% (583%) | 4.9 ± 0.64% (817%) | 5.0 ± 0.92% (833%) | 0.4 ± 0.14% (100%) | 6.2 ± 3.61% (1550%) | 6.8 ± 1.27% (1700%) | 6.2 ± 0.71% (1550%) |

Tompkins (1993a)
*Statistical analyses were performed using one way ANOVA and Dunnett's tests.*

**Study Reference:** Tompkins (1992)
**Study Design:** The oral toxicity of propanil (technical grade, 97.2 to 98.3%) was evaluated in a registrant-submitted study using male and female outbred beagle dogs (2 per dose group) for a period of

13 weeks. The dietary levels were 0, 1000, 5000, 10,000, and 20,000 ppm corresponding to: 0, 45, 225, 450, 900 mg/kg/day. Test article was administered in food for one week (week 0) followed by a rest during weeks 1 and 2 because of significantly reduced food intake in 5000 and 10,000 ppm treatment groups. Beginning at week 3, test article was administered in capsule form. The study was terminated at week eight because of excessive mortality.

**Results:** Complete mortality occurred at 450 and 900 mg/kg/day dose by week 4 and at 225 mg/kg/day by week 5. Clinical signs in treated groups included the following: decreased defecation, deceased urination, mucoid feces, mucoid feces with red material, salivation, emesis of food, yellowish skin/scleragums, hypoactivity, ataxia, decreased muscle tone, prostration, dehydration, and white frothy emesis. Decreases in body weight and body weight gain were observed in males and females at all dose levels. Propanil treatment resulted in changes to hematologic parameters during weeks 3 and 8 at all dose levels (≥ 1000 ppm) that included decreased red cell counts (m: -6-37%), decreased Hb levels (m: -11-32%), and decreased Hct levels (m: -1-27%). These changes were consistent with the propanil-mediated formation of metHb and the subsequent onset of hemolytic anemia. Signs of liver toxicity at all dose levels (≥ 1000 ppm) included increased AP levels (m/f: +5-457%/+35-764%) and increased total bilirubin levels (m: +100-17,900%). Evidence for kidney toxicity included elevated blood urea nitrogen levels (f: +18-100%). The LOEL was 1000 ppm (45 mg/kg/day) based on decreases in body weight and body weight gain and changes to hemotologic and serum biochemistry parameters.

***(iv) Dermal: Rabbit***

**Study Reference**: Margalitch and Ackerman (1990 )
**Study Design:** The dermal toxicity of propanil (technical grade, purity not reported) was evaluated in a registrant-submitted study using male and female New Zealand white rabbits (5 per dose group) for a period of 21 days. The treatment levels were 0, 250, 500, 1000 mg/kg/day applied to shaved, intact skin 6 hours per days/5 days per week.

**Results:** Mortalities occurred in the 250 mg/kg/day (1 female on day 14), 500 mg/kg/day (1 male on day 19), and 1000 mg/kg/day (1 female on day 14) dose groups. The following clinical observations were made in the 250 mg/kg/day group: abnormal gait and abnormal stance, decreased activity, flaccid body tone, and diarrhea in one female on day 12. Dose-related, non-significant decreases in average body weight gain and food consumption data were reported for all female treatment groups on day 20. Although gross necropsy findings indicated possible organ sites of toxicity that included the liver, testes, and stomach there was a notable absence of a consistent dose response in either gender. No compound related effects were reported for histopathology, relative/absolute organ weights, clinical chemistry, or hemotologic parameters. Protozoan infections were found to be responsible for liver hyperplasia, kidney nephritis, meningioencephalitis, and pericholangitis confounding the assignment of any of the above effects to propanil treatment. A NOEL was found to be 1000 mg/kg/day as no treatment-related effects were evident.

***(v) Dermal Irritation: Rabbit***

**Study Reference:** Larson (1961d)

**Study Design:** The dermal toxicity of propanil (Stam F-34, purity not reported) was evaluated in adult male rabbits (6) for a period of 14 days. The treatment consisted of a 1:9 dilution applied to shaved skin around the trunk.

**Results:** Slight scaling was observed on the ventral surface of 4 animals by day 7 that persisted for up to 3 days post-treatment.

**Table 9. Summary of Subchronic Studies for Propanil**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | 3-Month Feeding (10/sex/dose) (0, 0.01, 0.033, 0.1, 0.33, 1, and 5 ppm or (m/f) 0/0, 5/4, 19/15, 54/46, 169/148, 460/491 and 2632/2268 mg/kg/day) | (m/f) = 19/15 mg/kg/day | (m/f) = 54/46 mg/kg/day | ↑ relative spleen weight (f), ↑ neutrophil counts (f), and ↓ Hb levels (m) | Larson, (1961e); Ambrose *et al.* (1972) |
| Rat | 13-Week Feeding (5/sex/dose) (0, 300, 1000, 2000, and 4000 ppm or (m/f) 0/0, 23/28, 76/93, 151/184, and 318/364 mg/kg/day) | (m/f) = 23/28 mg/kg/day | (m/f) = 76/93 mg/kg/day | ↓ body weight (m and f), ↓ food consumption (m and f), and changes to hematologic parameters including Hct, Hb levels, and RBC counts (f) | Billington (1992) |
| Rat | 30-Day Feeding; 17-day treatment (10/sex/dose) (0, 300, 500, 700 ppm or (m/f) 0/0, 25/28, 41/41, and 57/67 mg/kg/day) | (m/f) < 25/28 mg/kg/day | (m/f) = 25/28 mg/kg/day | ↑ metHb levels (m and f) | O'Neill (2002) |
| Mouse | 3-Month Feeding (10/sex/dose) (0, 25, 200, 1600, and 12800 ppm or (m/f) 0/0, 7/10, 49/78, 442/566, and 5325/6467 mg/kg/day) | (m/f) = 49/78 mg/kg/day | (m/f) = 442/566 mg/kg/day | ↑ liver and spleen weights and ↑ incidence of liver lesions (m and f) | McLaughlin (1983) |
| Mouse | 13-Week Feeding (10/sex/dose) (0, 400, 650, 900, and 1150 ppm or (m/f): 0/0, 71/98, 120/155, 166/238, and 200/266 mg/kg/day) | (m/f) < 71/98 | (m/f) = 71/98 | ↑ metHb levels (m and f) | Tompkins (1993b) |
| Dog | 8-Week Feeding (2/sex/dose) (0, 1600, 2800, and 4000 ppm or (m/f) 0/0, 57/44, 93/99, and 114/81 mg/kg/day) | (m/f) < 57/44 | (m/f) = 57/44 | ↑ signs of methemoglobinemia and signs of spleen and liver toxicity | Tompkins (1993a) |

**Table 9. Summary of Subchronic Studies for Propanil**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Dog | 13-Week Feeding (2/sex/dose) (0, 1000, 5000, 10,000, and 20,000 or 0, 45, 225, 450, and 900 mg/kg/day | (m/f) < 45 mg/kg/day | (m/f) = 45 mg/kg/day | ↓ body weight and body weight gain (m and f), and changes to hematology (m) and serum biochemistry (m and f) | Tompkins (1992) |
| Rabbit | 21-Day Dermal (5/sex/dose) (0, 250, 500, and 1000 mg/kg/day) | (m/f) = 1000 mg/kg/day | (m/f) >1000 mg/kg/day | No effects observed at any dose | Dykstra and Gardner (1991) |

## E) Reproductive Toxicity

### 1) Summary

The reproductive toxicity database for propanil includes registrant-submitted studies (Table 11). In studies of the reproductive toxicity of propanil in rats, parental toxicity was characterized by decreased body weight and body weight gain and signs of toxicity to the spleen (e.g., increased weight and hemosiderin deposition). The effects of propanil on reproduction were characterized by decreased sperm and primordial follicle counts. Weanling pups treated with propanil had reduced body weight, increased testes and liver weights and delays for the completion of balanopreputial separation and vaginal perforation.

### 2) Oral: Two-Generation Rat Reproduction

**Study Reference:** Stump (1998)
**Study Design:** The effects of propanil (technical grade, 98%) on reproduction and development were tested in a registrant-submitted dietary, 2-generation, 2-litter study using Sprague-Dawley Crl:CD®BR rats (30 rats/sex/dose in the $F_0$ generation). The control groups (0 ppm) received basal diet while the test groups received dietary doses of 60, 150, and 600 ppm corresponding to (m/f): 0, 4/5, 11/13, 43/51 mg/kg/day. The dose levels were based on the results for a range-finding study. The $F_0$ generation was treated prior to mating (weeks 0-10), during the mating period (weeks 10-12) and during a post-mating interval (weeks 12-19) until euthanasia, necropsy, spermatogenesis evaluation (males), histopathological examination (0 and 600 ppm only), and hormone analysis (males at 0 and 600 ppm only). $F_1$ pups were weaned on post-natal day (PND) 21. Following weaning on PND 21, one (1) $F_1$ pup/litter/dose was randomly selected for complete necropsy, organ weight collection and histopathological examination (0 and 600 ppm only), 30 $F_1$ pups/litter/dose were randomly selected as the F1 generation, and all remaining $F_1$ pups were euthanized and necropsied. Developmental landmark evaluations were performed on $F_1$ generation pups during study weeks 18-21. The $F_1$ generation was treated following weaning and prior to mating (weeks 16-29), during the mating period (weeks 29-31) and during a post mating interval (weeks 31-39) until euthanasia (see $F_0$ for necropsy examinations). $F_2$ pups were weaned on PND 21, euthanized, and necropsied (weeks 35-37).

**Results**

Select data are summarized in Table 10.

*Parental Toxicity*

One $F_0$ male from the control group was euthanized in extremis on week 5 and two $F_1$ female mortalities occurred at 150 and 600 ppm during weeks 17 and 18. The latter mortalities were not be attributed to propanil treatment because they were not preceded by obvious clinical signs and because no deaths occurred in any treated groups in the $F_0$ generation or at dose levels up to 1800 ppm in a dose ranging study. Significant ($p < 0.05$ or 0.1) reductions in body weight were observed at 600 ppm in $F_0$ males (weeks 4, 7, 8, 15-18: -5 to -7%), $F_0$ females (weeks 2-10, 18, 19: -5 to -9%; Gestation Days 0-20: -7 to -8%; Lactation Days 1-21: -4 to -10%), $F_1$ males (weeks 18-39: -8 to -14%), and $F_1$ females (weeks 19-29 and 38: -6 to -12%; Gestation Days 0-20: -9 to -13%; Lactation Days 1-21: -8 to -12%). Significant body weight reductions were also observed at 150 ppm during gestation in $F_1$ females (Gestation Days 0-11: -5 to -8%, $p < 0.05$ or 0.01) but the authors did not consider these treatment related effects because they did not persist through gestation. Significantly ($p < 0.05$ or 0.01) decreased body weight gains were observed at all dose levels in $F_0$ and $F_1$ males and $F_0$ females and at 60 and 600 ppm in $F_1$ females while food consumption was significantly ($p < 0.05$ and 0.01) decreased in $F_0$ females (600 ppm), $F_1$ males (600 ppm), and $F_1$ females ($\geq$ 150 ppm). The study authors considered the decreases in body weight gains and food consumption at the low and mid doses to be "transient or isolated" and not adverse effects of propanil treatment.

A pattern of treatment-related splenic toxicity in the $F_0$ and $F_1$ generations included significantly ($p < 0.05$ or 0.01) increased absolute ($F_0$ (f): +24%; $F_1$ (f): +31%) and brain ($F_0$ (f): +24%; $F_1$ (f): +30%) or body weight-adjusted ($F_0$ (m/f): +10/+34%; $F_1$ (m/f): +13/+50%) spleen weights and significantly ($p < 0.05$) increased incidences of macrophages pigmented with hemosiderin (oxidized Hb) in the high dose groups. Statistical significance ($p < 0.05$) for incidences of splenic pigmented macrophages was also reached by $F_0$ males at 60 ppm and $F_0$ females and $F_1$ males and females at 150 ppm. The incidences at the low and mid doses were not considered toxicologically relevant because they were similar in severity to the incidences in the concurrent control groups. On the other hand, the incidences with the highest severity were overwhelmingly in the high dose groups and coincident with increased spleen weight. The above splenic effects were consistent with the formation of excess metHb.

Significantly ($p < 0.05$ or 0.01) increased absolute, body or brain-adjusted organ weights in $F_0$ or $F_1$ generation animals at the high dose level included those for the liver, kidneys, ovaries, testes, adrenals, brain, prostate, pituitary, seminal vesicle and coagulating gland, and the left epididymis.

Reduced epididymal ($F_0$: -22%; $p < 0.01$) and testicular sperm numbers ($F_1$: -9%; $p < 0.05$) and sperm production rates ($F_0/F_1$: -5/-18%; NS) were observed in $F_0$ and $F_1$ males at the high dose. The counts of primordial follicles (-15%; NS) and corpora lutea (-12.6%; NS) were also reduced in $F_1$ females at 600 ppm. There were no significant changes in the circulating levels of estradiol ($E_2$), testosterone (T), and luteinizing hormone (LH) at 600 ppm.

*Pup Toxicity*

Significant reductions in body weight were observed at 600 ppm in $F_1$ pre-weanlings (PND 7 and 21: -6%, $p < 0.05$) and $F_2$ pre-weanlings (PND 1-21: -7 to -10%, $p < 0.05$ or 0.01).

Significantly ($p < 0.05$ or 0.01) increased body or brain-adjusted organ weights in $F_1$ generation pups at the high dose level included those for the liver, testes, and adrenals.

Male and female pups treated with propanil developed more slowly in key areas compared to controls. The time for the group completion of vaginal perforation, a landmark for female puberty, was delayed by 4 days at 150 ppm and 7 days at 600 ppm while the timing for the group completion of balanopreputial separation, a landmark for male puberty, by all pups in a treatment group was for delayed by 3 days at 60 and 150 ppm and 8 days at 600 ppm. Furthermore, there was a statistically significant ($p < 0.01$) delay for the average day of balanopreputial separation in males at the high dose level: 45.9 days vs. 42.9 days for concurrent controls.

The NOEL for parental toxicity was 150 ppm (11mg/kg/day) based on decreased body weights, organ weight changes to the spleen, brain, ovaries, adrenals, pituitary gland, liver, kidneys, testes, epididymis, and seminal vesicle /coagulating gland, and an increased incidence and severity of spleen pigmentation by macrophages with hemosiderin deposits at the LOEL of 600 ppm (43 mg/kg/day). The NOEL for reproductive toxicity was also 150 ppm (11mg/kg/day) based on decreased sperm counts at the LOEL of 600 ppm (43 mg/kg/day). The NOEL for pup toxicity was 150 ppm (11 mg/kg/day), based on increased testes and liver weights and the delayed completion of balanopreputial separation at the LOEL of 600 ppm (43 mg/kg/day).

**Table 10. Propanil-Induced Effects in a 2-Generation Reproductive Toxicity Study with Sprague-Dawley Crl:CD®BR rats**

| **Sex** | **$F_1$ Male** | | | |
|---|---|---|---|---|
| **Legend** | **$p < 0.05$** | | **$p < 0.01$** | |
| **Dose (ppm):** | **0** | **60** | **150** | **600** |
| **Dose (mg/kg/day)** | **0** | **4** | **11** | **43** |
| | **Balanopreputial Separation (n = 30)** | | | |
| **Day of Group completion** | 45 | 48 | 48 | 53 |
| **Average Day of Completion (± SD)** | 42.9 ± 1.35 | 43.3 ± 2.05 | 43.9 ± 1.99 | 45.9 ± 2.38 |

Stump (1998)
*Statistical analyses were performed using one way ANOVA and Dunnett's tests.*

### 3) Oral: Three-Generation Rat Reproduction

**Study References:** Borzelleca *et al.* (1966); Ambrose *et al.* (1972)
**Study Design:** The effects of propanil (Stam F-34, 97% AI) on reproduction and development were tested in a registrant-submitted, dietary, 3-generation, 6-litter study using albino, Wistar rats (20 rats/sex/dose in parental $F_0$ generation). The control groups (0 ppm) received basal diet while the test

groups received dietary levels of 100, 300, and 1000 ppm that corresponded to approximately 0, 5, 15, 50 mg/kg/day. The $F_0$ generation was treated prior to mating (11 weeks) and during the first mating period (3 weeks). Litters with more than 10 pups were reduced to this number on PND 5. All $F_{1a}$ rats were sacrificed and necropsied following weaning. $F_0$ rats were re-mated (3 weeks), sacrificed, and necropsied at the time of weaning for $F_{1b}$ pups. $F_{1b}$ pups (25 rats/sex/dose) were raised on parental diets until PND 105, mated twice in the same manner as the $F_0$ generation to produce $F_{2a}$ and $F_{2b}$ litters, sacrificed and necropsied. $F_{2b}$ rats were continued in the same manner as $F_{1b}$ rats to produce $F_{3a}$ and $F_{3b}$ litters. Histopathological examinations were performed on 10 male and female $F_{3b}$ rats.

**Results**

No adverse effects were identified at any dose and a maximum tolerated dose (MTD) was not achieved. The NOEL for parental, reproductive, and pup toxicities was 1000 ppm (50 mg/kg/day).

**Table 11. Summary of Reproductive Toxicity Studies for Propanil**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | 2-Generation Reproduction; dietary exposure (30/sex/dose) (0, 60, 150, and 600 ppm or (m/f) 0/0, 4/5, 11/13, and 43/51 mg/kg/day) | Parental Systemic, Reproductive, and Pup (m/f) = 11/13 mg/kg/day | Parental Systemic, Reproductive, and Pup (m/f) = 43/51 mg/kg/day | *Parental Systemic LOEL* ↓ body weight (m and f), ↑ absolute and/or relative (to body or brain) spleen (m and f), kidneys (m), testes (m), adrenal gland (m and f), ovaries (f), brain (m and f), epididymis (m), and seminal vesicle/coagulating gland (m) weights, and an ↑ incidence and severity of splenic hemosiderosis (m and f). *Reproductive LOEL* ↓ sperm counts (m). *Pup LOEL* ↑ testes and liver weights and the delay of balanopreputial separation (m). | Stump (1998) |
| Rat | 3-Generation Reproduction; Dietary exposure (20/sex/dose) (0, 100, 300, and 1000 ppm or 0, 5, 15, 50 mg/kg/day) | Parental Systemic, Reproductive, and Pup = 50 mg/kg/day | Parental Systemic, Reproductive, and Pup > 50 mg/kg/day | Parental Systemic, Reproductive, and Pup LOELs were not determined. | Borzelleca *et al.* (1966) |

## F) Developmental Toxicity

### 1) Summary

The developmental toxicity database for propanil includes registrant-submitted studies (Table 13). The developmental toxicity of propanil was evaluated in rats and rabbits. No developmental effects were attributed to treatment with propanil in either rats or rabbits.

#### *(i) Oral: Rat*

**Study References:** Gallo (1980); Ruckert (1999)
**Study Design:** The effects of propanil (Stam Technical, 85% AI) on development were tested in a registrant-submitted study using female, albino, BLU:SD rats (25 dams/dose). The control and test groups received 0, 0.8, 4, 20, and 100 mg/kg propanil in corn oil (10 mL/kg) by gavage on gestation days 6 to 15, the time period for major organogenesis. Sexually mature (approximately 13 weeks of age and with an average weight of 250 g) females were mated offsite, 3:1 with sexually mature males until 125 pregnant dams were produced and delivered to the laboratory site. Gestation Day 0 (GD 0) was determined by the presence of a vaginal sperm plug following each mating period. Dams were housed individually and group assignment was randomized. All dams were sacrificed on GD 20 and the fetuses were delivered by caesarian section. Endpoints included clinical observation of dams, necropsy evaluations of numbers of corpora lutea, implantation sites, early/late resorption sites, live/dead fetuses, body weight of live fetuses, sex of fetuses, and soft tissue and/or skeletal abnormalities.

**Results:** The NOEL for maternal and developmental toxicities was 100 mg/kg/day. No effects were attributed to any dose of propanil for either dams or fetuses.

***(ii) Oral: Rabbit***

**Study References:** Florek (1980); O'Neill (1993)
**Study Design:** The effects of propanil (Stam Technical, 85% AI) on development were tested in a registrant-submitted study using New Zealand White Rabbits (20 does/dose). The control and test groups received 0, 4, 20, and 100 mg/kg propanil in corn oil (1 mL/kg) by gavage on GD 6 to 18, the time period for major organogenesis. Sexually mature (approximately 189 to 204 days of age and with an average weight of 2.76 to 5.83 kg) females were mated onsite, 1:1 with sexually mature and proven males on 4 consecutive days. Insemination was considered GD 0. Does were housed individually and group assignment was randomized. All does were sacrificed on GD 30 and their fetuses were delivered by caesarian section. Endpoints included clinical observation of dams, necropsy evaluations of numbers of corpora lutea, implantation sites, early/late resorption sites, live/dead fetuses, body weight of live fetuses, sex of fetuses, and soft tissue and/or skeletal abnormalities.

**Results:** Representative data are summarized in Table 12. Five pregnant does in the 100 mg/kg/day were found dead on study days 13-20. Clinical signs and necropsy findings reported for the mortalities included loss of righting reflex, decreased motor activity, diarrhea, lacrimation, blood in cage pan, parovarian cyst near right oviduct, and resorption of all implantations. A significant reduction in average body weight vs. controls was observed between gestation days 6 to 12 at the high dose (100 mg/kg/day; $p \leq 0.01$). Acute treatment-related effects included the aforementioned reduction in average body weight and increased incidences of mortality and blood in the cage pan observed between GD 7 and 16. The NOEL for maternal toxicity was 20 mg/kg/day based on increased mortality and decreased body weight observed at the LOEL (100 mg/kg/day). The developmental NOEL was 100 mg/kg/day.

**Table 12. Propanil-Induced Effects in a Developmental Study with New Zealand White Rabbits**

| Sex | Does | Does | Does | Does |
|---|---|---|---|---|
| **Dose (mg/kg/day):** | **0** | **4** | **20** | **100** |
| **n:** | **20** | **20** | **20** | **20** |
| **Legend:** | **p < 0.05** | **p < 0.01** | | |
| **Maternal Body Weight as Percentage of Control (%) and as (kg)** | | | | |
| **GD 6** | 4.73 ± 0.60 kg (100%) | 4.78 ± 0.54 kg (101%) | 4.65 ± 0.40 kg (98%) | 4.61 ± 0.46 kg (97%) |
| **GD 12** | 4.72 ± 0.58 kg (100%) | 4.80 ± 0.54 kg (102%) | 4.65 ± 0.36 kg (99%) | 4.42 ± 0.42 kg (94%) |
| **Maternal Body Weight Gain (g)** | | | | |
| **GD 6-12** | -0.01 kg | 0.02 kg | 0.00 kg | -0.19 kg |

Florek (1980); O'Neill (1993)
*Statistical analyses were performed using Bartlett's test of homogeneity of variances, analysis of covariance, and one way ANOVA.*

**Table 13. Summary of Developmental Toxicity Studies for Propanil**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Developmental Toxicity; Oral Gavage; 10 doses (25 dams/dose) (0, 0.8, 4, 20, and 100 mg/kg/day) | Maternal and Developmental = 100 mg/kg/day | Maternal and Developmental > 100 mg/kg/day | No effects observed at any dose for either dams or fetuses | Gallo (1980); Ruckert, (1999) |
| Rabbit | Developmental Toxicity; Oral Gavage; 13 doses (20 does/dose) (0, 4, 20, and 100 mg/kg) | Maternal = 20 mg/kg/day Developmental = 100 mg/kg/day | Maternal = 100 mg/kg/day Developmental > 100 mg/kg/day | *Maternal LOEL* ↑ mortality and ↓ body weight change. | Florek (1980); O'Neill, (1993) |

## G) Genotoxicity

### 1) Summary

The genotoxicity database for propanil includes registrant-submitted studies and studies reported in the open literature (Table 14). Under the conditions of the tests conducted and in the test systems used, propanil was not a mutagen or a clastogen with the exception of positive results obtained for a cytotoxicity assay using Escherichia coli (W3110 and p3478), Bacillus subtilis (H17 and M45), and a Drosophila wing spot assay. On the other hand, 3,4-DCA (see Toxicity of Propanil Metabolites and Contaminants) was shown to be capable of genotoxic effects including chromosomal aberrations (CA), sister-chromatid exchanges (SCE), mitotic spindle disruptions, and aneuploidy under assay conditions although the mechanistic details for the above effects have not been described. Taken together, there is limited evidence that propanil may have genotoxic activity most likely mediated by one or more of its metabolites by way of an unknown pathway.

#### *(i) In Vitro Mutagenicity*

**Study Reference:** Simmon (1979)
The mutagenicity of propanil with and without metabolic activation (± MA) was tested in a series of *in vitro* assays described below. The results for reverse mutation assays using Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) or Escherichia coli (WP2) were negative at all dose levels tested (88% AI; 10, 50, 100, 250, 500, 1000, and 5000 or 1, 10, 50, 100, 500, and 1000 µg/plate, respectively). Negative results were also obtained for a mitotic recombination assay using Saccharomyces cerevisiae (D3) (0.01 to 5% w/v) and a test for unscheduled DNA synthesis (UDS) using human fibroblasts (WI-38) (0.1 to 1000 µg/plate). Propanil was cytotoxic to Salmonella typhimurium strains at ≥ 1000 µg/plate and Saccharomyces cerevisiae (D3) at ≥ 1%. On the other hand, positive results were obtained for a genotoxicity assay using Bacillus subtilis (H17 and M45) but not Escherichia coli (W3110 and p3478) as indicated by an increased zone of inhibition for the repair-deficient strain (M45) vs. that for repair-proficient strain (H17) of the former pair (≥ 0.1 mg/plate; -MA).

**Study Reference:** Shirasu *et al.* (1980)
The mutagenicity of propanil (98% AI) was tested with an *in vitro* recombination assay using Bacillus subtilis (H17, M45) and an *in vitro* reversion assay (± MA) using Escherichia coli (WP2 hcr) and Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100). The results for the recombination and reversion assays were negative for mutagenicity with respective applied doses ± MA (0, 20, 100, 200, 500, 100, and 2000 µg/disk and 0, 1, 5, 10, 50, 100, 500, 1000, and 5000 µg/plate).

**Study Reference:** Kruszewski *et al.* (1984)
The mutagenicity and cytotoxicity of propanil (Stam Technical, 88% AI) were tested with *in vitro* assays using Chinese hamster ovary cells (CHO-K1-BH4). The cytotoxicity of propanil was first tested ± MA to find levels that produced acceptable levels of cell survival. The propanil concentrations tested for mutagenicity were (-MA) 0, 15, 75, 125, and 150 µg/mL (0, 13.2, 66, 110, 132 µg/mL AI) and (+MA) 0, 100, 115, 130, and 140 µg/mL (88, 101, 114, and 123 µg/mL AI), respectively. The results for both mutation assays were negative. Survival ranged from 6% to 101% (- MA) and from (+ MA) 18% to 98%.

**Study Reference:** San and Reece (2001)
The ability of propanil (Technical, 97% AI; 1, 5, 25, 50 and 100 µg/mL) to cause unscheduled DNA synthesis (UDS) was tested *in vitro* using primary hepatocytes harvested from Sprague-Dawley rats. No increase in UDS (as mean net nuclear counts) was observed for treated cells (≤ 100 µg/mL) although dose-responsive cytotoxicity (as released lactate dehydrogenase (LDH) activity) was observed for 1 and 25-100 µg/mL dose levels. Normal cell morphology was observed for cells treated at dose levels ≤ 25 µg/mL.

***(ii) In Vivo Clastogenicity***

**Study Reference:** Gudi and Krsmanovic (2001)
The ability of propanil (Technical, 98% AI; 0, 100, 200, and 400 mg/kg by IP route) to cause chromosomal aberrations *in vivo* was tested with a mammalian erythrocyte micronucleus test using male and female ICR mice (5/sex/dose/time point). The results were negative, with no treatment-related increases in the relative counts of polychromatic erythrocytes (PCE) or micronucleated PCEs in bone marrow specimens harvested at either 24 or 48 hours. On the other hand, reductions in the ratio of PCEs to total erythrocytes (2 to 25%) were observed in the treatment groups consistent with adequate bone

marrow bioavailability of propanil. Clinical signs in males and females included lethargy (≥ 100 mg/kg), piloerecton (≥ 100 mg/kg), prostration (400 mg/kg), irregular breathing (400 mg/kg), and crusty eyes (400 mg/kg).

**Study Reference:** O'Neill *et al.* (1983)
The ability of propanil (Stam Technical, 88% AI; 0, 26.5, 106, and 265 mg/kg by per oral (PO) route) to cause chromosomal aberrations *in vivo* was tested with a cytogenetic assay using male CD-1 mice (8 per dose/time-point). Treatment did not increase incidence of chromosomal aberrations in bone marrow specimens harvested 6, 24, or 48 hours after 1 treatment or 6 hours after the final dose in the 5-dose regimen. The acute NOEL was 26.5 mg/kg based on incidences of decreased motor activity and piloerection at 106 mg/kg.

**Study Reference(s):** Kaya *et al.* (2000)
The ability of propanil (98% AI; 0.1, 0.5, 1, 2, 5, and 10 mM) to cause somatic mutations and recombination *in vivo* was evaluated in a wing spot test using Drosophila melanogaster larvae and reported in the open literature. The test used larvae strains with standard and high p450 bio-activation capacity. Significantly ($p < 0.05$) positive results were obtained at ≥ 5 mM and ≥ 0.5 mM for the standard and high p450 bio-activation capacity crosses, respectively.

**Table 14. Summary of Genotoxicity Studies of Propanil**

| Test Type/System | Dose Levels | ± S9 | Results | References |
|---|---|---|---|---|
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) | 10 to 5000 µg/plate | + & - | Negative | Simmon (1979) |
| *In vitro* mutagenicity; reverse mutation; Escherichia coli (WP2) | 1 to 1000 µg/plate | + & - | Negative | Simmon (1979) |
| *In vitro* mutagenicity; mitotic recombination; Saccharomyces cerevisiae (D3) | 0.01 to 5% w/v | + & - | Negative | Simmon (1979) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; human fibroblasts (WI-38) | 0.1 to 1000 µg/plate | + & - | Negative | Simmon (1979) |
| *In vitro* mutagenicity; recombination; Bacillus subtilis (H17 and M45) | 0.1 to 1000 µg/plate | + & - | Positive for M45 (-S9) | Simmon (1979) |
| *In vitro* mutagenicity; reverse mutation; Escherichia coli (W3110 and p3478) | 0.1 to 1000 µg/plate | + & - | Negative | Simmon (1979) |
| *In vitro* mutagenicity; recombination; Bacillus subtilis (H17 and M45) | 20 to 2000 µg/disk | + & - | Negative | Shirasu *et al.* (1980) |
| *In vitro* mutagenicity; reverse mutation; Escherichia coli (WP2) | 1 to 5000 µg/plate | + & - | Negative | Shirasu *et al.* (1980) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA1535, TA1537, TA1538, TA98, and TA100) | 1 to 5000 µg/plate | + & - | Negative | Shirasu *et al.* (1980) |
| *In vitro* mutagenicity and cytotoxicity; Chinese hamster ovary cells (CHO-K1-BH4) | 13 to132 µg/mL<br>88 to123 µg/mL | -<br>+ | Negative<br>Negative | Kruszewski *et al.* (1984) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; primary rat hepatocytes | 1 to 1000 µg/plate | + & - | Negative | San and Reece (2001) |

**Table 14. Summary of Genotoxicity Studies of Propanil**

| Test Type/System | Dose Levels | ± S9 | Results | References |
|---|---|---|---|---|
| *In vivo* Clastogenicity; mammalian erythrocyte micronucleus test; mice (5/sex/dose/timepoint) | 0, 100, 200, and 400 mg/kg by IP route | NA | Negative | Gudi and Krsmanovic (2001) |
| *In vivo* Clastogenicity; cytogenetic assay; male mice (8 per dose/time-point) | 0, 26.5, 106, and 265 mg/kg by oral gavage | NA | Negative | O'Neill *et al.* (1983) |
| *In vivo* Clastogenicity; wing spot test; Drosophila melanogaster larvae (standard and high p450 bio-activation capacity); from open literature | 0.1, 0.5, 1, 2, 5, and 10 mM | NA | Positive for both strains | Kaya *et al.* (2000) |

## H) Chronic Toxicity and Carcinogenicity

### 1) Summary

Chronic toxicity and carcinogenicity studies are used to characterize their long-term or life time toxicities and their potential to cause cancer in rodent and non-rodent animal models. Data from the endpoints of chronic studies may also be applicable to the establishment of acute, short-term, and subchronic regulatory toxicity levels. The chronic toxicity database for propanil is comprised of registrant-submitted studies and studies reported in the open literature (Table 19). The signs of chronic propanil intoxication included decreases in body weight gain, changes in hematologic parameters, increased organ weights (e.g., spleen, kidney, liver, ovaries, and testes), increased macro and microscopic organ pathologies (liver, spleen, lungs, ovary, uterus), changes in biochemistry parameters, and changes in urinalysis parameters. Changes to hematologic and biochemistry parameters and observed signs of organ pathology for the spleen were consistent with effects related to the formation of metHb formation and hemolytic anemia. Three tumor types were increased with propanil treatment: testicular interstitial tumors (rat), hepatocellular adenomas (rat and mouse), and lymphoma (mouse).

### 2) Chronic Toxicity or Combined Carcinogenicity in Animals

#### *(i) Oral: Rat*

**Study Reference:** Bellringer (1994)
**Study Design:** A registrant-submitted study was conducted to evaluate the chronic, oral toxicity and carcinogenicity of propanil (technical grade, 96.5 to 99.5%) in male and female Crl:CD(SD)BR rats (5 to 6-weeks old at the beginning of study) for periods of 52 (satellite groups; 20 per sex/dose) and 104 weeks (main groups; 50 per sex/dose). The dietary levels (0, 200, 600, and 1800 ppm) were based on results from a 13-week dose range-finding study and corresponded to the following dose levels calculated using body weight and food consumption data (main group males/females): 0/0, 9/12, 28/38, and 88/145 mg/kg/day. End-points included clinical observations of health and mortality, body weight, food consumption, opthalomoscopic examinations, hematology, clinical chemistry, urinalysis, and post-mortem macro and microscopic tissue examination.

**Results:** Representative data are summarized in Table 15. Dose responsive decreases in body weight gain compared to controls were observed in main group males and/or females at all dose levels (≥ 200

ppm) during weeks 0-1 (m/f: -13-98%/-7-43%; $p < 0.01$), 1-4 (m/f: -7-30%/-3-37% and 1-13 (m/f: - 6-30%/-10-42%; $p < 0.05$ or 0.01). Significance ($p < 0.05$ or 0.01) was achieved at 200 ppm for males and at 600 ppm for females. Significance ($p < 0.05$ or 0.01) was also achieved at 600 ppm or 1800 ppm for the body weight decreases compared to controls in main group males and females during the above time-periods and at weeks 52 and 104 (m/f: -9-19%/-3/43%), demonstrating that the observed body weight effects were not reversed over the course of the study.

Significant and dose responsive decreases ($p < 0.05$ or 0.01) in food consumption were observed at 600 ppm in main group males during week 1 and weeks 2-4, 2-13, 2-26, 2-52, 2-78, 2-104, and 1-104. Corresponding increases in food utilization during weeks 1-26 suggest to DPR that the decreased body weight gain in the treated groups was the result of acute and chronic toxicity and not an artifact of poor food palatability.

Statistically significant differences ($p < 0.05$ or 0.01) in hemotologic parameters (packed cell volume (PCV), Hb levels, RBC counts, and metHb levels) were observed in females at all dose levels between weeks 13 and 52. The largest magnitude changes were observed in the metHb levels of females during week 52 (+45-196%). As noted in the study, changes to hematologic parameters were consistent with the treatment related formation of metHb.

Absolute and relative spleen weights were significantly increased in a dose-related manner in satellite group females (adjusted for body weight as covariate) at ≥ 200 ppm (Absolute: +14-90%, $p < 0.01$; Relative +7-143%, $p < 0.05$ or 0.01) and in satellite group males at ≥ 600 ppm (Absolute: +19-35%, $p < 0.05$ or 0.01; Relative +27-53%, $p < 0.01$). Increased incidences of splenic enlargement were noted at all dose levels in satellite group males (week 52) and in main group males and females (through week 104) with significance ($p < 0.05$ or 0.01) reached at ≥ 600 ppm in males and at 1800 ppm in females. Increased incidences of hemosiderosis (total, minimal, and moderate) were observed in main group males (≥ 200 ppm) through week 104 with significance reached at ≥ 200 ppm ($p < 0.05$ or 0.01). Taken together, DPR considers the above results to be consistent with the known chronic toxicity of propanil to the spleen, with males being the more sensitive gender.

Significantly ($p < 0.01$) increased relative kidney weights were noted at 1800 ppm for satellite group males (52 weeks) and main (104 weeks) and satellite (52 weeks) group females while absolute kidney weights were increased for main group males. Signs of kidney toxicity included increased incidences of hemosiderin in kidney proximal convoluted tubular epithelium in main (through week 104) and satellite (week 52) group males and females at all dose levels with significance at 600 or 1800 ppm ($p < 0.01$). Furthermore, statistically significant differences ($p < 0.05$) from controls were observed at week 52 for average urea nitrogen in satellite group males at doses ≥ 200 ppm and females at doses ≥ 600 ppm. DPR considers the pattern of pathologic changes described above to be consistent with kidney toxicity mediated by the effects of chronic propanil induced chronic hemolytic anemia on the kidney functions as primary reservoir organs.

Absolute liver weights were significantly ($p < 0.01$) increased in main (104 weeks) group females at 1800 ppm (+34%). Relative liver weights were also significantly ($p < 0.05$ and 0.01) increased in satellite (week 52) (m/f: +13/17%) and main (104 weeks) (m/f: +16/65%) group males and females: at 1800 ppm.

Coincident with the above were dose-responsive increases in incidences of bile duct hyperplasia in main group (through 104 weeks) males and females ($p < 0.05$ or 0.01 at ≥ 600 or 1800 ppm), pericholangitis[1] in main group males and females ($p < 0.05$ or 0.01 at ≥ 600 or 1800 ppm), and granulomatous inflammation in main group males and females ($p < 0.05$ and 0.01 at (m/f) ≥ 600 ppm/1800 ppm). Significantly ($p < 0.05$ or 0.01) reduced triglyceride levels in satellite group males (weeks 26 and 52) and females (weeks 52 and 78) were observed at ≥ 600. Reduced triglyceride levels and reduced bodyweights are health effects associated with improved cardiovascular health. However, when considered together with the above liver endpoints, DPR considers the changes in lipids to be consistent with a pattern of liver toxicity that is initiated by the proximal hydrolysis of propanil and activation of 3,4-DCA by liver aryl acylamidase and CYP450,subsequently damaging hepatocytes and causing metabolic perturbations including those involving fatty acid metabolism.

Absolute and relative thyroid gland weights were significantly ($p < 0.05$ or 0.01) increased at ≥ 600 ppm in satellite (week 52) and main (week 104) group males: (+22-29% and +20%). Significantly ($p < 0.05$) increased relative thyroid gland weights were also observed in main (week 104) group males at 1800 ppm (+67%). Significantly increased absolute testes and epididymides weights were observed in satellite (week 52) and main (week 104) group males at 1800 ppm (+11 and 27%) while relative weights were significantly increased in satellite (week 52) (+13-37%) and main (week 104) (+60%) group males at ≥ 600 and 1800 ppm, respectively. Dose-responsive pathologic changes observed in main group males included epididymides absent spermatozoa (+6-24%; ≥ 200 ppm), testicular focal interstitial cell hyperplasia (+6-66%; ≥ 600 ppm; $p < 0.05$ at 1800 ppm), reduced secretions in seminal vesicles (+2-20%; ≥ 600 ppm; $p < 0.05$ at ≥ 600 ppm), and prostate atrophy (+26%; 1800 ppm; $p < 0.01$). The pattern of pathologic changes described above results suggests potential anti-thyroid activity and anti-androgenic activity of propanil at the level of the androgen receptors in the testes and epididymides, seminal vesicles and in the pituitary gland (Kojima *et al.*, 2004; Kojima *et al.*, 2010).

Treatment-related pathologic changes to other sites were observed at all dose levels (≥ 200 ppm) and included, enlarged cervical lymph nodes (males at 52 weeks), thickening or swelling of the cervix (females at 52 weeks), small prostate (males at 104 weeks), thickening of the uterus (females at 104 weeks), enlarged adrenals (female decedents), and increased degree of minimal macrophage aggregations in mesenteric lymph nodes (females at 52 weeks). A statistically significant increase in axonal degeneration was observed in female rats at the high dose level (1800 ppm) suggesting the possibility of neurotoxicity.

Benign testicular interstitial tumors and hepatocellular adenomas were increased with propanil treatment. The study authors found a significant dose-responsive trend in the total number of animals with benign testicular interstitial tumors whether or not the top dose (1800 ppm) was included in the analysis (World Health Organization (WHO) International Agency for Research on Cancer (IARC) analysis of tumor incidence: $p < 0.001$ and $p = 0.043$, respectively). The total number of animals with benign testicular interstitial tumors exceeded the maximum spontaneous incidence rates in male historical controls at doses ≥ 600 ppm and the incidence of this tumor in male rats at 1800 ppm was considered treatment-related. DPR performed a Fisher's exact test using terminal necropsy data and the total number of animals with

[1] Inflammation of the tissue surrounding the hepatic bile ducts (Dorland, W. A. N. 2012. Dorland's illustrated medical dictionary, 32nd Edition, pp. v. W.B. Saunders Co., Philadelphia.)

tumors over the number of animals alive in each dose group at the time the animal with the first observed tumor was found dead or sacrificed in extremis (at risk on week 86). In both cases, a significantly ($p < 0.001$) increased incidence in main group males was noted at the 1800 ppm dose level.

The study authors found a significant trend in the incidences of benign hepatocellular adenoma (IARC analysis of tumor incidence: $p = 0.002$). The increased incidence in main group females at 1800 ppm exceeded the spontaneous incidence rates in historical controls. As such, the incidence of adenoma in female rats at 1800 ppm was considered treatment-related. DPR performed a Fisher's exact test using terminal necropsy data and using the total number of animals with tumors over the number of animals alive in each dose group at the time the animal with the first observed tumor was found dead or sacrificed in extremis (at risk on week 79). The incidence of this tumor did not reach significance for at-risk animals or at terminal necropsy. Hepatocellular carcinomas were observed in males but there was no clear dose response suggesting a treatment related increase in malignancy.

**Conclusion**

The chronic LOEL (males/females) for the study was 200 ppm ((m/f) 9/12 mg/kg/day) based on reduced PCV, Hb, and RBC values, increased metHb levels, and toxicity to spleen (increased weight and incidences of splenic enlargement and hemosiderin). Acute and subchronic effects were observed at 200 ppm ((m/f) 9/12 mg/kg/day) and included decreased body weight gains during the first week of the study and increased metHb levels during study week 13, respectively.

**Table 15. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD Rats**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 600 | 1800 | 0 | 200 | 600 | 1800 |
| Main Group Dose (mg/kg/day): | 0 | 9 | 28 | 88 | 0 | 12 | 38 | 145 |
| Satellite Group Dose (mg/kg/day): | 0 | 10 | 31 | 99 | 0 | 14 | 43 | 154 |
| N (main/satellite): | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| | Weeks: 0 to 1 | | | | | | | |
| Body Weight Gain as Percentage of Control (%) and as (g) (Main Group) | 46 ± 7.3 g (100%) | 40 ± 8.4 g (87%) | 27 ± 8.4 g (59%) | 1 ± 7.3 g (2%) | 15 ± 5.7 g (100%) | 14 ± 5.0 g (93%) | 8 ± 4.3 g (53%) | -8 ± 6.3 g (-53%) |
| Week 1 Body weight (g) (Main Group)[1] | 328 ± 24 g (100%) | 322 ± 23 g (98%) | 310 ± 24 g (95%) | 283 ± 18 g (86%) | 199 ± 17 g (100%) | 202 ± 15 g (102%) | 192 ± 11 g (96%) | 178 ± 12 g (89%) |
| Week 1 Food Consumption as Percentage of Control (%) and as (g food) (Main Group) | 203 g (100%) | 196 g (97%) | 179 g (88%) | 147 g (72%) | 161 g (100%) | 159 g (99%) | 145 g (90%) | 134 g (83%) |
| Week 1 Food Utilization as Percentage of Control (%) and as (g food (f) /g body weight gain (bwg)) (Main Group) | 4.5 g f/g bwg (100%) | 4.8 g f/g bwg (107%) | 6.6 g f/g bwg (147%) | 163.8 g f/g bwg (3640%) | 10.5 g f/g bwg (100%) | 11.2 g f/g bwg (107%) | 18.6 g f/g bwg (177%) | NA |
| Weeks | metHb Levels as Percentage (%) of Control and as (% Hb ± SD ) (n = 10) | | | | | | | |
| 13 (Satellite Group) | 1.92 ± 0.308% (100%) | 2.06 ± 0.329% (107%) | 2.52 ± 0.258% (131%) | 3.53 ± 0.825% (184%) | 1.70 ± 0.252% (100%) | 2.27 ± 0.200% (134%) | 2.74 ± 0.415% (161%) | 3.52 ± 0.349% (207%) |
| 26 (Satellite Group) | 1.78 ± 0.499% (100%) | 2.01 ± 0.429% (113%) | 2.55 ± 0.932% (143%) | 2.91 ± 0.344% (163%) | 1.51 ± 0.382% (100%) | 2.06 ± 0.768% (136%) | 2.12 ± 0.307% (140%) | 3.14 ± 0.448% (208%) |
| 52 (Satellite Group) | 1.33 ± 0.464% (100%) | 1.18 ± 0.258% (89%) | 1.89 ± 0.803% (142%) | 2.21 ± 0.304% (166%) | 0.93 ± 0.151% (100%) | 1.35 ± 0.422% (145%) | 2.04 ± 0.293% (219%) | 2.75 ± 0.347% (296%) |
| 78 (Main Group) | 2.15 ± 0.642% (100%) | 2.16 ± 0.384% (100%) | 2.73 ± 0.535% (127%) | 3.40 ± 0.617% (158%) | 2.06 ± 0.529% (100%) | 2.22 ± 0.469% (108%) | 3.17 ± 0.960% (154%) | 4.89 ± 0.990% (237%) |
| 104 and 105 (Main Group) | 1.53 ± 0.465% (100%) | 1.72 ± 0.621% (112%) | 2.49 ± 0.719% (163%) | 3.55 ± 0.577% (232%) | 1.50 ± 0.346% (100%) | 1.64 ± 0.470% (109%) | 2.27 ± 0.502% (151%) | 3.36 ± 0.970% (224%) |
| Spleen Parameters | | | | | | | | |
| Organ Weight Relative to Body Weight as Percentage (%) of Controls and as (% x 100) (Satellite Group at 52 Weeks) | 15% (100%) | 14% (93%) | 19% (127%) | 23% (153%) | 14% (100%) | 15% (107%) | 21% (150%) | 34% (243%) |
| Spleen Enlargement: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104) [2] | 1/15 (7%) | 4/17 (24%) | 10/23 (43%) | 22/31*** (71%) | 3/19 (16%) | 3/18 (17%) | 6/20 (30%) | 23/33*** (70%) |

**Table 15. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD Rats**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 600 | 1800 | 0 | 200 | 600 | 1800 |
| Main Group Dose (mg/kg/day): | 0 | 9 | 28 | 88 | 0 | 12 | 38 | 145 |
| Satellite Group Dose (mg/kg/day): | 0 | 10 | 31 | 99 | 0 | 14 | 43 | 154 |
| N (main/satellite): | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| Spleen Enlargement: Incidences/Total Animals and as Percentage (%) (Main Group All) [2] | 10/50 (20%) | 9/50 (18%) | 16/50 (32%) | 27/50*** (54%) | 3/50 (6%) | 7/50 (14%) | 8/50 (16%) | 29/50*** (58%) |
| Total Hemosiderosis: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104) [2] | 4/15 (27%) | 12/17 (71%) | 18/23 (78%) | 29/31*** (94%) | 19/19 (100%) | 3/18 (17%) | 6/20 (30%) | 33/33 (100%) |
| Total Hemosiderosis: Incidences/Total Animals and as Percentage (%) (Main Group All) [2] | 11/50 (22%) | 23/50 (46%) | 34/50*** (68%) | 42/50*** (84%) | 48/50 (96%) | 31/50 (62%) | 34/50 (68%) | 46/50 (92%) |
| **Kidney Parameters** | | | | | | | | |
| Total Brown Pigment in Proximal Convoluted Tubular Epithelium: Incidences/Total Animals and as Percentage (%) (Satellite Group at Week 52) [2] | 0/19 (0%) | 2/19 (11%) | 4/20 (20%) | 16/20*** (80%) | 0/20 (0%) | 3/19 (16%) | 3/20 (15%) | 17/20*** (85%) |
| Total Brown Pigment in Proximal Convoluted Tubular Epithelium: Incidences/Total Animals and as Percentage (%) (Main Group All) [2] | 2/50 (4%) | 2/50 (4%) | 7/50 (14%) | 25/50*** (50%) | 0/50 (0%) | 2/50 (4%) | 17/50*** (34%) | 38/50*** (76%) |
| **Liver Parameters** | | | | | | | | |
| Total Bile Duct Hyperplasia: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104)[2] | 1/15 (7%) | 4/17 (24%) | 8/23 (35%) | 19/31*** (61%) | 1/19 (5%) | 3/18 (17%) | 5/20 (25%) | 31/33 (94%) |
| Total Bile Duct Hyperplasia: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 5/50 (10%) | 8/50 (16%) | 19/50*** (38%) | 32/50*** (64%) | 5/50 (10%) | 6/50 (12%) | 15/50 (30%) | 39/50*** (78%) |
| Total Pericholangitis: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104)[2] | 4/15 (27%) | 7/17 (41%) | 17/23 (74%) | 25/31*** (81%) | 3/19 (16%) | 6/18 (33%) | 8/20 (40%) | 26/33*** (79%) |
| Total Pericholangitis: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 9/50 (18%) | 13/50 (26%) | 26/50*** (52%) | 39/50*** (78%) | 3/50 (6%) | 8/50 (16%) | 14/50 (28%) | 39/50*** (78%) |
| Total Granulomatous Inflammation: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104)[2] | 0/15 (0%) | 1/17 (6%) | 0/23 (0%) | 9/31 (29%) | 1/19 (5%) | 2/18 (11%) | 16/20*** (80%) | 32/33*** (97%) |

**Table 15. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD Rats**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 600 | 1800 | 0 | 200 | 600 | 1800 |
| Main Group Dose (mg/kg/day): | 0 | 9 | 28 | 88 | 0 | 12 | 38 | 145 |
| Satellite Group Dose (mg/kg/day): | 0 | 10 | 31 | 99 | 0 | 14 | 43 | 154 |
| N (main/satellite): | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 | 50/20 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| Total Granulomatous Inflammation: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 0/50 (0%) | 1/50 (2%) | 0/50 (0%) | 15/50*** (30%) | 1/50 (2%) | 3/50 (6%) | 25/50*** (50%) | 43/50*** (86%) |
| **Testes, Epididymides, and Prostate Parameters** | | | | | | | | |
| Organ Weight: Absolute as Percentage (%) of Controls and as (g) (Week 52)[4] | 4.81 g (100%) | 4.94 g (103%) | 4.97 g (103%) | 5.33 g (111%) | NA | NA | NA | NA |
| Organ Weight Relative to Body Weight as Percentage (%) of Controls and as (% x 100) (Satellite Group at Week 52) | 70% (100%) | 73% (104%) | 79% (113%) | 96% (137%) | NA | NA | NA | NA |
| Total Spermatozoa Absent in Epididymides: Incidences/Total Animals and as Percentage (%) (Main Group at Week 104)[2] | 3/15 (6%) | 6/17 (12%) | 8/23 (16%) | 15/31 (30%) | NA | NA | NA | NA |
| Total Spermatozoa Absent in Epididymides: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 10/50 (20%) | 15/50 (30%) | 18/50 (36%) | 19/50 (38%) | NA | NA | NA | NA |
| Total Focal Interstitial Cell Hyperplasia: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 4/50 (8%) | 1/50 (2%) | 7/50 (14%) | 37/50*** (74%) | NA | NA | NA | NA |
| Total Reduced Secretions in Seminal Vesicles: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 12/50 (24%) | 13/50 (26%) | 21/50 (42%) | 22/50 (44%) | NA | NA | NA | NA |
| Total Prostate Atrophy: Incidences/Total Animals and as Percentage (%) (Main Group All)[2] | 5/50 (10%) | 3/50 (6%) | 4/50 (8%) | 18/50 (36%) | NA | NA | NA | NA |
| **Neoplastic Findings (No. Animals with Tumors/No. Animals per Group At Risk)** | | | | | | | | |
| Testes: Benign Interstitial Cell Tumor (Total/At Risk on Week 86[3])[2] | 3/39 | 3/34 | 8/40 | 29/40*** | NA | NA | NA | NA |
| Testes: Benign Interstitial Cell Tumor (Week 104)[2] | 2/15 | 2/17 | 3/23 | 25/31*** | NA | NA | NA | NA |

**Table 15. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD Rats**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| **Dose (ppm):** | **0** | **200** | **600** | **1800** | **0** | **200** | **600** | **1800** |
| **Main Group Dose (mg/kg/day):** | **0** | **9** | **28** | **88** | **0** | **12** | **38** | **145** |
| **Satellite Group Dose (mg/kg/day):** | **0** | **10** | **31** | **99** | **0** | **14** | **43** | **154** |
| **N (main/satellite):** | **50/20** | **50/20** | **50/20** | **50/20** | **50/20** | **50/20** | **50/20** | **50/20** |
| **Legend:** | **p < 0.05** | | | | **p < 0.01** | | | |
| **Liver: Benign Hepatocellular Adenoma (Total/At Risk on Week 84/79 (m/f)[3])** [2] | 0/39 | 3/34 | 0/40 | 0/40 | 1/37 | 0/40 | 1/41 | 6/47 |
| **Liver: Benign Hepatocellular Adenoma (Week 104)** [2] | 0/15 | 1/17 | 0/23 | 0/31 | 0/19 | 0/18 | 0/20 | 4/33 |
| **Liver: Hepatocellular Carcinoma (Total/At Risk on Week 84/79 (m/f)[3])** [2] | 1/39 | 0/34 | 3/40 | 0/40 | 0/37 | 0/40 | 0/41 | 0/47 |

Bellringer (1994)

Statistical analyses were conducted on raw or transformed data based on pre-tests for heterogeneity of variance. One way ANOVA or analysis of ranks were used based on remaining heterogeneity followed by post-hoc Student's t or Williams tests.

ANCOVA was used in place of ANOVA for absolute organ weights when ANOVA with terminal body weight as a covariate revealed a significant relationship at the 10% level.

[1] Statistical analysis performed by DPR: ANOVA with post-hoc T3 Dunnet's Test; equal variances were not assumed.

[2] Statistical analysis performed by DPR: Fisher's Exact Test (*** $p < 0.001$)

[3] The number of animals at-risk for each tumor type and gender was based on the number of animals in each dose group that were alive during the 5-week window immediately preceding the death of the animal with the first identified tumor in any dose group.

[4] Absolute organ weight data adjusted for body weight as covariate.

### *(ii) Oral: Mouse*

**Study Reference:** Tompkins (1994)
**Study Design:** A registrant-submitted study was conducted to evaluate the chronic, oral toxicity and carcinogenicity of propanil (technical grade, 97%) in Crl:CD-1® (ICR)BR mice. After a pre-test period, the animals were tested for 52 (80 per sex/dose) and 104 weeks (80 per sex/dose). The dietary levels (0, 500, and 1000 ppm) were based on the results of a 13-week range-finding study and corresponded to (m/f): 0/0, 75/89, and 150/174 mg/kg/day. End-points included clinical observations, body weight, food consumption, hematology, and post-mortem macro and microscopic tissue examination.

**Results:** Representative data are summarized in Table 16. While there were no obvious treatment related increases in the numbers of mortalities with propanil treatment, the first mortalities for males in treated groups (≥ 500 ppm) occurred earlier than for corresponding controls. The numbers of animals euthanized in extremis were higher in all treated groups (≥ 500 ppm) than for controls. Clinical signs also included blue extremities, and hypoactivity consistent with the propanil's acute hematologic toxicity. Significant ($p < 0.05$ or 0.01) decreases in body weight compared to controls were observed at 1000 ppm in males (weeks 17-19, 49, 55, 63, 65, and 66; -3.2 to -5.1%) and females (weeks 4, 7, 43, 49, 50, and 61; -2.7 to -4.8%). Significant ($p < 0.05$ or 0.01) decreases in body weight gain and food consumption were also occasionally observed at in males and females at all treatment levels.

Differences from control values were noted for metHb levels at all dose levels (≥ 500 ppm) (males and females at 52 and 104 weeks: +183-1409%), counts of erythrocytes with insoluble, bound Hb (Heinz Bodies) (males at 104 weeks), and reticulocytes (males at 104 weeks). Significance was reached at 500 ppm by metHb levels and counts of erythrocytes with Heinz bodies in males (males; $p < 0.05$) and at 1000 ppm for reticulocyte counts (males; $p < 0.01$). Significantly increased absolute and relative (to body) spleen weights were observed in females at 1000 ppm level ($p < 0.01$). DPR considers that, when taken together, the hematologic and organ weight effects are consistent with the treatment-related formation of metHb and splenic toxicity.

Increased incidences of malignant lymphoma were observed in female mice (Table 16). Malignant lymphoma localized in the spleen was found to be the cause of death for female mice found dead or killed in extremis. Other issues with signs of malignant lymphoma included the adrenal glands, heart, aorta, bone marrow, lymph nodes, epididymides, esophagus, eyes, gall bladder, gut, kidneys, liver, lungs, pancreas, prostate, seminal vesicles, skeletal muscle, stomach, thymus, thyroid, trachea, urinary bladder, mesentery, brain, ovaries, oviducts, mammary glands, salivary glands, skin, spinal cord, uterus, cervix, and salivary glands.There was a significant dose response for lymphoma localized in the spleen (Peto survival adjusted-trend test: $p < 0.01$) and pair-wise significance for lymphoma localized in the spleen and for all tissues (Fisher's exact test; $p < 0.05$ at 1000 ppm).The study authors found the rate of incidence was above the mean but did not exceed the maximum spontaneous incidence rates in female historical controls. The study authors also concluded that the data was "suggestive" of a treatment related increase in malignant lymphoma in the high dose females. DPR performed Fisher's exact tests using the total number of animals with tumors in all tissues over the number of animals alive in each dose group at the time the animal with the first observed tumor was found dead or sacrificed in extremis (at risk on

week 32) and the number of animals with tumors found dead or killed in extremis. Significantly ($p < 0.05$) increased incidences were noted in females at the 1800 ppm dose level.

Significant ($p < 0.05$) increases in the total incidences of hepatocellular adenoma in the liver were observed in high dose group males found dead or killed in extremis. The study authors found no significance for the combined male incidences with pairwise or trend tests and that the rate of incidence was above the mean but did not exceed the maximum spontaneous incidence rates in male historical controls. They therefore concluded that the tumors were not an effect of treatment. DPR performed Fisher's exact tests using the total number of animals with tumors over the number of animals alive in each dose group at the time the animal with the first observed tumor was found dead or sacrificed in extremis (at risk on week 52) and the number of animals with tumors found dead or killed in extremis. Significantly ($p < 0.05$) increased incidences were noted for males animals found dead or killed in extremis at the 1800 ppm dose level. DPR also performed Cochran-Armitage and Poly 3 tests using the total number of animals with tumors over the animals at risk on week 52 (Bailer and Portier, 1988; Bieler and Williams, 1993). Based on the results, DPR concluded that there was not a statistically significant dose response for the above tumor whether or not the lifespans of the test animals were considered. Hepatocellular carcinomas were also observed in male mice but there was no clear dose response for these tumors.

**Conclusion**

The LOEL for chronic toxicity in mice was 500 ppm ((m/f) 75/89 mg/kg/day) based on increased clinical signs, hematologic toxicity related to sharply increased levels of metHb, and increased incidences of Heinz Bodies.

**Table 16. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD-1 Mice**

| Sex | Male | Male | Male | Female | Female | Female |
|---|---|---|---|---|---|---|
| **Dose (ppm):** | **0** | **500** | **1000** | **0** | **500** | **1000** |
| **Dose (mg/kg/day):** | **0** | **75** | **150** | **0** | **89** | **174** |
| **n:** | **80** | **80** | **80** | **80** | **80** | **80** |
| **Legend:** | **p < 0.05** | | | **p < 0.01** | | |
| **No. of Mortalities** | 32 | 21 | 22 | 25 | 20 | 25 |
| **Timing of first mortality (week)** | 31 | 22 | 16 | 19 | 24 | 11 |
| **No. Animals Euthanized in Extremis** | 2 | 11 | 14 | 6 | 16 | 14 |
| **Timing of First Euthanization in Extremis (week)** | 93 | 39 | 25 | 29 | 15 | 65 |
| **Extremities Appear Blue (no. occurrences/no. animals affected)** | 0/0 | 22/5 | 205/19 | 0/0 | 17/3 | 142/15 |
| **Hypoactivity (no. occurrences/no. animals affected)** | 4/4 | 27/9 | 24/9 | 8/6 | 10/8 | 14/13 |
| **metHb as (% ± SD) and as Percentage (%) of Control** | | | | | | |
| **52 Weeks** | 1.4 ± 1.3% (100%) | 6.3 ± 2.0% (450%) | 11.2 ± 5.8% (800%) | 0.9 ± 1.0% (100%) | 6.4 ± 5.0% (711%) | 10.5 ± 8.6% (1167%) |

**Table 16. Propanil-Induced Effects in a 2-Year Chronic Carcinogenicity Study with CD-1 Mice**

| Sex | Male | Male | Male | Female | Female | Female |
|---|---|---|---|---|---|---|
| **Dose (ppm):** | **0** | **500** | **1000** | **0** | **500** | **1000** |
| **Dose (mg/kg/day):** | **0** | **75** | **150** | **0** | **89** | **174** |
| **n:** | **80** | **80** | **80** | **80** | **80** | **80** |
| **Legend:** | **p < 0.05** | | | **p < 0.01** | | |
| **104 Weeks** | 1.1 ± 0.9% (100%) | 10.6 ± 9.4% (964%) | 16.6 ± 7.3% (1509%) | 1.8 ± 1.7% (100%) | 5.1 ± 4.6% (283%) | 8.7 ± 2.9% (483%) |
| **Heinz Bodies as (% ± SD)** | | | | | | |
| **104 Weeks** | 0.0 ± 0% | 0.1 ± 0.1% | 0.1 ± 0.1% | 0.0 ± 0.1% | 0.0 ± 0.1% | 0.0 ± 0.1% |
| **Absolute Organ Weights as (g) and as Percentage of Control (%)** | | | | | | |
| **Spleen** | | | | | | |
| **52 Weeks** | 0.1106 g (100%) | 0.1173 g (106%) | 0.1397 g (126%) | 0.1045 g (100%) | 0.1379 g (132%) | 0.1689 g (162%) |
| **Relative Organ Weights as (g) and as Percentage of Control (%)** | | | | | | |
| **Spleen** | | | | | | |
| **52 Weeks** | 0.323 g (100%) | 0.319 g (99%) | 0.394 g (122%) | 0.320 g (100%) | 0.442 g (138%) | 0.527 g (165%) |
| **Neoplastic Findings: Malignant Lymphoma (No. Animals with Tumors/No. Animals per Group Examined or At Risk)** | | | | | | |
| **All Tissues (Found Dead and Killed in Extremis/Examined** | 1/36 | 4/36 | 1/39 | 2/31 | 4/36 | 9/39 |
| **All Tissues (Week 104)** | 2/25 | 0/27 | 0/22 | 2/30 | 0/25 | 4/22 |
| **All Tissues (Total/At Risk on Week 21/32 (m/f)[2])**[1] (f only) | 3/61 | 4/63 | 1/60 | 4/59 | 4/59 | 13/58 |
| **Neoplastic Findings: Hepatocellular Adenoma (No. Animals with Tumors/No. Animals per Group Examined or At Risk)** | | | | | | |
| **Found Dead and Killed in Extremis/Examined** | 1/36 | 3/36 | 8/39 | 1/31 | 0/36 | 0/39 |
| **(Week 104)** | 7/25 | 6/27 | 3/22 | 0/30 | 2/25 | 1/22 |
| **Total/At Risk on Week 52/102 (m/f)** **1,2,3** (m only) | 8/58 | 9/57 | 11/56 | 1/26 | 2/27 | 1/24 |
| **Neoplastic Findings: Hepatocellular Carcinoma (No. Animals with Tumors/No. Animals per Group At Risk)** | | | | | | |
| **Total/At Risk on Week 52/102 (m/f)** [2] (m only) | 3/58 | 1/57 | 0/56 | 0/26 | 0/27 | 0/24 |

Tompkins (1994)

Statistical analyses performed were two-tailed and compared control and treated groups by sex.

Analyses included one-way ANOVA with post-hoc Dunnet's Test (body weight, body weight gain, food consumption, hematological data, and organ weights.

Terminal mortality data was evaluated using Fisher's Exact Test (one-tailed).

[1]Statistical analysis performed by DPR: Fisher's Exact Test..

[2]The number of animals at-risk for each tumor type and gender was based on the number of animals in each dose group that were alive in the week immediately preceding the death of the animal with the first identified tumor in any dose group.

[3]Statistical analysis performed by DPR: Poly 3 (Bailer and Portier, 1988; Bieler and Williams, 1993), and Cochran-Armitage Tests.

**Study Reference:** Weatherholz (1983)

**Study Design:** A registrant-submitted study was conducted to evaluate the chronic, oral toxicity and carcinogenicity of propanil (technical grade, 98%) in CD-1® mice. The animals were tested for 2 years. There were 2 control groups (66 per sex/dose) and 3 treatment groups (80 per sex/dose). The dietary levels (0, 5, 30 and 180 ppm) corresponded to (m/f): 0/0, 0.71/0.88, 4.39/5.35, 26.1/32.4 mg/kg/day. A

sixth group (80 per sex/dose) also received 180 ppm (85.4% purity) that corresponded to 26.2/31.5 mg/kg/day. End-points included clinical observations, body weight, food consumption, hematology, and post-mortem macro and microscopic tissue examination.

**Results:** Representative data are summarized in Table 17. There were no clear treatment related effects on survival, body weight, food consumption, or hematological parameters including metHb levels at any dose level. Increased incidences of hepatitis and centrilobular hepatocytic enlargement (m), bilateral retinal degeneration (m and f), dilated stomach mucosal glands (m and f), kidney regenerative epithelium (m and f), spleen hemosiderin (m and f), heart myocarditis (m), cystic thyroid follicles (m), and thyroiditis (f) were observed in the high dose groups. That increased incidences of specific lesions in the liver, eye, kidneys, heart, spleen, and thyroid gland were only observed in high dose group receiving the test article with lower purity suggests that these effects may have been caused by contaminants and not by propanil. No oncogenicity was observed.

**Conclusion**

The chronic NOEL for propanil in mice was 30 ppm ((m/f) 4/5 mg/kg/day) based on increased incidences of hemosiderin deposition in the spleen in males and females in the 180 ppm group (26/32 mg/kg/day).

**Table 17. Propanil-Induced Effects in a 2-Year Chronic Toxicity Study with Mice**

| **Dose (ppm)** | | | **0** | **0** | **5** | **30** | **180** | **180** |
|---|---|---|---|---|---|---|---|---|
| **Male Dose (mg/kg/day)** | | | **0.00** | **0.00** | **0.71** | **4.39** | **26.10** | **26.20** |
| **Female Dose (mg/kg/day)** | | | **0.00** | **0.00** | **0.88** | **5.35** | **32.40** | **31.50** |
| **Non-neoplastic Findings: weeks 53 and 105** | | | | | | | | |
| | **Legend:** | **p < 0.05** | **p < 0.01** | | | | | |
| **Liver: centrilobular hepatocytic enlargement** | **no. animals affected/no. animals examined** | **male** | 12/53 | 9/52 | 15/64 | 16/65 | 21/68 | 27/68 |
| **Liver: hepatitis** | **no. animals affected/no. animals examined** | **male** | 13/53 | 14/53 | 17/65 | 18/65 | 26/68 | 24/68 significant for "slight" |
| **Eye: bilateral retinal degeneration** | **no. animals affected/no. animals examined** | **male** | 1/25 | 2/26 | 0/2 | 0/4 | 3/35 | 7/38 |
| **Stomach: dilated mucosal glands** | **no. animals affected/no. animals examined** | **male** | 16/33 | 19/41 | 7/21 | 5/14 | 32/49 | 26/46 |
| **Kidneys: regenerative epithelium** | **no. animals affected/no. animals examined** | **male** | 28/53 | 27/53 | 49/64 | 36/65 | 41/68 | 46/67 |
| **Heart: myocarditis** | **no. animals affected/no. animals examined** | **male** | 1/54 | 0/55 | 5/65 | 1/64 | 6/69 | 10/69 |

**Table 17. Propanil-Induced Effects in a 2-Year Chronic Toxicity Study with Mice**

| Dose (ppm) | | | 0 | 0 | 5 | 30 | 180 | 180 |
|---|---|---|---|---|---|---|---|---|
| Male Dose (mg/kg/day) | | | 0.00 | 0.00 | 0.71 | 4.39 | 26.10 | 26.20 |
| Female Dose (mg/kg/day) | | | 0.00 | 0.00 | 0.88 | 5.35 | 32.40 | 31.50 |
| Non-neoplastic Findings: weeks 53 and 105 | | | | | | | | |
| | Legend: | p < 0.05 | p < 0.01 | | | | | |
| Spleen: hemosiderin pigment | no. animals affected/no. animals examined | male | 27/53 | 38/53 | 36/64 | 40/63 | 39/68 significant for "moderate" | 44/66 |
| Thyroid Gland: cystic follicles | no. animals affected/no. animals examined | male | 6/54 | 5/53 | 13/63 significant for "minimal" | 8/64 | 12/68 significant for "minimal" | 11/66 |
| Eye: bilateral retinal degeneration | no. animals affected/no. animals examined | female | 0/31 | 1/30 | 0/1 | 0/3 | 0/39 | 4/35 |
| Stomach: dilated mucosal glands | no. animals affected/no. animals examined | female | 18/39 | 13/37 | 7/15 | 8/23 | 21/52 | 19/42 |
| Kidneys: regenerative epithelium | no. animals affected/no. animals examined | female | 16/54 | 17/56 | 23/69 | 28/67 | 22/69 | 34/67 |
| Spleen: hemosiderin pigment | no. animals affected/no. animals examined | female | 50/53 | 42/56 | 54/69 significant for "moderate" | 51/66 | 63/69 significant for "moderate" | 55/68 |
| Thyroid Gland: thyroiditis | no. animals affected/no. animals examined | female | 2/54 | 2/54 | 3/68 | 6/67 | 2/68 | 9/67 |

Weatherholz (1983)

*Statistical analysis performed using Fisher's "exact" test.*

### *(iii) Oral: Dog*

**Study Reference:** Tompkins (1993c)

**Study Design:** A registrant-submitted study was conducted to evaluate the oral chronic toxicity and carcinogenicity of propanil (technical grade, 96.9-98.5%) in outbred beagle dogs for 52 weeks (4 per sex/dose). The dietary levels (0, 200, 600, and 3200 ppm) were based on results for an 8-week dose range-finding study and corresponded to (m/f): 0/0, 5/6, 45/42, and 79/85 mg/kg/day. End-points included clinical observations, mortality, body weight, food consumption, opthalomoscopic examinations, hematology, clinical chemistry, urinalysis, and post-mortem macro and microscopic tissue examination.

**Results:** Representative data are summarized in Table 18. Decreases in body weight and body weight gain were observed at 3200 ppm in males between weeks 1 and 6 while "slight" decreases in body weight gain were also observed in females between weeks 1 and 3. The decreases in body weight gain observed in males between weeks 1 and 6 were occasionally significant ($p < 0.05$ or 0.01). Food consumption was decreased at 3200 ppm in males and females during weeks 1 to 8 with significance ($p < 0.05$ or 0.01) reached during weeks 2 to 6 in males.

The values for several hematologic parameters were significantly ($p < 0.05$ or 0.01) changed in a dose responsive manner with the commencement of propanil treatment and at all dose levels consistent with the propanil-mediated formation of metHb and the onset of hemolytic anemia. The above changes included decreased red cell counts (weeks 12, 25, and 39 (F): -9 to -12%), decreased Hb levels (week 51(m): -9 to -25%; weeks 12 and 25 (f):-10 to -22%), decreased hematocrit values (week 25 (f): -9 to -18%). Dose-responsive increases in metHb levels in males and females during weeks 12, 25, 39, and 51 reached significance in males at 200 ppm (week 51; $p < 0.05$ or 0.01) and in females at 600 ppm ($p < 0.01$). Increased incidences of remnant DNA in erythrocytes (Howell-Jolly bodies) and erythrocytes with insoluble, bound Hb (Heinz Bodies) were also reported for males and females at all dose levels.

Pathologic changes indicative of liver toxicity with propanil treatment were noted at all doses tested and included increases in absolute (m/f: +14-40%/+11-49%; $p < 0.05$ at 3200 ppm) and relative (to body weight) organ weight (m/f: +5-38%/+2-48%; $p < 0.01$ at 3200 ppm), and increased incidences of endogenous reticuloendothelial (RE) cells with minimal or mild pigmentation ("hemosiderosis") in males. Treatment-related pathological changes were noted in the spleen (increased absolute organ weight (f): +38% at 3200 ppm), thyroid and parathyroid glands (increased absolute (m: +49%; 3200 ppm) and relative organ weights (m: +56%; 3200 ppm), and kidneys (increased incidences of pigmentation in proximal tubules; ≥ 200 ppm).

**Conclusion**

The chronic LOEL for propanil in dogs was 200 ppm ((m/f) 5/6 mg/kg/day) based on changes to hematologic parameters including increased metHb levels, decreased RBC counts, Hb levels, and hematocrit values, increased incidences of Heinz Bodies and hemosiderosis. Subchronic effects of propanil treatment included changes to hematologic parameters including increased metHb levels at all treatment levels (≥ 200 ppm or ≥ 4/5 mg/kg/day) during weeks 12 and 25 and reached significance at the 1600 ppm dose level (45/42 mg/kg/day).

**Table 18. Propanil-Induced Effects in a 1-Year Chronic Toxicity Study with Outbred Beagle Dogs**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 1600 | 3200 | 0 | 200 | 1600 | 3200 |
| Dose (mg/kg/day): | 0 | 5 | 45 | 79 | 0 | 6 | 42 | 85 |
| n: | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| Week | Red Cells as (mil/µL ± SD) and as Percentage (%) of Control | | | | | | | |
| -1 | 6.08 ± 0.299 mil/µL (100%) | 6.41 ± 0.208 mil/µL (105%) | 5.71 ± 0.543 mil/µL (94%) | 6.06 ± 0.571 mil/µL (100%) | 6.24 ± 0.469 mil/µL (100%) | 6.40 ± 0.285 mil/µL (103%) | 6.19 ± 0.122 mil/µL (99%) | 6.04 ± 0.194 mil/µL (97%) |
| 12 | 6.75 ± 0.412 mil/µL (100%) | 6.54 ± 0.420 mil/µL (98%) | 5.75 ± 0.638 mil/µL (86%) | 5.36 ± 0.297 mil/µL (80%) | 6.97 ± 0.425 mil/µL (100%) | 6.09 ± 0.376 mil/µL (87%) | 5.77 ± 0.211 mil/µL (83%) | 5.36 ± 0.217 mil/µL (77%) |
| 25 | 6.85 ± 0.258 mil/µL (100%) | 6.49 ± 0.249 mil/µL (95%) | 5.65 ± 0.209 mil/µL (82%) | 5.12 ± 0.148 mil/µL (75%) | 6.99 ± 0.529 mil/µL (100%) | 6.20 ± 0.172 mil/µL (89%) | 5.63 ± 0.223 mil/µL (81%) | 5.27 ± 0.103 mil/µL (75%) |

**Table 18. Propanil-Induced Effects in a 1-Year Chronic Toxicity Study with Outbred Beagle Dogs**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 1600 | 3200 | 0 | 200 | 1600 | 3200 |
| Dose (mg/kg/day): | 0 | 5 | 45 | 79 | 0 | 6 | 42 | 85 |
| n: | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| 39 | 7.19 ± 0.381 mil/µL (100%) | 7.77 ± 1.530 mil/µL (108%) | 6.26 ± 0.915 mil/µL (87%) | 5.49 ± 0.368 mil/µL (76%) | 6.79 ± 0.177 mil/µL (100%) | 6.16 ± 0.167 mil/µL (91%) | 5.69 ± 0.192 mil/µL (84%) | 5.16 ± 0.258 mil/µL (76%) |
| 51 | 7.52 ± 0.401 mil/µL (100%) | 6.84 ± 0.133 mil/µL (91%) | 6.75 ± 0.403 mil/µL (90%) | 5.55 ± 0.135 mil/µL (74%) | 7.00 ± 0.256 mil/µL (100%) | 6.78 ± 0.302 mil/µL (97%) | 6.43 ± 0.386 mil/µL (92%) | 6.21 ± 0.187 mil/µL (89%) |
| Week | Hemoglobin as (g/dL ± SD) and as Percentage (%) of Control | | | | | | | |
| -1 | 13.5 ± 0.43 g/dL (100%) | 14.5 ± 0.78 g/dL (107%) | 13.0 ± 1.04 g/dL (96%) | 13.8 ± 0.96 g/dL (102%) | 14.0 ± 1.24 g/dL (100%) | 14.2 ± 0.88 g/dL (101%) | 14.4 ± 0.80 g/dL (103%) | 13.6 ± 0.32 g/dL (97%) |
| 12 | 15.1 ± 0.82% (100%) | 15.2 ± 1.23% (101%) | 13.5 ± 0.92% (89%) | 12.6 ± 0.61% (83%) | 15.6 ± 0.99% (100%) | 13.9 ± 0.85% (89%) | 13.6 ± 0.77% (87%) | 12.4 ± 0.41% (79%) |
| 25 | 15.6 ± 0.54 g/dL (100%) | 14.9 ± 0.76 g/dL (96%) | 13.4 ± 0.63 g/dL (86%) | 12.1 ± 0.26 g/dL (78%) | 15.7 ± 0.87 g/dL (100%) | 14.2 ± 0.44 g/dL (90%) | 13.4 ± 0.93 g/dL (85%) | 12.2 ± 0.22 g/dL (78%) |
| 39 | 15.4 ± 1.10 g/dL (100%) | 14.7 ± 0.21 g/dL (95%) | 13.7 ± 0.88 g/dL (89%) | 12.0 ± 0.43 g/dL (78%) | 15.3 ± 0.47 g/dL (100%) | 14.3 ± 0.33 g/dL (93%) | 13.4 ± 0.66 g/dL (88%) | 12.0 ± 0.68 g/dL (78%) |
| 51 | 17.4 ± 1.30 g/dL (100%) | 15.8 ± 0.38 g/dL (91%) | 15.7 ± 0.31 g/dL (90%) | 13.0 ± 0.48 g/dL (75%) | 15.6 ± 0.79 g/dL (100%) | 15.4 ± 0.44 g/dL (99%) | 15.1 ± 1.34 g/dL (97%) | 14.6 ± 0.70 g/dL (94%) |
| Week | Hematocrit as (% ± SD) and as Percentage (%) of Control | | | | | | | |
| -1 | 41.2 ± 1.71% (100%) | 43.5 ± 2.59% (106%) | 39.3 ± 3.44% (95%) | 41.7 ± 3.26% (101%) | 41.9 ± 3.80% (100%) | 43.8 ± 2.73% (105%) | 43.3 ± 3.03% (103%) | 41.1 ± 0.62% (98%) |
| 12 | 46.3 ± 3.21% (100%) | 46.0 ± 3.91% (99%) | 42.4 ± 3.74% (92%) | 40.5 ± 1.75% (87%) | 47.1 ± 3.46% (100%) | 42.2 ± 2.97% (90%) | 42.1 ± 2.47% (89%) | 39.4 ± 1.98% (84%) |
| 25 | 47.0 ± 1.62% (100%) | 44.9 ± 2.63% (96%) | 41.6 ± 1.84% (89%) | 37.9 ± 1.10% (81%) | 47.0 ± 2.95 % (100%) | 42.8 ± 1.37% (91%) | 40.7 ± 1.97% (87%) | 38.6 ± 0.34% (82%) |
| Week | Methemoglobin (%) | | | | | | | |
| -1 | 0.0 ± 0.00 | 0.1 ± 0.10 | 0.1 ± 0.19 | 0.1 ± 0.10 | 0.1 ± 0.06 | 0.0 ± 0.05 | 0.1 ± 0.25 | 0.0 ± 0.05 |
| 12 | 0.0 ± 0.00 | 0.4 ± 0.26 | 3.5 ± 1.35 | 4.4 ± 1.05 | 0.0 ± 0.00 | 0.4 ± 0.26 | 3.2 ± 0.89 | 6.2 ± 1.19 |
| 25 | 0.0 ± 0.00 | 0.6 ± 0.42 | 2.6 ± 0.53 | 4.2 ± 0.78 | 0.0 ± 0.00 | 0.6 ± 0.08 | 3.2 ± 0.97 | 6.3 ± 0.57 |
| 39 | 0.3 ± 0.13 | 1.0 ± 0.43 | 2.6 ± 0.70 | 4.2 ± 0.65 | 0.1 ± 0.14 | 0.7 ± 0.05 | 3.8 ± 1.04 | 7.0 ± 1.87 |
| 51 | 0.0 ± 0.05 | 0.8 ± 0.24 | 1.9 ± 0.31 | 3.3 ± 0.48 | 0.0 ± 0.00 | 0.9 ± 0.13 | 2.7 ± 0.85 | 4.8 ± 1.13 |
| Week | Howell-Jolly Bodies (Total No. per Group/4 Animals per Group)[1] | | | | | | | |
| -1 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.50 ± 0.58 | 0.00 ± 0.00 | 0.00 ± 0.00 |

**Table 18. Propanil-Induced Effects in a 1-Year Chronic Toxicity Study with Outbred Beagle Dogs**

| Sex | Male | Male | Male | Male | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|
| Dose (ppm): | 0 | 200 | 1600 | 3200 | 0 | 200 | 1600 | 3200 |
| Dose (mg/kg/day): | 0 | 5 | 45 | 79 | 0 | 6 | 42 | 85 |
| n: | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Legend: | p < 0.05 | | | | p < 0.01 | | | |
| 12 | 0.00 ± 0.00 | 0.00 ± 0.00 | 1.75 ± 0.50 | 2.25 ± 0.50 | 0.00 ± 0.00 | 0.00 ± 0.00 | 1.25 ± 0.96 | 2.00 ± 0.00 |
| 25 | 0.00 ± 0.00 | 0.25 ± 0.50 | 1.00 ± 0.00 | 2.50 ± 0.58 | 0.00 ± 0.00 | 0.00 ± 0.00 | 1.00 ± 0.82 | 1.75 ± 0.50 |
| 39 | 0.00 ± 0.00 | 0.00 ± 0.00 | 1.00 ± 0.00 | 2.50 ± 0.58 | 0.00 ± 0.00 | 0.00 ± 0.00 | 0.75 ± 0.96 | 1.00 ± 0.00 |
| 51 | 0.00 ± 0.00 | 0.25 ± 0.50 | 1.25 ± 0.50 | 1.50 ± 0.58 | 0.00 ± 0.00 | 0.50 ± 0.58 | 1.00 ± 0.82 | 1.00 ± 0.00 |
| Week | Heinz Bodies (per 1000 RBC)[1] | | | | | | | |
| 25 | 0.00 ± 0.00 | 0.25 ± 0.50 | 3.75 ± 0.96 | 10.75 ± 3.30 | 0.00 ± 0.00 | 0.25 ± 0.50 | 3.00 ± 0.82 | 15.00 ± 3.16 |
| 51 | 0.75 ± 0.96 | 0.50 ± 0.58 | 2.50 ± 1.29 | 7.75 ± 2.75 | 1.00 ± 0.82 | 2.75 ± 1.26 | 11.25 ± 5.97 | 8.00 ± 3.37 |
| Organ Toxicity: Kidney Parameters as No. of Incidences | | | | | | | | |
| Pigment, Endogenous Proximal Tubules (minimal, mild, and moderate) | 0/4 | 4/4 | 4/4 | 4/4 | 0/4 | 1/4 | 4/4 | 4/4 |

Tompkins (1993c)
Statistical analyses performed were two-tailed and compared control and treated groups by sex.
Analyses included one-way ANOVA with post-hoc Dunnet's Test (body weight, body weight gain, food consumption, hematological data, and organ weights.
[1] Statistical analysis performed by DPR using GraphPad Prism 7.00: 1-way ANOVA with Dunnett's post-test

**Study Reference:** Ambrose *et al.* (1972**)**
**Study Design:** An open-literature study was conducted to evaluate the oral chronic toxicity and carcinogenicity of propanil (technical grade, 97%) in purebred beagle dogs. Testing was conducted for 2 years (2 per sex/dose). The dietary levels (0, 100, 600, and 3000 (weeks 1-4) and 4000 (weeks 5-104) ppm) corresponding to: 0, 2.5, 15, and 75 and 100 mg/kg/day. Dose levels were not reported but were instead estimated assuming 0.025 kg food/kg body weight. End-points included Clinical observations, mortality, body and select organ weight, hematology, clinical chemistry, urinalysis, and post-mortem macro and microscopic tissue examination.

**Results:** Decreases were observed in bodyweights (-23%) at the study's terminus and body weight gains from week 6 were concurrent with decreases in food conversion at 4000 ppm. Increased kidney weight (relative to body weight) (+27%) was noted at 4000 ppm. Also, average relative (to body weight) spleen weights were depressed at the 100 and 600 ppm dose levels (-11-42%; $p < 0.05$ at 100 ppm level). No additional pathology data was reported. The NOEL was 600 ppm (15 mg/kg/day) on the basis of reduced body weight and body weight gain and increased kidney weight observed at the LOEL of 4000 ppm (100 mg/kg/day).

**Table 19. Summary of Chronic Studies for Propanil**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | (m/f) < 9.0/11.5 mg/kg/day | (m/f) = 9.0/11.5 mg/kg/day | ↓ PCV, Hb, and RBC values, ↑ metHb levels, incidences of hemosiderosis, toxicity to spleen (↑ weight and incidences of splenic enlargement and hemosiderin) (m and f) | Bellringer (1994) |
| Mouse | Chronic Feeding and Carcinogenicity; Two-year dietary exposure (80/sex/dose) (0, 500, and 1000 ppm or (m/f) 75/89, and 150/174 mg/kg/day) | (m/f) < 74.9/88.6 mg/kg/day | (m/f) = 74.9/88.6 mg/kg/day | ↑ clinical signs of toxicity (m and f), ↑ metHb levels (m and f), and ↑ counts of erythrocytes with Heinz Bodies (m). | Tompkins (1994) |
| Mouse | Chronic Feeding and Carcinogenicity; Two-year dietary exposure (66 (controls) or 80/sex/dose) 0, 0, 5, 30, 180 and 180 ppm or (m/f) 0/0, 0/0, 0.71/0.88, 4.39/5.35, 26.1/32.4, and 26.2/32.4 mg/kg/day). | (m/f) = 4/5 mg/kg/day | (m/f) = 26/32 mg/kg/day | ↑ incidences of hemosiderin deposition in the spleen (m and f). | Weatherholz (1983) |
| Dog | Chronic Feeding; One-year dietary exposure (4/sex/dose) (0, 200, 600, and 3200 ppm or (m/f) 0/0, 5/6, 45/42, and 79/85 mg/kg/day). | (m/f) < 5/6 mg/kg/day | (m/f) 5/6 mg/kg/day | Changes to hematologic parameters including ↑ metHb levels, ↓ RBC counts, Hb levels, and hematocrit values, ↑ incidences of Heinz Bodies and hemosiderosis (m and f) | Tompkins (1993c) |
| Dog | Chronic Feeding; One-year dietary exposure (2/dose) (0, 100, 600, and 3000 or 4000 ppm or 0, 2.5, 15, and 75 or 100 mg/kg/day). | (m/f) = 15 mg/kg/day | (m/f) = 100 mg/kg/day | ↓ body weight and pathological changes to the kidneys (m and/or f) | Ambrose *et al.* (1972) |

# I) Immunotoxicity

## 1) Summary

Immunotoxicity studies are used to characterize their short-term systemic toxicities with special emphasis on endpoints related to the functions of organs and cells that make up the acquired immune systems in relevant animal models. The immunotoxicity database for propanil includes one registrant-submitted study. The signs of propanil immunotoxicity included increased splenic antibody production (i.e., IgM).

**2) Animal Studies**

***(i) Oral: Rat***

**Study Reference:** Padgett (2007)
**Study Design:** The oral immunotoxicity of propanil (technical grade, 99.7%) was evaluated in a registrant-submitted study using male and female Crl:CD(SD) rats (approximately 7-weeks old at the beginning of study) for a period of 29 days (10 per sex/dose). The dietary levels (0, 50, 200, and 600 ppm) corresponded to the following dose levels (males/females): 0/0, 4/5, 16/19, and 48/56 mg/kg/day. Positive control groups received basal diet daily and cyclophosphamide (CP) (50 mg/kg/day by the IP route) on study days 24-27. End-points included clinical observations, mortality, body weight, food consumption, hematology, post-mortem macro and microscopic tissue examination, and splenic antibody forming cell (AFC) assay.

**Results:** Representative data are summarized in Table 20. Significant ($p < 0.05$ or 0.01) decreases in bodyweight (f: -9%) and body weight gain (m/f: -18 to -19%/-29 to 42%) were observed at 600 ppm. Significantly decreased body weight gains in males (-18%; $p < 0.01$) and females (-29 to -42%; $p < 0.05$ or 0.01) were observed within the first week of treatment at 600 ppm. Changes to hematologic parameters included decreased RBC counts (f: +5 to +16% at ≥ 200 ppm), hemoglobin levels (m/f:+6% at 600 ppm/ +6 to +16% at ≥ 200 ppm), hematocrit (m/f:+6% at 600 ppm/ +6 to +14% at ≥ 200 ppm), increased percentage of reticulocytes (m/f: +60% at 600 ppm/ +209% at 600 ppm), and increased reticulocyte counts (males: +6 to +51%; females: +20 to +159%; $p < 0.01$ at doses ≥ 600 ppm for both sexes). Spleen weight increases were responsive to dose. Absolute and relative spleen (to body and brain weight) were elevated at 600 ppm in males (+13 to +22%; relative to body or brain: $p < 0.05$ or 0.01) females (+19 to +30%; relative to body: $p < 0.01$). The pattern of changes to the above hematologic and splenic parameters was consistent with the acute propanil treatment-related formation of metHb. Splenic antibody production (i.e., IgM AFC/$10^6$ Spleen Cells and IgM AFC/Spleen ($x10^3$)) was elevated in females at all dose levels (≥ 50 ppm) (+49 to +76%). While this effect was not dose-responsive or significant, it was consistent with the pattern of propanil-mediated B-cell toxicity reported in the open-literature for *in vivo* and human population-based studies (Barnett *et al.*, 1992; Salazar *et al.*, 2005; Salazar *et al.*, 2006).

**Conclusions**

The systemic NOEL was 200 ppm (16/19 mg/kg/day) based on decreased body weight and body weight gains in males and females, and signs of anemia in females at the LOEL (600 ppm or 48/56 mg/kg/day). The immunotoxicity NOEL was 600 ppm (48/56 mg/kg/day). Acute effects of propanil treatment included significantly decreased body weight gains in males and females that were observed within the first week of treatment at 600 ppm (48/56 mg/kg/day).

**Table 20. Propanil-Induced Effects in an Immunotoxicity Study with CD Rats**

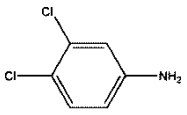
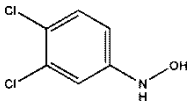
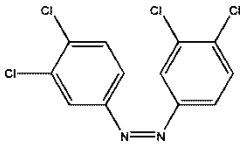
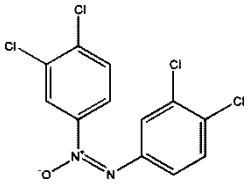
| Sex | Male | Male | Male | Male | Male | Female | Female | Female | Female | Female |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (ppm)** | **0** | **50** | **200** | **600** | **Positive Control** | **0** | **50** | **200** | **600** | **Positive Control** |
| **Dose (mg/kg/ day)** | **0** | **4** | **16** | **48** | **50 CP** | **0** | **5** | **19** | **56** | **50 CP** |
| **n** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** | **10** |
| **Legend:** | **p < 0.05** | | | | | **p < 0.01** | | | | |
| **Parameter** | **Average Parameter Values (as Percentage of Control Values** | | | | | | | | | |
| **Body Weight Gain (Days 0-3)** | 14 ± 4 g (100%) | 12 ± 12 g (86%) | 15 ± 15 g (107%) | 10 ± 10 g (71%) | 14 ± 14 g (100%) | 12 ± 2.8 g (100%) | 12 ± 3.7 g (100%) | 10 ± 2.9 g (83%) | 7 ± 2.1 g (58%) | 11 ± 4.6 g (92%) |
| **Body Weight Gain (Days 0-7)** | 55 ± 5.4 g (100%) | 50 ± 5.8 g (91%) | 56 ± 9.9 g (102%) | 45 ± 9 g (82%) | 55 ± 5.6 g (100%) | 28 ± 7.2 g (100%) | 26 ± 3.9 g (92%) | 25 ± 5.1 g (89%) | 20 ± 4.6 g (71 %) | 22 ± 8.2 g (79%) |

Padgett (2007)
Statistical analyses included one-way ANOVA with post-hoc Dunnet's Test (body weight gain)

## J) Toxicity of Propanil Metabolites and Contaminants

A summary of toxicologically relevant metabolite species and contaminants of propanil is provided in Table 21.

**Table 21. Important Metabolites and Contaminants of Propanil**

| Metabolite Identity | Structures and Molecular Weights |
|---|---|
| 3,4-Dichloroaniline (3,4-DCA) |  <br>Molecular Weight: 162.02 g/mol<br>Molecular Formula: $C_6H_5Cl_2N$<br>(NCBI, 2013) |
| N-hydroxy-3,4-Dichloroaniline (N-OH-3,4-DCA) |  <br>Molecular Weight: 178.02 g/mol<br>Molecular Formula: $C_6H_5Cl_2NO$<br>(NCBI, 2013) |
| 3,3',4,4'-tetrachloroazobenzene (TCAB) |  <br>Molecular Weight: 320.00 g/mol<br>Molecular Formula: $C_{12}H_6Cl_4N_2$<br>(NCBI, 2013) |
| 3,3',4,4'-tetrachloroazoxybenzene (TCAOB) |  <br>Molecular Weight: 336.00 g/mol<br>Molecular Formula: $C_{12}H_6Cl_4N_2O$<br>(NCBI, 2013) |

### 1) 3,4-DCA and N-OH-3,4-DCA

#### *(i) Summary*

The toxicities of 3,4-DCA and N-OH-3,4-DCA are relevant to any assessment of the risk posed by propanil because they are the metabolites known to be critical intermediates in the formation of metHb

and thiyl-Hb adducts. The toxicity of 3,4-DCA is particularly important because of its possible presence as a residue in treated post-treatment soil, plants, and harvested grains.

### *(ii) Metabolism and Pharmacokinetics*

#### ii(a) Summary

The metabolism and elimination pathways of 3,4-DCA largely overlap with those of propanil. The metabolism and pharmacokinetics database for 3,4-DCA is comprised of IP-route, *in vivo* and *in vitro* studies reported in the open literature. In consideration of the above, the studies summarized in this section were considered relevant because they provided additional information about the hematologic toxicity of propanil (i.e., the kinetics of metHb formation) and the sensitivities of test animals with respect to the extrapolation of experimental to regulatory limits of human exposure. The rates of metHb formation from 3,4-DCA and propanil in the mouse were rapid while the potency of the former was 2-fold higher than the latter consistent with the two-pathway scheme observed in the propanil FIFRA rat ADME study (Singleton and Murphy, 1973; Wu, 1991). The relative species sensitivity to treatment with 3,4-DCA (as % metHb formation over control) was rat > mouse > guinea pig with differences that were likely due to in part to differences in absorption, inter-compartmental transport, and/or rates oxidative metabolism (Chow and Murphy, 1975). While propanil IP absorption and clearance from the site of toxic action in the rat had a time-scale measured in hours in the rat, N-OH-3,4-DCA absorption and clearance from the site of toxic action had a time-scale measured in minutes (McMillan *et al.*, 1991a). The magnitude of the hemolytic anemia end-point in the rat was correlated with the total exposure (AUC) (McMillan *et al.*, 1991a).

### *(iii) Acute Toxicity*

#### iii(a) Summary

The acute toxicity database for 3,4-DCA consists of registrant-submitted studies (Table 22). The ratio of the rat oral $LD_{50}$ values (as mg/kg body weight) for propanil over 3,4-DCA was estimated to be between 1.5 and 1.8, strikingly similar to the ratio of molecular weight for both compounds (1.3). This suggests to DPR that, under the conditions of the studies used to obtain the $LD_{50}$ values, both compounds had similar per-oral ADME such that the toxicities of both compounds were equivalent on a per-mole basis. Clinical signs of acute 3,4-DCA toxicity in the rat and/or mouse included cyanosis, diarrhea, narcosis, irregular respiration, reduced reflexes, prostration, unresponsiveness to sound, paralysis, and mortality. Additional signs of acute toxicity included elevated metHb levels and pathological changes to the kidneys, liver, and lungs.

#### iii(b) Oral: Rat and Mouse

Three registrant-submitted studies were conducted to assess the acute oral toxicity of 3,4-DCA in the rat and mouse (Table 22) (ECB, 2006b; ECB, 2006l; ECB, 2006m). The $LD_{50}$ values for the rat ranged from 530 (female) to 888 mg/kg (male) while the $LD_{50}$ values for the mouse ranged from 470 (female) to 510 mg/kg (male). The results show slight species and gender differences. Clinical signs were reported to appear within minutes of treatment, were similar to those for propanil, and included cyanosis, diarrhea, narcosis, reduced reflexes, paralysis, and mortality. The dose mass ratios of highest female and male rat

oral $LD_{50}$ values for propanil over 3,4-DCA were as follows: (f) (960 mg/kg)/(530 mg/kg) = 1.8 and (m) (1302 mg/kg)/(888 mg/kg) = 1.5.

### iii(c) Inhalation: Rat

Three registrant-submitted studies were conducted to assess the acute inhalation toxicity of 3,4-DCA in the rat (Table 22) (ECB, 2006d; ECB, 2006j; ECB, 2006g). The mass median aerodynamic particle diameter (MMAD) was only reported for 1 study and was 1.8 µm. The MMAD suggests that the primary deposition for the test article was in the bronchial and deep lung regions (< 5 µm) while the deposition for the subpopulations of larger particles (5 to 10 µm) was in the nasopharyngeal region (Raabe *et al.*, 1988; SOT, 1992; Pauluhn, 2003). An $LC_{50}$ could only be calculated for one study and was 3.3 mg/L (528 mg/kg) based on mortalities at doses above 2.8 mg/L (448 mg/kg). In the same study elevated metHb levels of approximately 28% were seen in surviving animals while levels of 47 to 62% were seen in mortalities. While no mortalities were reported for a single dose level of 0.631 mg/L (101 mg/kg) in one study, an Approximate Lethal Concentration (ALC) was reported to be 0.065 mg/L (10 mg/kg) in another. Clinical observations were similar to those for propanil and included cyanosis, cool-to-touch and pale skin, ocular and nasal discharge, irregular respiration, loss of righting and corneal reflexes, elevated metHb levels, hypoactivity, salivation, cyanosis, prostration, and unresponsiveness to sound. No "remarkable" necropsy findings were reported. The ratio of $LD_{50}$ values for propanil over 3,4-DCA in the rat could not be calculated due to the lack of a value for propanil but, based on the information provided, it is likely that it would be $\geq 1$.

### iii(d) Dermal: Rat

Two registrant-submitted studies were conducted to assess the acute dermal toxicity of 3,4-DCA in the rat (Table 22) (ECB, 2006m; ECB, 2006c). The dose level was 1000 mg/kg in both studies. There were no mortalities, $LD_{50}$ values, clinical observations, or remarkable necropsy findings reported for either study.

### iii(e) Dermal: Rabbit

Two registrant-submitted studies were conducted to assess the acute dermal toxicity of 3,4-DCA in the rabbit (Table 22) (ECB, 2006h; ECB, 2006n). The dose levels used were 130 to 1500 mg/kg and 400 to 2500 mg/kg. In the first study, no $LD_{50}$ was reported but mortalities were reported for doses $\geq 300$ mg/kg while in the second study the $LD_{50}$ was reported to be between 631 and 1000 mg/kg and mortalities were reported for doses $\geq 1000$ mg/kg. Clinical observations included cyanosis, salivation, lachrymation, ataxia, and prostration with 24 hours of dosing. Necropsy observations included kidney, liver, and lung involvement.

**Table 22. Summary of Acute Toxicity Studies and Corresponding Results for 3,4-DCA**

| Study Type | Species | Sex | Toxicity Category | Result (mg/kg or other) | References |
|---|---|---|---|---|---|
| Oral $LD_{50}$ | Rat | M | III | $LD_{50}$ = 570 to 880 | ECB (2006b); ECB (2006l); ECB (2006m) |
| Oral $LD_{50}$ | Rat | F | III | $LD_{50}$ = 530 | ECB (2006l) |
| Oral $LD_{50}$ | Mouse | M | III | $LD_{50}$ = 510 | ECB (2006l) |
| Oral $LD_{50}$ | Mouse | F | III | $LD_{50}$ = 470 | ECB (2006l) |

**Table 22. Summary of Acute Toxicity Studies and Corresponding Results for 3,4-DCA**

| Study Type | Species | Sex | Toxicity Category | Result (mg/kg or other) | References |
|---|---|---|---|---|---|
| Dermal $LD_{50}$ | Rat | Combined | III | $LD_{50}$ > 1000 | ECB (2006m); ECB (2006c) |
| Dermal $LD_{50}$ | Rabbit | Combined | III | 631 < $LD_{50}$ < 1000 | ECB (2006h); ECB (2006n) |
| Inhalation $LC_{50}$ (4-Hour, Whole Body) | Rat | Combined | III | $LC_{50}$ > 0.631 to 3.3 mg/L (101 to 528 mg/kg) (1) (MMAD: 1.8 µm) ALC = 0.065 mg/L (10.4 mg/kg) | ECB (2006d); ECB (2006j); ECB (2006g) |

MMAD: Mass median aerodynamic particle diameter

(1) Equivalent dosages were calculated by using the rat default breathing rate of 0.96 $m^3$/kg/day in the following equations:
Dose (mg/kg/day) = Concentration (mg/L) x (1000 L/$m^3$) x (0.96$m^3$/ kg day) x (4hours/ 24 hours) (1 day exposure)

### *(iv) Subchronic Toxicity*

#### iv(a) Summary

The subchronic toxicity database for 3,4-DCA consists of two registrant-submitted studies (Table 23). The subchronic effects of 3,4-DCA toxicity in the rabbit and/or rat included metHb formation, hemolytic anemia, and enlarged spleens.

#### iv(b) Dermal: Rabbit

**Study Reference:** ECB (2006i)
**Study Design and Results:** A registrant-submitted study was conducted to assess the dermal toxicity of 3,4-DCA (technical grade, 99.9%) in male rabbits (10 per dose group) for a period of 21 days. Ten, 6-hour daily applications of acetone or a 10% solution of 3,4-DCA in acetone were applied to dorsal skin (0 and 60 mg/kg/day). Hematologic parameters were changed with 3,4-DCA treatment in a pattern consistent with metHb formation and the onset of hemolytic anemia on treatment days +0, +5, and +10. The changes included decreased RBC counts, decreased Hct levels, decreased Hb levels, and increased metHb levels. On post-treatment day +1 all treated rabbits had dark brown spleens consistent with hemosiderin deposits while 2 rabbits had spleens that were enlarged and heavy. Enlarged and heavy spleens in 3,4-DCA treated animal persisted to post-treatment day +13. Skin effects observed in 3,4-DCA and vehicle treated animals on post-treatment day +1 included thickening, crust-formation, and necrosis that did not completely clear by post-treatment day +13.

#### iv(c) Inhalation: Rat

**Study Reference:** ECB (2006k)
**Study Design and Results:** A registrant-submitted study was conducted to assess the inhalation toxicity of 3,4-DCA (technical grade, 99.35%) in male Crl:CD BR rats (20 rats per dose group) for a period of 14 days. The treatment atmospheres were 0, 10, 45, 200 mg/$m^3$ (0, 2.4, 10.8, 48.0 mg/kg/day) and contained both vapor and particles. Exposures were nose-only, 6 hours per day and 5 days per week. MetHb levels were elevated at all dose levels and returned to control group levels 3 days after the final treatment while

RBC levels decreased significantly (significance level not reported in source document) during the post-treatment period in the 2.4 and 10.8 mg/kg/day dose groups. The subchronic NOEL was 2.4 mg/kg/day based on treatment-related increases in metHb at the LOEL (10.8 mg/kg/day).

**Table 23. Summary of Subchronic Studies for 3,4-DCA**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rabbit | 21-day dermal exposure; (10/dose) (0 and 60 mg/kg/day) | (m) < 60 mg/kg/day | (m) = 60 mg/kg/day | Changes to hematologic parameters consistent with hemolytic anemia, splenic hemosiderosis and enlargement, skin thickening, crust and necrosis. | ECB (2006i) |
| Rat | 14-day Inhalation exposure(6 hr/day; 5 days/week); (20/dose) (0, 10, 45, 200 mg/m$^3$ or 0, 2.4, 10.8, 48.0 mg/kg/day) | (m) = 2.4 mg/kg/day | (m) = 10.8 mg/kg/day | ↑ metHb levels. | ECB (2006k) |

### *(v) Reproductive Toxicity*

#### v(a) Summary

The reproductive toxicity database for 3,4-DCA consists of one open literature study (Table 24). The reproductive effects of 3,4-DCA toxicity in the mouse included increased reduced sperm counts and motility and increased head and tail abnormalities.

**Study Reference:** Eissa *et al.* (2012)
**Study Design and Results:** The ability of 3,4-DCA ((98%) AI; 0, 14, 28, and 55 mg/kg in corn oil by oral gavage) to cause chromosomal aberrations, decreased sperm quality, and histopathological changes to the liver and testis in male Swiss albino mice after 30 days of treatment and 35 days post-treatment for spermatogenic end-points was tested (10/dose/timepoint). Effects included significant, dose-responsive reductions in the mitotic indices and dose-responsive increases in the number and frequency of chromosomal aberrations in bone marrow cells and spermatocytes (≥ 14 mg/kg/day). Histopathological examination of the liver and testis revealed effects at the middle dose (≥ 28 mg/kg/day). Sperm counts and motility were reduced while head and tail abnormalities were increased (≥ 14 mg/kg/day). All of the spermatogenic effects were significant and dose-responsive.

**Table 24. Summary of Reproductive Toxicity Studies for 3,4-DCA**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Clastogenicity and Male Reproductive Toxicity; Oral Gavage; 30 daily doses and 35 days post-treatment (10/dose/timepoint) (0, 14, 28, and 55 mg/kg/day) | >14 mg/kg/day | 14 mg/kg/day | ↓sperm counts and motility, ↑head and tail abnormalities | Eissa *et al.* (2012) |

***(vi) Developmental Toxicity***

**vi(a) Summary**

The developmental toxicity database for 3,4-DCA consists of one registrant-submitted study (Table 25). The developmental effects of 3,4-DCA toxicity in the rat included increased incidences of post-implantation loss and delayed skeletal ossification.

**vi(b) Oral: Rat**

**Study Reference:** ECB (2006f)
**Study Design and Results:** A registrant-submitted study was conducted to assess the maternal and developmental toxicity of 3,4-DCA (grade not specified) in pregnant, female Crl:CD BR inseminated dams (28 in per group). The control and test groups received 0, 5, 25, and 125 mg/kg 3,4-DCA in aqueous carboxymethylcellulose/Tween 80 (10 mL/kg) by gavage on gestation days 6 to 15 that corresponded to the time period for major organogenesis. All dams were sacrificed on GD 20 and the fetuses were delivered by caesarian section. Body weight gain and food consumption were significantly reduced at ≥ 25 mg/kg/day. Incidences of post-implantation loss were "slightly" increased and the ossification of "a few skeletal elements" was significantly delayed at the high dose level (125 mg/kg/day). The NOEL for maternal toxicity was 5 mg/kg/day based on reduced body weight gain and food consumption at the LOEL (25 mg/kg/day). The NOEL for reproductive and developmental toxicities was 25 mg/kg/day based on increased incidences of post-implantation loss and delayed skeletal ossification at the LOEL (125 mg/kg/day).

**Table 25. Summary of Developmental Toxicity Studies for 3,4-DCA**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Developmental Toxicity; Oral Gavage; 10 doses (28 dams/dose) (0, 5, 25, and 125 mg/kg/day) | Maternal and = 5 mg/kg/day Reproductive and Developmental = 25 mg/kg/day | Maternal = 25 mg/kg/day Reproductive and Developmental = 125 mg/kg/day | Maternal: ↓ body weight gain and food consumption. Reproductive and Developmental: ↑incidences of post-implantation loss and delayed skeletal ossification | ECB (2006f) |

***(vii) Genotoxicity***

### vii(a) Summary

The genotoxicity database for 3,4-DCA consists of studies reported in the open literature (Table 26). Positive evidence of genotoxicity included increases in chromosomal aberrations (CA), sister-chromatid exchanges (SCE), mitotic indices, frequencies of metaphases/c-metaphases, and mitoses with spindle disturbances while negative results were obtained for microbial mutagenicity and DNA repair assays.

### vii(b) In Vitro Mutagenicity

**Study Reference:** McMillan *et al.* (1988)
**Study Design and Results:** The genotoxicities of propanil, its metabolites, and structurally related species were tested in a series of *in vitro* assays. No mutagenic activity was observed for any compound (propanil, N-OH-propanil, 3,4-DCA, N-OH-3,4-DCA, N-OH-3,4-dichloroformanilide (DCFA), N-OH-3,4-dichloroacetanilide (DCAA), TCAB, or TCAOB) in a Salmonella typhimurium (TA97, TA98, TA100, and TA100) reversion assay with and without S-9 pre-activation (≤ 250 µg/plate). Although propanil, 3,4-DCA, N-OH-3,4-DCA, TCAB, and TCAOB were cytotoxic to CHO cells, they were not able to induce mutations under the conditions of the assay. Similarly, propanil, N-OH-propanil, 3,4-DCA, N-OH-3,4-DCA, 3,4-DCAA, N-OH-3,4- DCAA, TCAB, and TCAOB were not positive for UDS in rat hepatocytes although they were similarly cytotoxic (0.5-1000 µg/mL). A final experiment demonstrated that N-OH-3,4-DCA had very low binding to DNA relative to that for the positive control (N-hydroxy-2-aminofluorene (AAF)) at pH 5 or 7. The above results provide mechanistic support for the lack of genotoxicity observed for propanil and its N-hydroxylated metabolite species despite the superficial similarities to other N-hydroxylated aryl amines with known genotoxicity. The authors suggested that the basis for the above finding may be the negative induction and steric effects conferred by the two halogen groups.

**Study Reference:** Rashid *et al.* (1987b)
**Study Design and Results:** The *in vitro* microbial mutagenicity of propanil metabolites (3,4-DCA and 3,4-DCA-succinamide) were tested with a reverse mutation assay using Salmonella typhimurium (TA98 and TA100). The results for the above assays were negative with no increase in number of revertants with and without metabolic activation of either compound (≤ 1000 µg/plate). The study authors chose the metabolites because 3,4-DCA was known to be conjugated to lignin, released, and subsequently conjugated by microbes.

**Study Reference:** Yoshimi *et al.* (1988)
**Study Design and Results:** The genotoxicities of several aniline derivatives were tested in a rat hepatocyte *in vitro* DNA repair test. Negative results for DNA repair were obtained for the propanil metabolite 3,4-DCA and the structurally similar compounds 2,4-DCA and 3,5-DCA although the latter compounds elicited a low level of UDS at $10^{-4}$ and $10^{-5}$ M, respectively.

**Study Reference:** Osano *et al.* (2002)
**Study Design and Results:** The genotoxicities of chloroacetanilide and formamidine pesticides and their degradation products were tested for genotoxicity in the in vitro Mutatox test for microbial mutagenicity using *Vibrio fischeri*. The Mutatox test is sensitive to DNA damage and intercalation, inhibition of DNA synthesis, induction of SOS repair, and base substitution of frame-shift mutations. Only the results for

3,4-DCA will be described here. The authors reported negative and positive results with and without S9 activation, respectively.

### vii(c) In Vitro Clastogenicity

**Study References:** Bauchinger *et al.* (1989); Salassidis and Bauchinger (1990)
**Study Design and Results:** The ability of the propanil metabolite 3,4-DCA to cause chromosomal aberrations (CA) and sister-chromatid exchanges (SCE) was tested *in vitro* with and without metabolic activation in human lymphocytes. Positive results were obtained for CA and SCE with and without activation at the 0.125 and 1 mM treatment levels. Metabolic activation (S-9 mix) increased the SCE frequency 3-fold at the highest treatment level (1 mM). The ability of a 3-hour 3,4-DCA treatment to induce mitotic spindle disruptions was evaluated in Chinese hamster V79 cells. Parameters that were increased in a dose responsive (0.25-1.0 mM) manner included mitotic index, frequency of metaphases/c-metaphases, and mitoses with spindle disturbances (primarily the initial c-mitotic type with ball metaphases) consistent with spindle toxicity. On the other hand, the polyploidy index was not significantly increased with treatment. When the above experiments were subsequently repeated using an improved spindle staining technique, a dose responsive increase in the frequency of monopolar metaphases was observed at 3 hours as well as a significant ($p < 0.001$) increase in the number of aneuploid cells at the highest treatment level (1 mM) after a 20 hour treatment corresponding to at least 2 cell cycles.

### vii(d) In Vivo Clastogenicity

**Study Reference:** Eissa *et al.* (2012)
**Study Design and Results:** The ability of propanil (3,4-DCA (98%) AI; 0, 14, 28, and 55 mg/kg in corn oil by oral gavage) to cause chromosomal aberrations, decreased sperm quality, and histopathological changes to the liver and testis in male Swiss albino mice after 30 days of treatment and 35 days post-treatment for spermatogenic end-points was tested (10/dose/timepoint). Effects included significant, dose-responsive reductions in the mitotic indices and dose-responsive increases in the number and frequency of chromosomal aberrations in bone marrow cells and spermatocytes (≥ 14 mg/kg/day). Histopathological examination of the liver and testis revealed effects at the middle dose (≥ 28 mg/kg/day). Sperm counts and motility were reduced while head and tail abnormalities were increased (≥ 14 mg/kg/day). All of the spermatogenic effects were significant and dose-responsive.

**Table 26. Summary of Summary of Genotoxicity Studies of 3,4-DCA and Related Metabolites**

| Test Type/System | Compound Tested | ± S9 | Results | References |
|---|---|---|---|---|
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA97, TA98, and TA100) | 3,4-DCA, N-OH-3,4-DCA, OH-3,4-dichloromanilide (DCFA), OH-3,4-acetanilide (DCAA) | + & - | All Negative | McMillan *et al.* (1988) |

**Table 26. Summary of Summary of Genotoxicity Studies of 3,4-DCA and Related Metabolites**

| Test Type/System | Compound Tested | ± S9 | Results | References |
|---|---|---|---|---|
| *In vitro* mutagenicity and cytotoxicity; Chinese hamster ovary cells (CHO) | 3,4-DCA, N-OH-3,4-DCA, OH-3,4-DCFA, OH-3,4-DCAA | + & - | All Negative | McMillan *et al.* (1988) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; primary rat hepatocytes | 3,4-DCA, N-OH-3,4-DCA, OH-3,4-DCFA, OH-3,4-DCAA | + & - | All Negative | McMillan *et al.* (1988) |
| *In vitro DNA binding at pH 5 and 7* | N-OH-3,4-DCA | NA | All Negative | McMillan *et al.* (1988) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA98 and TA100) | 3,4-DCA and 3,4-DCA-succinamide | + & - | All Negative | Rashid *et al.* (1987a) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; primary rat hepatocytes | 3,4-DCA, 2,4-DCA, and 3,5-DCA | + & - | Negative (3,4-DCA and 2,4-DCA) Positive (3,5-DCA) | Yoshimi *et al.* (1988) |
| *In vitro* genotoxicity; Mutatox; *Vibrio fischeri* | 3,4-DCA | + & - | Negative and Positive | Osano *et al.* (2002) |
| *In vitro* Clastogenicity (CA and SCE); Human lymphocytes | 3,4-DCA | + & - | Positive | Bauchinger *et al.* (1989) |
| *In vitro* clastogenicity (Mitotic spindle disruptions); Chinese hamster V79 cells. | 3,4-DCA | + & - | Positive | Bauchinger *et al.* (1989); Salassidis and Bauchinger, (1990) |
| Clastogenicity and Male Reproductive Toxicity; Oral Gavage; 30 doses (10/dose/timepoint) (0, 14, 28, and 55 mg/kg/day); chromosomal aberrations, sperm counts, motility, and morphology, and liver/testis histopathology | 3,4-DCA | NA | ↓ mitotic indices, ↑ number and frequency of chromosomal aberrations in bone marrow cells and spermatocytes | Eissa *et al.* (2012) |

### 2) TCAB and TCAOB

#### *(i) Summary*

The toxicities of TCAB and TCAOB are relevant to any assessment of the risk posed by propanil because they are present as contaminants in propanil formulations and are also the products of microbial metabolism. As such, DPR maintains that they may contribute to propanil's toxicity because of their presence as residues in post-treatment soil, plants, and harvested grains.

#### *(ii) Metabolism and Pharmacokinetics*

### ii(a) Summary

The metabolism and pharmacokinetics database for TCAB and TCAOB is comprised of NTP studies and studies reported in the open literature. The major route of excretion for TCAB and TCAOB in the rat was in feces consistent with low oral bioavailability. The elimination curves for both compounds were biphasic with rapid early phases followed by a slow terminal phases that might be longer than 20 days. Major urinary metabolites of TCAB included sulfate esters of hydroxylated mono or dichlorinated aniline species consistent with extensive reduction of the azo bond. The study authors considered it plausible that the latter process was mediated by the gut microbiota. N-acetylated urinary metabolites were also identified.

### ii(b) Animal Pharmacokinetic and ADME Studies

**Study Reference:** NTP (2010)
**Study Design:** The National Toxicology Program (NTP) conducted three studies to characterize the *in vivo* pharmacokinetics and disposition of TCAB. In the Pilot Study, female Sprague-Dawley rats (8 per group) were treated in 2 groups with treatment regimens described as follows:
Group A: 3 mg/kg TCAB for 7 days by oral gavage prior to IV injection; Group B: no TCAB pretreatment; Groups A and B: 3 mg/kg TCAB by the IV route. Timed blood samples were collected and end-points included the quantification of administered dose in collected samples. This study was to provide data to aid in the selection of blood sampling time-points for the Special Study.

In the Special Study, female Sprague-Dawley rats (10/6 per dosed/control group) were treated with 0, 0.1, 3.0, and 100 mg/kg TCAB 5 days per week for 3 months by oral gavage. Timed blood, fat, liver and lung samples were collected and end-points included quantification of administered dose in collected samples. In the Core Study, female Sprague-Dawley rats (10 per dosed group) were treated with 0, 0.1, 0.3, 1, 3, 10, 30, and 100 mg/kg TCAB 5 days per week for 3 months by oral gavage. Fat, liver and lung samples were collected 24 hours after last oral dose and end-points included quantification of administered dose in collected samples.

**Results:** The elimination curve for TCAB was biphasic. The values for the following PK parameters for TCAB were similar with or without TCAB pre-treatment: initial (0.7 and 1.0 hours) and terminal (6.0 and 5.8 hours) $t_{½}$ and mean residence time (MRT) (1.8 and 2.1 hours). Based on the area under the curve (AUC) and maximum blood concentration (Cmax) values, oral absorption of TCAB decreased with increasing doses. Liver and fat tissues had similar TCAB elimination $t_{½}$ values that were both greater than that for lung tissue. TCAB concentrations in all of the above tissues increased in a manner that was less than proportional to the administered dose. The lung to fat ratios of TCAB levels ranged from 0.0004 to 0.005 for males and 0.00055 to 0.00814 for females.

**Study Reference:** Burant and Hsia (1984)
**Study Design:** An open-literature study was conducted to assess the ADME of species derived from TCAB and TCAOB. Male Sprague-Dawley rats were dosed with 10 mg of either [$^{14}$C]TCAB or [$^{14}$C]TCAOB by oral gavage. Timed urine, feces samples were taken for five days as were post-mortem tissue and carcass samples following euthanization. Endpoints included quantification of radioactivity as percentage of administered dose in collected samples.

**Results:** The major route of excretion for TCAB and TCAOB was in feces. Forty-eight hours after dosing, 55 and 27% of the administered TCAB dose were excreted in feces while 50 and 20% of the administered TCAB dose were excreted in urine. The elimination curves for both compounds were biphasic with rapid early phases followed by a slow terminal phases that might be longer than 20 days. TCAB and TCAOB had biological half-lives of 18 and 34 hours versus the 16 to 31 days previously reported for TCDD. The reduced half-lives of both compounds largely explain their reduced oral toxicities compared to that for TCDD (e.g., rat oral $LD_{50}$ values: ≥ 5000 mg/kg for TCAB vs. 22-45 µg/kg for TCDD). The highest residual levels of TCAB and TCAOB were found in fat.

**Study Reference:** Pillai *et al.*, 1996)
**Study Design:** Three open-literature studies were conducted to assess the ADME of species derived from TCAB. In the first study, male F344 rats were dosed with either 3.2 or 32 mg/kg [$^{14}$C]TCAB by oral gavage to determine oral disposition of the parent compound. Timed urine, feces samples were taken for 96 hours as were post-mortem tissue and carcass samples following euthanization. Endpoints included quantification of radioactivity as percentage of administered dose in collected samples. In the second study, male F344 rats with jugular vein cannulae (JVC) were dosed with 3.2 mg/kg [$^{14}$C]TCAB administered as a bolus into the jugular vein in order to characterize the biliary excretion of the parent compound. Timed bile samples were taken for 6 hours. Endpoints included quantification of radioactivity as percentage of administered dose and metabolite identification in collected samples. In the third study, male JVC F344 rats were dosed with 3.2 mg/kg TCAB administered IV into the jugular vein in order to characterize the IV pharmacokinetics and oral bioavailability of the parent compound. Timed blood samples were taken for 96 hours. Endpoints included quantification of parent compound in collected samples.

**Results:**
The majority of the administered dose was accounted for with 39-45% excreted in urine and 53-56% excreted in feces within 48 hours of dosing and with less than 6% remaining after 96 hours. Thirty-three percent (33%) of the IV dose was excreted in bile within 6 hours of dosing with 21% excreted in feces consistent with enterohepatic recirculation. The absolute oral bioavailability and the $t_{1/2}$ of TCAB were found to be 0.3 and 3.3 hours, respectively. Major urinary metabolites included sulfate esters of hydroxylated mono or dichlorinated aniline species consistent with extensive reduction of the azo bond. N-acetylated urinary metabolites were also identified. The study authors hypothesized that the observed azo reduction was mediated by gut microbiota. The major biliary metabolite was likely TCAB. The above results stand in contrast to those for *in vitro* studies with rat microsomes where the most abundant metabolite was ring-hydroxylated TCAB (Hsia and Kreamer, 1981).

### *(iii) Acute Toxicity*

**Oral and IP: Rat and Mouse**

The effects of acute TCAB or TCAOB exposure were reported for four open-literature studies. The only oral $LD_{50}$ value reported for TCAB was ≥ 5000 mg/kg (Burant and Hsia, 1984). TCAB and TCAOB had similar binding affinities to the AhR (as the dissociation constant or Kd) as TCDD but TCAOB was 18,000-fold less potent than TCDD (as the biological potency or ED50 for liver CYP1A1 expression) in

Mice (C57BL/6J) treated with a single IP dose of each per level (dose levels not reported) (Poland *et al.*, 1976). The reduced potency of TCAOB is consistent with its more rapid metabolic inactivation (Poland *et al.*, 1976; Burant and Hsia, 1984). P450 activity was induced in Sprague-Dawley rats treated with between one and five daily IP doses (1 to 25 mg/kg/day) of either TCAB or TCAOB (most potent) in a dose dependent and persistent manner coincident with increased liver weights (Hsia and Kreamer, 1979a). In another study with Sprague-Dawley rats treated with a similar dosing regimen to the above, TCAB and TCAOB (25 mg/kg/day) caused liver hypertrophy characterized by enlarged (+50%) hepatocytes with granular cytoplasm, enlarged vacuoles bounded by endoplasmic reticulum and often full of concentric membranous arrays possibly related to increased expression of membrane bound P450 or the sequestration of damaged organelles (Schrankel *et al.*, 1980). An increased mitotic index and incidence of mitotic figures were also noted in hepatocytes.

### *(iv) Subchronic Toxicity*

#### iv(a) Summary

The subchronic toxicity database for TCAB and TCAOB is comprised of NTP studies and studies reported in the open literature (Table 27). TCAB is from 2 to 6 orders of magnitude less potent than TCDD when all endpoints are considered. This may be related to differences in values of elimination $t_{1/2}$. The effects of subchronic TCAB or TCAOB treatment in the rat and/or mouse were largely similar included decreased body weight and/or body weight gain, responsive anemia, disruption to thyroid hormone signaling, increased hepatic enzyme activities, and pathologic changes to the spleen, thymus, liver, lung, kidneys, testes and stomach.

#### iv(b) Oral: Rat

NTP conducted three studies to assess the subchronic, oral toxicity of TCAB in the rat. In the first rat TCAB study, F344 rats (5 of each gender per dose group) were treated with 0, 12.5, 32, 80, 200, and 500 mg/kg TCAB, 5 days per week for 16 days total by oral gavage (van Birgelen, 1998a). The LOEL was 12.5 mg/kg based on increased hematopoietic cell proliferation in the spleen and decreased thymus weight. Toxic effects also included increased liver weight (80 mg/kg), increased lung weight (32mg/kg), increased spleen weight (500 mg/kg), and increased renal tubule hyaline droplet accumulation in the cytoplasm of renal cortical epithelial cells and chronic nephropathy (80 mg/kg).

In the second rat TCAB study, F344 rats (10 of each gender per dose group) were treated with 0, 0.1, 1, 3, 10, and 30 mg/kg TCAB, 5 days per week for 13 weeks total by oral gavage (van Birgelen, 1998a; van Birgelen *et al.*, 1999). The LOEL was 0.1 mg/kg/day based on decreased thyroxine (T4) levels. The pattern of thyroid toxicity included increased (weak) TSH levels at 3 mg/kg/day. Decreased T4 and a weak TSH response may have been the result of the TCAB-mediated co-induction of hepatic T4-glucuronyl transferase. Alternately, TCAB or a metabolite may have acted as a weak T4 agonist or antagonist suppressing T4 signaling at the receptor and while supplying negative feedback to TSH production. Toxic effects also included increased hyperplasia of the forestomach (3 mg/kg/day), increased liver weight (1 mg/kg/day), increased spleen weight, hematopoietic cell proliferation in the spleen and responsive anemia (10 mg/kg/day), decreased thymus weight and thymic atrophy (10 mg/kg/day), and increased hepatic P450 1A (30 mg/kg/day).

In the third rat TCAB study, SD rats (10 of each gender per dose group) were treated with 0, 0.1, 0.3, 1.0, 3.0, 10, 30 and 100 mg/kg/day TCAB, 5 days per week for 14 weeks total by oral gavage (NTP, 2010). The LOEL was 0.1 mg/kg/day based on decreased body weight gain, dose-responsive reductions in the levels of total and free thyroxine (T4), increased relative and absolute right kidney weights, induction of hepatic 7-ethoxyresorfin-O-deethylase (EROD) and 7-pentoxyresorfin-O-deethylase (PROD) activities, increased relative and absolute liver weights, dose-responsive induction of lung EROD activity, and increased relative and absolute spleen weights. Toxic effects also included a pattern of hematology results consistent with normochromatic responsive anemia, dose-responsive increases in tissue residual TCAB (0.1 mg/kg/day), increased incidences of thymic atrophy (0.3 mg/kg/day) and decreased relative and/or absolute thymus weights (1.0 mg/kg/day), increased incidences of midzonal to diffuse hepatocytic hypertrophy (1.0 mg/kg) and midzonal hepatocytic cytoplasmic fatty vacuolization (3.0 mg/kg), increased relative and absolute lung weights (3.0 mg/kg), increased incidences of bronchiolar metaplasia of the alveolar epithelium, and interstitial mononuclear cell infiltration (10.0 mg/kg), and increased incidences of splenic hematopoietic cell proliferation and hemosiderin deposition (10.0 mg/kg/day).

NTP also conducted two studies to assess the subchronic, oral toxicity of TCAOB in the rat. In the first rat TCAOB study, F344 rats (5 of each gender per dose group) were treated with 0, 12.5, 32, 80, 200, and 500 mg/kg TCAOB, 5 days per week for 16 days total by oral gavage (van Birgelen, 1998b). The LOEL was 12.5 mg/kg/day based on decreased body weight gain, increased liver and lung weights and decreased thymus weight. Toxic effects also included decreased body weight (80 mg/kg/day) and decreased heart weight (200 mg/kg/day).

In the second rat TCAOB study, F344 rats (10 of each gender per dose group) were treated with 0, 0.1, 1, 3, 10, and 30 mg/kg TCAOB, 5 days per week for 13 weeks total by oral gavage (van Birgelen, 1998b). The LOEL was 0.1 mg/kg/day based on decreased platelet counts, dose-dependent decreases in thyroxine (T4) levels, decreased epididymal spermatozoa motility. Toxic effects also included increased liver weight (1 mg/kg/day), increased hepatic P450 1A (1 mg/kg/day, increased incidences of treatment-related responsive anemia (1 mg/kg/day), weak TSH levels (1 mg/kg/day), decreased terminal body weight (3 mg/kg/day), increased hyperplasia of the forestomach (3 mg/kg/day), decreased body weight gain (3 mg/kg/day), decreased triiodothyronine (T3) levels (10 mg/kg/day), increased hematopoietic centrilobular degeneration (10 mg/kg/day) and hematopoietic cell proliferation in the liver (30 mg/kg/day). increased mortality (30 mg/kg/day), and increased incidences and severities or cardiomyopathy and nephropathy.

An open-literature study was conducted to assess the subchronic, oral toxicity of TCAB or TCAOB in the SD rat (10 male rats per dose group) 5 days per week for a period of 120 days (Hsia *et al.*, 1980). The dietary levels were 0 and 1000 ppm and corresponded to 0 and 25 or 24 mg TCAB or TCAOB/kg/day. Treatment with either TCAB or TCAOB led to decreased body weight but the effect was more pronounced with the latter. Major effects of treatment with either compound included aplastic anemia (decreased Hct and Hb levels) and a similar pattern of liver toxicity that included increased liver weights, increased hepatic microsomal P450 and AHH activities and increased blood glutamic-oxalacetic transamidase activity. Spleen and testes weights were also increased with TCAOB treatment.

### iv(c) Oral: Mouse

NTP conducted two studies to assess the subchronic, oral toxicity of TCAB in the mouse. In the first mouse TCAB study, B6C3F1 mice (5 of each gender per dose group) were treated with 0, 1, 3.2, 10, 32, and 100 mg/kg TCAB, 5 days per week for 16 days total by oral gavage (van Birgelen, 1998a). The NOEL was 32 mg/kg/day based on increased hematopoietic cell proliferation in the spleen and increased incidences of thymic atrophy at the LOEL (100 mg/kg/day).

In the second mouse TCAB study, B6C3F1 mice (10 of each gender per dose group) were treated with 0, 0.1, 1, 3, 10, and 30 mg/kg TCAB, 5 days per week for 13 weeks total by oral gavage (van Birgelen, 1998a; van Birgelen *et al.*, 1999). The NOEL was 0.1 mg/kg/day based on increased hyperplasia of the forestomach at the LOEL (1 mg/kg/day). Toxic effects also included decreased epididymal sperm density (3 mg/kg/day) and increased liver and spleen weight (10 mg/kg/day) and decreased thymus weight (30 mg/kg/day).

NTP also conducted two studies to assess the subchronic, oral toxicity of TCAOB in the mouse. In the first mouse TCAOB study, B6C3F1 mice (5 of each gender per dose group) were treated with 0, 1, 3.2, 10, 32, and 100 mg/kg TCAOB, 5 days per week for 16 days total by oral gavage (van Birgelen, 1998b). The NOEL was 1 mg/kg/day based on increased liver weight and decreased thymus weight at the LOEL (3.2 mg/kg/day). Toxic effects also included a dose-dependent trend of increased heart weight at 10 mg/kg/day and increased hematopoietic cell proliferation in the spleen, hepatic foci of inflammation and necrosis, and thymic atrophy at 100 mg/kg.

In the second mouse TCAOB study, B6C3F1 mice (10 of each gender per dose group) were treated with 0, 0.1, 1, 3, 10, and 30 mg/kg TCAOB, 5 days per week for 13 weeks total by oral gavage (van Birgelen, 1998b). The NOEL was 0.1 mg/kg/day based on increased liver weight at the LOEL (1.0 mg/kg/day). Toxic effects also included decreased thymus weight (3 mg/kg/day) and Increased hyperplasia of the forestomach, dilation of hair follicles, increased centrilobular hypertrophy of hepatocytes, increased hematopoietic cell proliferation in spleen, increased incidences of thymocyte necrosis, and increased incidences of splenic pigmentation (10 mg/kg/day).

**Table 27. Summary of Subchronic Studies for TCAB or TCAOB**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | 16-day (5 days/week); oral gavage exposure (5/sex/dose) (0, 12.5, 32, 80, 200, and 500 mg/kg/day TCAB) | (m/f) < 12.5 mg/kg/day | (m/f) = 12.5 mg/kg/day | ↑ hematopoietic cell proliferation (spleen) and ↓ thymus weight. | van Birgelen (1998a) |
| Rat | 13-week (5 days/week); oral gavage exposure (10/sex/dose) (0, 0.1, 1, 3, 10 and 30 mg/kg/day TCAB) | (m/f) < 0.1 mg/kg/day | (m/f) = 0.1 mg/kg/day | ↓ T4 levels. | van Birgelen (1998a); van Birgelen *et al.* (1999) |

**Table 27. Summary of Subchronic Studies for TCAB or TCAOB**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | 14-week (5 days/week); oral gavage exposure (10/sex/dose); (0, 0.1, 0.3, 1.0, 3.0, 10, 30 and 100 mg/kg/day TCAB) | (m/f) < 0.1 mg/kg/day | (m/f) = 0.1 mg/kg/day | ↓ body weight gain, decreased levels of total and free T4, ↑ relative and absolute right kidney weights, induction of EROD (liver and lung) and 7-PROD (liver) activities, ↑ relative and absolute liver weights, and ↑ relative and absolute spleen weights | NTP (2010) |
| Rat | 16-day (5 days/week); oral gavage exposure (5/sex/dose) (0, 12.5, 32, 80, 200, and 500 mg/kg/day TCAOB) | (m/f) < 12.5 mg/kg/day | (m/f) = 12.5 mg/kg/day | ↓ body weight gain, ↑ liver and lung weights, and ↓ thymus weight | van Birgelen (1998b) |
| Rat | 13-week (5 days/week); oral gavage exposure (10/sex/dose) (0, 0.1, 1, 3, 10 and 30 mg/kg/day TCAOB) | (m/f) < 0.1 mg/kg/day | (m/f) = 0.1 mg/kg/day | ↓ platelet counts, ↓ T4, ↓ epididymal spermatozoal motility | van Birgelen (1998b) |
| Rat | 120-day (5 days/week); dietary exposure (10/sex/dose) (0 and 1000ppm or 0 and 25 mg/kg/day TCAB) | (m/f) < 25 mg/kg/day | (m/f) = 25 mg/kg/day | ↓ body weight, aplastic anemia, ↑ P450 (liver), AHH (liver), glutamic-oxalacetic transamidase (blood) | Hsia *et al.* (1980) |
| Rat | 120-day (5 days/week); dietary exposure (10/sex/dose) (0 and 1000ppm or 0 and 24 mg/kg/day TCAOB) | (m/f) < 24 mg/kg/day | (m/f) = 24 mg/kg/day | ↓ body weight, aplastic anemia, ↑ liver weights, ↑ P450 (liver), AHH (liver), glutamic-oxalacetic transamidase (blood) activities, and ↑ spleen and testes weights | Hsia *et al.* (1980) |
| Mouse | 16-day (5 days/week); oral gavage exposure (5/sex/dose) (0, 1, 3.2, 10, 32, and 100 mg/kg/day TCAB) | (m/f) = 32 mg/kg/day | (m/f) = 100 mg/kg/day | ↑ hematopoietic cell proliferation (spleen) and ↑ incidences of thymic atrophy | van Birgelen (1998a) |
| Mouse | 13-week (5 days/week); oral gavage exposure (10/sex/dose) (0, 0.1, 1, 3, 10 and 30 mg/kg/day TCAB) | (m/f) = 0.1 mg/kg/day | (m/f) = 1 mg/kg/day | ↑ hyperplasia of the forestomach | van Birgelen, (1998a); van Birgelen *et al.* (1999) |

**Table 27. Summary of Subchronic Studies for TCAB or TCAOB**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Mouse | 16-day (5 days/week); oral gavage exposure (5/sex/dose) (0, 1, 3.2, 10, 32, and 100 mg/kg/day TCAOB) | (m/f) = 1 mg/kg/day | (m/f) = 3.2 mg/kg/day | ↑ liver weight and ↓ thymus weight. | van Birgelen (1998b) |
| Mouse | 13-week (5 days/week); oral gavage exposure (10/sex/dose) (0, 0.1, 1, 3, 10 and 30 mg/kg/day TCAOB) | (m/f) = 0.1 mg/kg/day | (m/f) = 1 mg/kg/day | ↑ liver weight. | van Birgelen (1998b) |

### *(v) Reproductive Toxicity*

#### v(a) Summary

The reproductive toxicity database for TCAB and TCAOB is comprised of one NTP study and one study reported in the open literature (Table 28). TCAB acted as a female reproductive toxicant in rats by causing reduced numbers of $F_1$ pups per litter and reduced pup bodyweights. TCAB also caused neurotoxic effects in rat pups including decreased landing foot splay, forelimb grip strength, and hindlimb grip strength. In the mouse, TCAB treatment led to a reduced number of pups at birth and weaning per dam.

#### v(b) Oral: Rat

NTP conducted a Reproductive Assessment by Continuous Breeding (RACB) study to assess the reproductive toxicity of TCAB over 2 generations in the rat (NTP, 2004). Adult SD rats (20 of each gender per dose group) were given 0, 1, 3, and 10 mg/kg by oral gavage. $F_0$ adults were continuously bred to produce $F_{1a-c}$ pups and also outbred (10mg/kg groups) with naïve animals. $F_{1c}$ pups were raised and continuously bred to produce $F_{2a-c}$ pups. The reproductive LOEL was 1 mg/kg/day based on reduced numbers of $F_1$ pups per litter and reduced pup bodyweights. Based on the results for outbreeding, TCAB acted as a female reproductive toxicant. Neurotoxic effects were observed in pups that included decreased landing foot splay, forelimb grip strength ( 3 mg/kg/day) and decreased hindlimb grip strength (10 mg/kg/day). Parental toxicity included dose-related decreases in body weight and food consumption (F0 and F1; 1 mg/kg) and the following microscopic findings at the high dose (10 mg/kg/day): liver bile duct epithelial proliferation and granuloma ($F_1$), minimal retention of Step 19 spermatids in the testes ($F_0$ and $F_1$), chronic nephropathy ($F_0$ and $F_1$), diffuse minimal hematopoietic cell proliferation in spleen ($F_0$), and lymphocytic depletion of thymus ($F_1$).

#### v(c)Oral: Mouse

An open-literature study was conducted to assess the oral reproductive toxicity of TCAOB in Swiss Webster mouse dams (4 per group) (Bleavins *et al.*, 1985b). TCAOB (0, 0.1, 1, and 10 ppm or

approximately 0, 0.01, 0.1, and 1 mg/kg/day) was given in the diet 14 days prior to mating until PND 28. In a separate experiment, weanling mice were given 40 ppm or 4 mg/kg/day TCAOB for 28 days for the assessment of cytogenetic end-points. The reproductive NOEL was 1 ppm (0.1 mg/kg/day) based on a reduced number of pups at birth and weaning per dam and a reduced litter mass (PND 0, 7, 14, 21, 28) at the LOEL (10 ppm or 1 mg/kg/day). The pup and parent NOEL were also 1 ppm (0.1 mg/kg/day) based on a reduced plaque forming response in pups and a reduced thymus weight in dams and pups at the LOEL (10 ppm or 1 mg/kg/day). No increase in the incidences of sister chromatid exchange or isochromatid breaks chromosome were observed in the spleen cells of mice at the high dose level (40 ppm or 4 mg/kg/day).

**Table 28. Summary of Reproductive Toxicity Studies for TCAB or TCAOB**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | RACB; oral gavage exposure (20/sex/dose) (0, 1, 3, and 10 mg/kg/day) | Parental Systemic and Reproductive < 1 mg/kg/day | Parental Systemic and Reproductive = 1 mg/kg/day | *Parental Systemic LOEL* ↓ body weight and food consumption *Reproductive LOEL* ↓ numbers of F1 pups per litter and ↓ pup body weight. | NTP (2004) |
| Mouse | Reproductive Toxicity; dietary exposure (4/dams/dose) (0, 0.1, 1, and 10 ppm or (m/f) 0, 0.01, 0.1, and 1 mg/kg/day) | Parental Systemic, Reproductive, and Pup = 0.1 mg/kg/day | Parental Systemic, Reproductive, and Pup = 1 mg/kg/day | *Parental Systemic and Pup LOEL* ↓ plaque forming response in pups and a ↓ thymus weight in dams and pups *Reproductive LOEL* ↓ number of pups at birth and weaning per dam and a ↓ litter mass | Bleavins *et al.* (1985b) |

### *(vi) Developmental Toxicity*

#### vi(a) Summary

The developmental toxicity database for TCAB and TCAOB is comprised of studies reported in the open literature. Four developmental effects were considered to be characteristic of TCAOB treatment in the mouse: cleft palate, kidney hydronephrosis, hydrops (i.e., an accumulation of fluid, or edema, in at least two fetal compartments), and fetal death with a sensitive period for exposure between GD 10 and 12.

#### vi(b) IP: Mouse

The developmental effects of TCAB or TCAOB treatment were reported in a series of three open-literature studies that were conducted to characterize the role of the AhR-mediated signaling. In the first study of the series, embryos from pregnant NMRI (+/+AhR) and DBA/2J (-/-AhR) mouse dams were transferred to same or cross strain dams on GD 3 (D'Argy *et al.*, 1984). The pregnant dams were next treated with TCAOB (8 mg/kg) by the IP route on GD 12 and killed on GD 16 or 17. DBA fetuses had no malformations even if they developed in NMRI dams while almost all NMRI fetuses suffered from cleft palate even if they developed in DBA dams. The DBA strain lacked Ahr loci and was considered insensitive to TCDD's Ahr-mediated actions. The results showed that sensitivity and responsiveness to the developmental toxicity of TCAOB is dependent on AhR.

In the second study of the series, NMRI (+/+AhR), C57BL (+/+AhR), DBA/2J (-/-AhR), and AKR/NBom (-/-AhR) mouse dams were in or out bred (crosses and back-crosses) (Hassoun *et al.*, 1984). The pregnant dams were then treated with TCAOB (6-10 mg/kg) by the IP route on GD 12 and killed on GD17. NMRI females X (NMRI X DBA F1 males) resulted in more incidences of cleft palate than NMRI males X (NMRI X DBA F1 females) suggesting a maternal factor to TCAOB teratogenicity likely based on differences in the inducability of placental enzymes under AHr control between the strains. Four developmental effects were considered to be characteristic of TCAOB treatment: cleft palate, kidney hydronephrosis, hydrops (i.e., an accumulation of fluid, or edema, in at least two fetal compartments), and fetal death. The sensitive period for palates and kidneys between GD 11-12 (palatal closure occurs on GD 14) while the sensitive periods for fetal death and hydrops were GD10 and GD12.

In the final study of the series, pregnant NMRI (+/+AhR) mouse dams were treated with D,L-α-diflouromethyl ornithine (DFMO) (100-300 mg/kg, IP) on GD11-12 and TCAOB (4 mg/kg) on GD11-12. The animals were killed on GD17 (Hassoun and Arif, 1988). The authors hypothesized that TCDD and its congener TCAOB inhibited programmed cell death in the apical palatal epithelium leading to increased incidences of cleft palate. Ornithine decarboxylase (ODC) is a critical enzyme with high activity in fetal and placental tissues that is required for the regulation the growth and differentiation required for palatal formation. Its selective inhibition by DMFO reduced the incidence of TCAOB-induced cleft palate confirming an AhR-mediated pleiotropic response that includes increased ODC activity. On the other hand, DMFO treatment had no effect on the incidence of TCAOB-induced fetal death suggesting and independent pathway (i.e., AhR mediated increases in AHH activity).

### *(vii) Genotoxicity*

#### vii(a) Summary

The genotoxicity database for TCAB and TCAOB is comprised of NTP studies and studies reported in the open literature (Table 29). TCAB was found to be mutagenic based on positive results for microbial mutation and DNA repair assays while both compounds were clastogenic based on positive results in the mammalian erythrocyte micronucleus test.

#### vii(b) In Vitro Mutagenicity

NTP conducted two *in vitro* bacterial mutagenesis studies using *S. typhimurium* strains TA97, 98, 100, 1535 and 1537 (TCAB only) with and without rat liver S9 activation to characterize the genotoxic potential of TCAB and TCAOB (van Birgelen, 1998a; van Birgelen, 1998b). The only positive results for TCAB were with TA97 and S9 activation. No positive results were obtained for TCAOB. Three open literature studies *in vitro* studies were also reported. The first was an *in vitro* bacterial mutagenesis study conducted using *S. typhimurium* strains TA 98, 100, 1530, 1535, 1537, 1538, 1532, 1950, 1975, 1978, and G 46 with and without rat liver S9 activation to characterize the genotoxic potential of TCAB (Gilbert *et al.*, 1980). Specific assays included plate incorporation (mutation) and bacterial fluctuation (mutation rate). TCAB was weakly positive in the latter. The second was an *in vitro* [$^{3}$H]Thymidine incorporation assay in SD rat hepatocytes characterize the ability TCAB to elicit unscheduled DNA synthesis (UDS) (Hsia and Kreamer, 1979b). TCAB was positive for UDS in the assay and, as such, a potential carcinogen. In the third study TCAB was cytotoxic to mouse embryo fibroblasts (C3H/10T1/2 cells)

causing large vacuoles in the perinuclear cytoplasm within 24 hours of first exposure while longer exposures led to transformation and loss of contact inhibition (Hsia *et al.*, 1977). In the same study, TCAB was found to be weakly mutagenic in a Salmonella assay with mammalian microsomal activation.

**Study Reference:** McMillan *et al.* (1988)
**Study Design and Results:** The genotoxicities of propanil, its metabolites, and structurally related species were tested in a series of *in vitro* assays. No mutagenic activity was observed for any compound (propanil, N-OH-propanil, 3,4-DCA, N-OH-3,4-DCA, N-OH-3,4-dichloroformanilide (DCFA), N-OH-3,4-dichloroacetanilide (DCAA), TCAB, or TCAOB) in a Salmonella typhimurium (TA97, TA98, TA100, and TA100) reversion assay with and without S-9 pre-activation (≤ 250 µg/plate). Although propanil, 3,4-DCA, N-OH-3,4-DCA, TCAB, and TCAOB were cytotoxic to CHO cells, they were not able to induce mutations under the conditions of the assay. Similarly, propanil, N-OH-propanil, 3,4-DCA, N-OH-3,4-DCA, 3,4-DCAA, N-OH-3,4- DCAA, TCAB, and TCAOB were not positive for UDS in rat hepatocytes although they were similarly cytotoxic (0.5-1000 µg/mL). A final experiment demonstrated that N-OH-3,4-DCA had very low binding to DNA relative to that for the positive control (N-hydroxy-2-aminofluorene (AAF)) at pH 5 or 7. The above results provide mechanistic support for the lack of genotoxicity observed for propanil and its N-hydroxylated metabolite species despite the superficial similarities to other N-hydroxylated aryl amines with known genotoxicity. The authors suggested that the basis for the above finding may be the negative induction and steric effects conferred by the two halogen groups.

### vii(c) In Vivo Clastogenicity

NTP also conducted two *in vivo* mammalian erythrocyte micronucleus test studies using *B6C3F1 mouse (10 of each gender per dose group)* to characterize the clastogenic potential of TCAB and TCAOB (van Birgelen, 1998a; van Birgelen, 1998b; Witt *et al.*, 2000). Mice were treated with TCAB or TCAOB at 0, 50, 100, 150, 200 mg/kg/day for 3 days ip (Acute) or 0, 0.1, 3, 10, and 30 mg/kg 5 days per week for 13 weeks by oral gavage (Subchronic). Subchronic treatment with TCAB and TCAOB resulted in significant, increases in micronucleated normochromatic erythrocyte (MNNCE) counts at 10 mg/kg/day while the results for acute treatment with either compound were negative. The genotoxicities of TCAB and TCAOB were demonstrated.

An open-literature study was conducted to assess the oral reproductive toxicity of TCAOB in Swiss Webster mouse dams (4 per group) (Bleavins *et al.*, 1985b). TCAOB (0, 0.1, 1, and 10 ppm or approximately 0, 0.01, 0.1, and 1 mg/kg/day) was given in the diet 14 days prior to mating until PND 28. In a separate experiment, weanling mice were given 40 ppm or 4 mg/kg/day TCAOB for 28 days for the assessment of cytogenetic end-points. The reproductive NOEL was 1 ppm (0.1 mg/kg/day) based on a reduced number of pups at birth and weaning per dam and a reduced litter mass (PND 0, 7, 14, 21, 28) at the LOEL (10 ppm or 1 mg/kg/day). The pup and parent NOEL were also 1 ppm (0.1 mg/kg/day) based on a reduced plaque forming response in pups and a reduced thymus weight in dams and pups at the LOEL (10 ppm or 1 mg/kg/day). No increase in the incidences of sister chromatid exchange or isochromatid breaks were observed in the spleen cells of mice at the high dose level (40 ppm or 4 mg/kg/day).

**Table 29. Summary of Summary of Genotoxicity Studies of TCAB and TCAOB**

| Test Type/System | Compound Tested | ± S9 | Results | References |
|---|---|---|---|---|
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA97, TA98, and TA100) | TCAB, TCAOB | + & - | All Negative | McMillan *et al.* (1988) |
| *In vitro* mutagenicity and cytotoxicity; Chinese hamster ovary cells (CHO) | TCAB, TCAOB | + & - | All Negative | McMillan *et al.* (1988) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; primary rat hepatocytes | TCAB, TCAOB | + & - | All Negative | McMillan *et al.* (1988) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA97, TA98, TA100, TA1535 and TA1537) | TCAB | + & - | Negative except TA97+S9 | van Birgelen (1998a) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA97, TA98, TA100, and TA1535) | TCAOB | + & - | Negative | van Birgelen (1998a) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA 98, 100, 1530, 1535, 1537, 1538, 1532, 1950, 1975, 1978, and G 46) | TCAB | + & - | Negative | Gilbert *et al.* (1980) |
| *In vitro* mutagenicity; Fluctuation (mutation rate); Salmonella typhimurium (TA 98, 100, 1530, 1535, 1537, 1538, 1532, 1950, 1975, 1978, and G 46) | TCAB | + & - | Positive | Gilbert *et al.* (1980) |
| *In vitro* mutagenicity; unscheduled DNA synthesis; rat hepatocytes | TCAB | NA | Positive | Hsia and Kreamer (1979b) |
| *In vitro* mutagenicity; reverse mutation; Salmonella typhimurium (TA98) | TCAB | + & - | TCAB: "Weak" positive for TA98 (+S9) | Hsia *et al.* (1977) |
| *In vitro* mutagenicity; loss of contact inhibition; mouse fibroblast cells (C3H/10T1/2) | TCAB | NA | Positive | Hsia *et al.* (1977) |
| *In vivo* Clastogenicity; mammalian erythrocyte micronucleus test (3-day); mice (10/sex/dose) | TCAB | NA | Negative | van Birgelen (1998a); Witt *et al.* (2000) |
| *In vivo* Clastogenicity; mammalian erythrocyte micronucleus test (13-week); mice (10/sex/dose) | TCAB | NA | Positive | van Birgelen (1998a); Witt *et al.* (2000) |
| *In vivo* Clastogenicity; mammalian erythrocyte micronucleus test (3-day); mice (10/sex/dose) | TCAOB | NA | Negative | van Birgelen (1998b); Witt *et al.* (2000) |
| *In vivo* Clastogenicity; mammalian erythrocyte micronucleus test (13-week); mice (10/sex/dose) | TCAOB | NA | Positive | van Birgelen (1998b); Witt *et al.* (2000) |
| *In vivo* Clastogenicity; splenic SCE and isochromatid breaks; mice (10/sex/dose) | TCAOB | NA | Negative | Bleavins *et al.* (1985b) |

### *(viii) Chronic Toxicity*

#### viii(a) Summary

The chronic toxicity database for TCAB is comprised of NTP animal studies and human population-based studies reported in the open literature (Table 30). Chronic occupational exposures to TCAB in pesticide manufacturing workers led to chronic health problems and hospitalizations. Symptoms consistent with TCAB toxicity included chloracne and biochemistry results consistent with liver toxicity. Rats exposed to TCAB in a 2 year study showed increased mortality, decreased body weight, and pathological changes to the lungs, liver, oral cavity, forestomach, adrenals, and thyroid gland. Mice exposed to TCAB in a 2 year study showed increased mortality and pathological changes to the lungs, forestomach, skin, urethra, spleen and lymph nodes. Clear evidence of carcinogenicity was reported based on increases in cystic keratinizing epithelioma in the lungs and gingival squamous cell carcinoma in the oral mucosa of rats and

on increases in epithelial carcinoma in the urethra and alveolar/bronchial adenoma and carcinoma in the lungs of mice.

### viii(b) Occupational Human Studies

In 1976, the health problems of workers at the Eagle River Chemical Plant in West Helena, Arkansas came to the attention of the Occupational Safety and Health Administration (OSHA) following a site visit and an inspection of plant records (Morse and Baker, 1977; Morse *et al.*, 1979; Kimbrough, 1980). The plant was used to manufacture propanil and methomyl. Ninety-two percent (92%) of plant personnel employed on August 9, 1976 (102 of 111) were enrolled in a health hazard assessment study involving a questionnaire and physical examination with blood and urine analyses (Morse and Baker, 1977; Morse *et al.*, 1979). The workers were mostly male (96%) with an average employment or exposure duration of 2 years and an average age of 29 years (Morse and Baker, 1977; Morse *et al.*, 1979). Approximately 6% of the workers were hospitalized annually because of illnesses attributed to workplace exposures while 6.9% reported chronic health problems (Morse and Baker, 1977; Morse *et al.*, 1979). Thirty-eight percent of the workers (38%) had chloracne consistent with exposures to TCAB (Morse and Baker, 1977; Morse *et al.*, 1979). On the other hand, 39% had elevated reticulocyte counts, 15% were anemic, and 5.9% were cyanotic consistent with exposures to propanil and 3,4-DCA (Morse and Baker, 1977; Morse *et al.*, 1979). The reported symptoms were primarily observed in workers staffing production, safety, maintenance, and laboratory areas (Morse and Baker, 1977; Morse *et al.*, 1979).

In another case reported in the open literature, in 1976 and 1977 workers at two adjacent plants that produced 3,4-DCA and Diuron in the United Kingdom (UK) developed “mild” cases of chloracne with lesions confined to the periorbital region, upper cheeks, and forehead (Scarisbrick and Martin, 1981). The combined workforce (approximately 90) was all male. The study investigators identified the by-products of the 3,4-DCA manufacturing process in the tarry distillation residues (i.e., TCAB and to a much lesser extent, TCAOB) as the causative agents. Exposure to either occurred through dermal contact with contaminated interior surfaces and equipment at the plant. As well, 3,4-DCA was detected in the air samples. Representatives of the Health Safety Executive, Employment Medical Advisory Service (HSEEMA) monitored the course of chloracne in the workers and collected blood specimens for biochemical analyses. High triglyceride levels and gamma glutamyl transferase (GGT) activity in many of the workers suggested that hyperlipidemia, a risk factor for ischemic heart disease (IHD) was an effect of exposure (Scarisbrick and Martin, 1981). As a result, a controlled study was undertaken in 1978 with 89 workers, of which 30 had chloracne, and a control group recruited from an engineering factory 50 miles distant (Scarisbrick and Martin, 1981). The subjects were grouped by age and exposed subjects were grouped by whether or not they had visible chloracne lesions and subgrouped based on alcohol consumption. Triglyceride and cholesterol levels, and to a lesser extent GGT activity, were elevated in exposed groups and the effects were enhanced with higher alcohol consumption. A follow-up study was conducted after 18 months to assess changes in worker health resulting from the company’s exposure mitigation measures (reduced atmospheric emissions, site clean-up, use of personal protective equipment (PPE), and improved personal hygiene) (Scarisbrick and Martin, 1981). Data from the initial medical consultation found that many of the workers had life-style risk factors for hyperlidemia and IHD including obesity, high alcohol intake, and heavy smoking. Individuals considered at high risk for IHD were advised on appropriate lifestyle modifications. All of the follow-up biochemistry values were within

normal ranges showing that the mitigation measures were most likely effective (Scarisbrick and Martin, 1981).

### viii(c) Oral: Rat

NTP conducted two studies to assess the chronic, oral toxicity and carcinogenicity of TCAB in the rat and in the mouse. In the first study, SD rats (50 of each gender per dose group) were treated with 0, 10, 30 and 100 mg/kg TCAB, 5 days per week for 2 years by oral gavage (NTP, 2010). The LOEL was 10 mg/kg/day based on increased mortality, decreased body weight, lung toxicity (e.g., increased incidences of histocytic cellular infiltration, pigmentation, alveolar epithelium bronchiolar metaplasia, and cystic keratinizing epithelioma), liver toxicity (e.g., hepatocyte hypertrophy, centrilobular degeneration, hepatocellular necrosis, pigmentation, fatty change, bile duct hyperplasia, oval cell hyperplasia, nodular hyperplasia, hematopoietic cell proliferation, eosinophilic focus, mixed cell focus, multinucleated hepatocytes, bile duct cyst, toxic hepatopathy, cholangiofibrosis and cholangiocarcinoma), oral toxicity (e.g., increased incidences of gingival squamous, keratinizing hyperplasia, and incidences of gingival squamous cell carcinoma in oral mucosa), forestomach toxicity (e.g., increased incidences of squamous cell carcinoma and epithelial hyperplasia), and adrenal toxicity (e.g., increased incidences of degeneration cytoplasmic vacuolization, and hyperplasia of zona fasciculate). Toxic effects also included increased incidences of follicular cell adenoma and follicular cell hypertrophy, hyperplasia, inflammation of the thyroid gland (30 mg/kg/day), and squamous cell papilloma to the mouth (100 mg/kg/day). The authors based clear evidence of carcinogenicity on the incidences of cystic keratinizing epithelioma in the lungs and incidences of gingival squamous cell carcinoma in the oral mucosa. A supporting open literature report detailing the histological analysis of the oral mucosa supports the view that TCAB caused the progression from hyperplastic and cystic lesions towards malignancy (Ramot *et al.*, 2012).

In the second study, B6C3F1 mice (50 of each gender per dose group) were treated with 0, 3, 10 and 30 mg/kg TCAB, 5 days per week for 2 years by oral gavage (NTP, 2010). The LOEL was 3 mg/kg/day based on lung toxicity (e.g., increased incidences of alveolar/bronchial adenoma and carcinoma), forestomach toxicity (e.g., increased incidences of hyperplasia at the limiting ridge, focal epithelial hyperplasia, and mucosal lymphoid cell infiltration), and dermal toxicity (e.g., increased incidences of chronic active inflammation, epidermal hyperplasia, and ulcers). Toxic effects also included increased mortality at 10 mg/kg/day, urethra toxicity (e.g., increased incidences of a rare and invasive transitional epithelial carcinoma, dilation and chronic active inflammation of the ureter, and transitional epithelial hyperplasia at 10 mg/kg/day), lung toxicity (e.g., increased incidences of cystic keratinizing epithelioma (CKE) at 30 mg/kg/day and chronic active inflammation at 10 mg/kg/day), forestomach toxicity (e.g., increased incidences of squamous cell carcinoma at 30 mg/kg/day), urethra toxicity (e.g., increased incidences of epithelial carcinoma, dilation and chronic active inflammation of the ureter, and transitional epithelial hyperplasia at 10 mg/kg/day), dermal toxicity (e.g., increased incidences of subcutaneous fibrosarcoma or malignant schwannoma at 30 mg/kg/day), and toxicity to the spleen and lymph nodes (e.g., increased incidences of malignant lymphoma at 10 mg/kg/day). NTP based the finding of clear evidence of carcinogenicity on increased incidences of epithelial carcinoma in the urethra and alveolar/bronchial adenoma and carcinoma in the lungs. Two supporting open literature reports describe the further characterization of the neoplastic tissues and the most likely carcinogenic pathways for each (Singh *et al.*, 2010; Bhusari *et al.*, 2014). The increased incidences of non-neoplastic urinary of genital lesions were likely related to the obstruction and inflammation caused by carcinomas and hyperplasia

(Singh *et al.*, 2010). TCAB may facilitate this process by inhibiting the age-related decline in epithelial growth factor receptor (EGFR) mediating subsequent proliferations through AHr signal path as both receptors are locally expressed (Singh *et al.*, 2010). Tp53 genetic mutations are common in urethral carcinomas while Kras mutations are common to pulmonary adenoma and carcinoma and both genes are often mutated in human cancer (Bhusari *et al.*, 2014). That TCAB caused mutations in Tp53 and Kras suggest the direct genotoxicity of the parent molecule or its metabolites or the possibly indirect genotoxicity of AhR mediated oxidative stress (i.e., the production of ROS by induced enzymes) (Bhusari *et al.*, 2014). On the other hand, both types of tumors had transition mutations in the TP53 gene suggesting that TCAB or its metabolites can target guanine of cytosine bases and that the resulting mutations can lead to carcinogenesis (Bhusari *et al.*, 2014).

**Table 30. Summary of Chronic NOEL and LOEL Values for TCAB**

| Species | Exposure | NOEL | LOEL | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Chronic Feeding and Carcinogenicity; 2-Year Oral Gavage (50/sex/dose) | <10 mg/kg/day | 10 mg/kg/day | ↑ mortality (m), ↓ body weight (m), ↑ histological signs of toxicity to lungs (m and f), liver (m and f), oral mucosa (m and f), forestomach (m and f), and adrenal glands (m and f) | NTP (2010) |
| Mouse | Chronic Feeding and Carcinogenicity; 2-Year Oral Gavage (50/sex/dose) | <3 mg/kg/day | 3 mg/kg/day | ↑ histological signs of toxicity to lungs (f), forestomach (m and f), and skin (m) | NTP (2010) |

***(ix) Immunotoxicity***

**ix(a) Summary**

The immunotoxicity database for TCAOB is comprised of two studies reported in the open literature. The immunotoxic effects of TCAOB treatment in the mouse and/or rat included thymic atrophy, decreases in the counts of white blood cells (WBC) after sheep blood immunization, T-helper lymphocytes, and plaque forming cells, and decreased serum antibody levels, peritoneal macrophage chemiluminescence, and bone marrow cellularity.

**ix(b) Oral: Mouse**

An open-literature study was conducted to assess the immunotoxicity of TCAOB in mice (Bleavins *et al.*, 1985a). In this study, pregnant Swiss Webster mouse dams (6 per group) were given TCAOB (40 ppm or 4 mg/kg/day) in diet given to day 28 and then killed. Major effects included thymic atrophy, decreased counts of white blood cells (WBC) after sheep blood immunization, T-helper lymphocytes, and plaque forming cells, and decreased serum antibody levels.

**ix(c) IP: Rat**

An open-literature study was conducted to assess the immunotoxicity of TCAOB in rats (Olson *et al.*, 1984). In this study, male weanling and adult SD rats (6 per group) were treated with TCAOB (25 mg/kg)

by the IP route on study days 1, 6, 11, and 16. The animals were then immunized on study day 13 and assayed for immunotoxicity on study day 17. Major systemic effects included decreased body, kidney, heart, and testis weights, and increased liver weights. Major immunotoxic effects included decreased thymic weight, decreased spleen plaque forming cell counts and function, peritoneal macrophage chemiluminescence, and bone marrow cellularity. The authors reported that, in general, weanlings were affected by TCAOB treatment to a greater extent than were adults.

# IV Risk Assessment

## A) Hazard Identification

DPR identified the highest doses where propanil produced no toxicologically significant effects (points of departure or PODs) and used them to delineate threshold doses for non-carcinogenic effects. The PODs used were either experimentally-determined (i.e. NOELs) or data-derived. Data-derived POD values were used whenever toxicologically significant effects were observed at the lowest treatment level in a study or when low-dose extrapolation could be used to provide a more accurate no effect level than relying on a study's pre-determined treatment levels. DPR used a benchmark dose (BMD) approach to derive all of the PODs used for this RCD.

The BMD approach used by DPR involved using Benchmark Dose Software (BMDS; version 2.6.0.86) to fit a family of related mathematical models to the entire data set of a toxicologically-significant and supportable endpoint in order to estimate the threshold of toxicity. An end-point was considered for BMD analysis if its data showed a robust dose response. The threshold response level for a given toxicologic effect was 1 standard deviation (SD) for continuous data or 5 to 10% for quantal data (USEPA, 2012a). Each model resulted in the generation of a corresponding BMD value as well as a BMDL value representing a 95% lower bound of the BMD and a point of departure (POD) for the observed effect.

In the BMD approach used by DPR, the goodness-of-fit was then evaluated for each model over the full dose range to select a "best" model for each effect's data set. The evaluation process was based on a hierarchical examination of (a) the results for statistical tests for goodness-of-fit, (b) the lowest Akaike Information Criteria (AIC) score for relative goodness-of-fit, (c) closeness of BMD and BMDL to each other and to nearest dose levels for goodness-of-fit and model dependence, (d) visual inspection of lines over data points for goodness-of-fit and toxicological plausibility, (e) and the magnitude of residuals for goodness-of-fit. Where more than one set of BMD and BMDL values was generated for a given study, the lowest value for each end-point was reported and used for the comparisons used in the hazard identification process.

DPR also used the UF approach whenever toxicologically significant effects were observed at the lowest treatment level in a study and when the effect dataset(s) did not support the application of a BMD approach. This approach was preferentially used for toxicity studies of metabolites and degradants of propanil since the resulting estimated no-effect level (ENEL) would only be used to support regulatory levels. In each case, the LOEL value for a given effect was divided by a UF to generate an ENEL. A UF of either 3 or 10 was used based on the severity of the observed effect.

All of the critical PODs used for this risk assessment are based on BMDLs.

Propanil is considered by US EPA to have "low acute toxicity" based on the following classifications: oral ($LD_{50}$ = 1080 mg/kg) (category III); dermal ($LD_{50}$ > 2000 mg/kg), inhalation ($LC_{50}$ = 6.1 mg/L), and primary skin irritation (category IV); primary eye irritation (II) (USEPA, 2003). US EPA established an oral chronic reference dose (RfD) of 0.009 mg/kg/day, which is defined as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used" (USEPA, 2011). The RfD is considered to be the maximum safe daily exposure level of propanil. US EPA placed propanil into the category of chemicals with "suggestive evidence of carcinogenic potential by all routes of exposure but not sufficient to assess human carcinogenic potential" in part based on the lack of evidence for mutagenicity (USEPA, 2003).

### 1) Acute Toxicity

Acute toxicity studies with human subjects were not available, so studies using animal models were used to determine toxicity threshold levels. A summary of acute POD levels is provided in Table 31 that includes all relevant studies reporting results for acute or short-term exposures (1 to 7 days) to propanil by all routes tested.

#### *(i) Acute Oral Toxicity*

Ten studies had sufficient information in their reports to be useful in the determination of an acute, oral regulatory end-point for propanil (Table 31).

The lowest acute oral POD ($BMDL_{1SD}$ = 8.9 mg/kg/day ) was established from a chronic toxicity and carcinogenicity study using rats at doses ranging from 9 to 154 mg/kg/day (Bellringer, 1994). Decreases in body weight gain were observed at all dose levels (m/f) ≥ 9/12 mg/kg/day) at the first measurement after 7 days of treatment (m/f: -13 to -98%/-7 to -43%). These decreases were statistically significant ($p < 0.05$ or 0.01) at 9 mg/kg/day for males and at 28 mg/kg/day for females. Body weight effects were not reversed over the course of the study. Significant and dose responsive decreases ($p < 0.05$ or 0.01) in food consumption were observed at 23 mg/kg/day in males during week 1. Corresponding increases in food utilization at all dose levels during week 1 suggested that the decreased body weight gain in the treated groups may have been the result of treatment and not an artifact of poor food palatability. DPR obtained BMD results by modeling Week 0-1, male body weight-gain data using a two-parameter polynomial model and a 1SD effect level ($BMD_{1SD}/BMDL_{1SD}$ = 10.6/8.9 mg/kg/day).

Acute (≤ 7 days) decreases in body weight and/or body weight gain were also observed in the following studies:

- 3 repeated-dose feeding studies using rats with NOEL values of (m/f) 16/19, 23/28, and 54/46 mg/kg/day.
- 1 developmental toxicity study using rabbits with an oral gavage route of administration and a NOEL value of 20 mg/kg/day.
- 1 dermal toxicity study using rats with a LOEL of 500 mg/kg/day.

The second lowest acute, oral no effects level ($BMDL_{1SD}$ = 14.1 mg/kg/day) was from a subchronic feeding study specifically designed to assess the acute hematologic toxicity of propanil. This study used rats and doses ranging from 25 to 67 mg/kg/day (O'Neill, 2002). Dose responsive increases in metHb levels were observed at all dose levels during treatment days 1-7:

- Day 1 (m/f: +60 to 100%/+75 to 150%)
- Day 5 (m/f: +67 to 200%/+117 to 450%) (m /f: $p < 0.01$ at ≥ 25/28 mg/kg/day)
- Day 7 (m/f: +33 to144%/+ 125 to 400%) (m/f: $p < 0.01$ at ≥ 41/28 mg/kg/day)

DPR obtained BMD results by modeling Day 5, male metHb level data using an exponential 4 model and a 1 SD effect level ($BMD_{1SD}/BMDL_{1SD}$ = 16.6/14.1 mg/kg/day) (see BMD Outputs in Appendices).The formation of metHb and the development of methemoglobinemia and hemolytic anemia are considered to be the results of propanil's best-characterized toxic mode of action.

**Conclusion**

The $BMDL_{1SD}$ = 14.1 mg/kg/day from a subchronic feeding study in rats that had increased blood metHb levels at day 5 (O'Neill, 2002) was selected as the acute, oral POD for propanil. Support for the selection of this POD over the POD for body weight gain included:

- Increased blood metHb levels with propanil treatment are an effect consistent with propanil's best-characterized toxic mode of action (MOA). While decreased BW and BWG are supported by the data and regarded as indicators of general health, the corresponding MOA is not understood.
- Increased blood metHb levels were observed within 1 day of initial exposure and were persistent over the duration of study supporting its selection as a sign of acute toxicity. The effect was supported by related hematology end-points in other feeding studies with acute, subchronic, and chronic end-points.
- Corresponding metHb data were amenable to a robust modeling approach.
- A BMD approach and a 1SD BMR were also used by IRIS to derive an oral RfD based on metHb levels for nitrobenzene (USEPA, 2009).
- The selected POD was similar in magnitude to the lowest acute, oral POD in the propanil database (8.9 mg/kg/day).
- The selected POD is likely to be protective of other acute effects (hematologic, developmental, and immunotoxic) of propanil.

### *(ii) Acute Inhalation Toxicity*

Only one acute, inhalation toxicity was available for consideration (Durando, 2010c) (Table 31). The LOEL of 341 mg/kg was based on clinical observations including irregular respiration, hypoactivity, and/or hunched posture, ocular and nasal discharge, and facial staining in all rats upon removal from chamber. This study was designed to determine the limit of toxicity with a single, high dose level so subtle signs of toxicity may not have been noted. There were no mortalities for the study and an $LC_{50}$ could not be estimated.

**Conclusion**

There is insufficient information from route-specific studies to accurately estimate the acute toxicity of inhaled propanil. In cases like this one, DPR routinely assumes a default bioavailability of 100%. Consequently, the $BMDL_{1sd}$ value of 14.1 mg/kg/day used to characterize acute, oral risk was selected to characterize the acute inhalation risk of propanil.

***(iii) Acute Dermal Toxicity***

**Conclusion**

The data in the acute dermal database are of limited value for estimating a lower threshold of dermal toxicity because each of the available studies was conducted with a single, high dose level in order to estimate the dermal $LD_{50}$. Consequently, the $BMDL_{1sd}$ value of 14.1 mg/kg/day used to characterize acute, oral risk was selected to characterize the acute dermal risk of propanil.

**Table 31. Summary of Acute POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Acute Oral; gavage; (5/sex/dose) (1 dose: 750, 1080, and 1555 mg/kg) | < 750 mg/kg | 750 mg/kg | ↑ incidences of mortality, clinical signs, dark red adrenal glands, kidneys, reddened cortico-medullary junction, stomach areas, intestinal contents, urinary bladder contents, and kidneys with dilated pelvis and white precipitate. | Naas (1989b) |
| Rat | Acute Oral; gavage; (5/sex/dose) (1 dose: 500, 1250, 2500 and 5000 mg/kg) | < 500 mg/kg | 500 mg/kg | ↑ incidences of mortality, clinical signs, red lungs, discolored liver, and/or red/black GI tract, and a urinary bladder filled with pink fluid. | Chang *et al.* (1999c) |
| Rat | 30-Day Feeding; 17-day treatment(10/sex/dose) (0, 300, 500, 700 ppm or (m/f) 0/0, 25/28, 41/41, and 57/67 mg/kg/day) | $BMDL_{1SD}$ = 14.1 mg/kg/day | $BMD_{1SD}$ = 16.5 mg/kg/day | ↑ metHB levels (m) (Days 5). | O'Neill (2002) |
| Rat | 3-Month Feeding (10/sex/dose) (0, 0.01, 0.033, 0.1, 0.33, 1, and 5 ppm or (m/f) 0/0, 5/4, 19/15, 54/46, 169/148, 460/491 and 2632/2268 mg/kg/day) | (m/f) = 54/46 mg/kg/day | (m/f) = 169/148 mg/kg/day | ↓ body weight (m and f) (week 1) | Larson (1961e); Ambrose *et al.* (1972) |
| Rat | 13-Week Feeding (5/sex/dose) (0, 300, 1000, 2000, and 4000 ppm or (m/f) 0/0, 23/28, 76/93, 151/184, and 318/364 mg/kg/day) | (m/f) = 23/28 mg/kg/day | (m/f) = 76/93 mg/kg/day | ↓ body weight gain and ↑ food conversion (m and f) (week 1) | Billington (1992) |

**Table 31. Summary of Acute POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Oral Immunotoxicity; 29-day Feeding exposure (10/sex/dose) (0, 50, 200, and 600 ppm or (m/f) 0/0, 4/5, 16/19, and 48/56 mg/kg/day) | (m/f) = 16/19 mg/kg/day | (m/f) = 48/56 mg/kg/day | ↓ body weight gain (m and f) (days 0-3 and days 0-7) | Padgett (2007) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{1SD}$ = 8.9 mg/kg/day | $BMD_{1SD}$ = 10.6 mg/kg/day | ↓ body weight gain (m) (week 0-1) | Bellringer (1994) |
| Mouse | 2-Week Feeding (5/sex/dose) (0, 400, 650, 900, and 1150 ppm or (m/f) 71/98, 120/155, 166/238, and 200/266 mg/kg/day) | (m/f) < 2749/2769 mg/kg/day | (m/f) = 15899/18799 mg/kg/day | ↓ body weight (m and f) (week 1) | Didonato and Cruszan (1979) |
| Mouse | Cytogenetic Toxicity; Oral Gavage; 1 or 5 doses (24 or 8 males/dose) (0, 26.5, 106, and 265 mg/kg) | (m) = 26.5 mg/kg | (m) = 106 mg/kg | ↓ motor activity and piloerection | O'Neill *et al.* (1983) |
| Rabbit | Developmental Toxicity; Oral Gavage; 13 doses (20 does/dose) (0, 4, 20, and 100 mg/kg) | Maternal = 20 mg/kg/day | Maternal = 100 mg/kg/day | ↓ body weight (GD 6-12) and ↑ incidence(s) of blood in cage pan (1 animal on GD 7 and 1 animal on GDs 7 and 8); animals later died on GD 13 and 16 | Florek (1980); O'Neill, (1993) |
| Rat | Acute Dermal (5/sex/dose) (1 dose: 5000 mg/kg) | < 5000 mg/kg | 5000 mg/kg | ↓ body weight | Durando (2010a) |
| Rabbit | Acute Dermal (5/sex/dose) (1 dose: 2000 mg/kg | < 2000 mg/kg | 2000 mg/kg | ↑ incidence of red material around mouth, clear ocular discharge, erythema and edema, and open sore(s) on abdomen. | Naas (1989a) |
| Rat | Acute Inhalation (5/sex/dose) (1 dose: 341 mg/kg) | < 2.13 mg/L (< 341 mg/kg) | 2.13 mg/L (341 mg/kg) | ↑incidence of ocular and nasal discharge, irregular respiration, hypoactivity, and/or hunched posture, and facial staining. | Durando (2010c) |

### 2) Subchronic Toxicity

A summary of subchronic POD levels is provided in Table 32 and includes all relevant studies that reported results for subchronic exposures (~1 to 13 weeks) by all routes tested.

### *(i) Subchronic Oral Toxicity*

Fourteen studies are included in the subchronic, oral toxicity database for propanil (Table 32).

The lowest subchronic oral POD considered ($BMDL_{1SD}$ = 3.0 mg/kg/day) was from a 13-week, subchronic toxicity study using mice with doses that ranged from 71 to 266 mg/kg/day (Tompkins, 1993b). MetHb levels were increased for both sexes in all treatment groups (Week 13):

- Males: +1600 to 5333% or +16 to 53-fold ($p < 0.01$ at ≥ 120 mg/kg/day)
- Females: +1150 to 4500% or +12 to 45-fold ($p < 0.01$ at ≥ 155 mg/kg/day)

Signs of splenic toxicity were also apparent at all dose levels ((m/f) ≥71/98 mg/kg/day) including increased absolute and relative organ weights and increased incidences of splenic hemosiderin. All of these effects were consistent with the formation of metHb and the onset of hemolytic anemia.

DPR obtained BMD results by modeling Week 13, male metHb level data using a linear model and a 1 SD effect level ($BMD_{1SD}/BMDL_{1SD}$ = 4.6/3.0 mg/kg/day).

The second lowest subchronic oral POD level ($BMDL_{1SD}$ = 5.0 mg/kg/day) was from a 2-year, chronic toxicity and carcinogenicity study using rats with doses that ranged from 9 to 145 mg/kg/day (Bellringer, 1994). MetHb levels were increased for both sexes in all treatment groups (Week 13):

- Males: +7 to 84% ($p < 0.01$ at ≥ 31 mg/kg/day)
- Females: +34 to 107% ($p < 0.01$ at ≥ 14 mg/kg/day)

Dose responsive changes for several related hematologic parameters during Week 13 were also noted including decreased red cell counts, decreased Hb levels, and decreased PCV values. All of the above effects were consistent with the formation of metHb and the onset of hemolytic anemia.

DPR obtained BMD results by modeling Week 13, female metHb level data using the Hill model and a 1 SD effect level ($BMD_{1SD}/BMDL_{1SD}$ = 7.8/5.0 mg/kg/day) (see BMD Outputs in Appendices). BMD results were also obtained by modeling Week 13, male metHb level data using linear and polynomial (2) models and a 1 SD effect level ($BMD_{1SD}/BMDL_{1SD}$ = 15.5/11.2 mg/kg/day).

The formation of metHb and development of methemoglobinemia and hemolytic anemia are considered to be the results of propanil's best-characterized toxic mode of action. Changes in hematologic parameters consistent with propanil-mediated hematologic toxicity were also observed in the following studies with subchronic end-points:

- 3 subchronic feeding studies using rats and with NOEL values of (m/f) 11/13, 19/15, and 23/28 mg/kg/day (Larson, 1961e; Ambrose *et al.*, 1972; Billington, 1992; Bellringer, 1994; Stump, 1998).
- 1 subchronic feeding study using rats and with a $BMDL_{1SD}$ of 14.4 mg/kg/day (Day 21) (O'Neill, 2002)

- 1 subchronic feeding study using mice with a $BMDL_{1SD}$ value of 3 mg/kg/day (Tompkins, 1993b).
- 3 feeding studies (2 subchronic and 1 chronic) using dogs with LOELs ranging from 5 to 57 mg/kg/day (Tompkins, 1992; Tompkins, 1993c; Tompkins, 1993a).

**Conclusion**

The $BMDL_{1SD}$ = 5.0 mg/kg/day from a chronic toxicity study in rats based on the blood metHb level endpoint (Bellringer, 1994) was selected as the critical POD for evaluating subchronic oral exposures to propanil based on the following:

- Corresponding data were amenable to a robust, modeling approach.
- Increased blood metHb levels with propanil treatment were consistent with propanil's best-characterized toxic mode of action.
- The selected POD level was supported by a $BMDL_{1SD}$ value of 3 mg/kg/day for hematologic effects in the mouse but with less BMD model dependence.
- A BMD approach and a 1SD BMR were also used by IRIS to derive an oral RfD based on metHb levels for nitrobenzene (USEPA, 2009).
- The selected POD is likely protective of systemic (including hematologic), developmental, and immunotoxic effects of propanil.
- The selected POD was over 3-fold lower than the lowest subchronic POD for putative propanil-mediated endocrine disruption ($BMDL_{1SD}$ = 18 mg/kg/day; delay of balanopreputial separation (Stump, 1998)).

***(ii) Subchronic Inhalation Toxicity***

**Conclusion**

There are no subchronic studies of the inhalation toxicity of propanil. In the absence of such data, it is DPR practice to assume a default of 100% absorption. Consequently, the $BMDL_{1SD}$ = 5.0 mg/kg/day used to characterize the subchronic, oral risk was selected to characterize the subchronic risk of propanil exposure by inhalation.

***(iii) Subchronic Dermal Toxicity***

**Conclusion**

There are no acceptable subchronic studies of the dermal toxicity of propanil. Consequently, the $BMDL_{1SD}$ = 5.0 mg/kg/day used to characterize the subchronic, oral risk was selected to characterize the subchronic risk of propanil dermal exposure.

**Table 32. Summary of Subchronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | 3-Month Feeding (10/sex/dose) (0, 0.01, 0.033, 0.1, 0.33, 1, and 5 ppm or (m/f) 0/0, 5/4, 19/15, 54/46, 169/148, 460/491 and 2632/2268 mg/kg/day) | (m/f) = 19/15 mg/kg/day | (m/f) = 54/46 mg/kg/day | ↑ relative spleen weight (f), ↑ neutrophil counts (f), and ↓ Hb levels (m). | Larson (1961e); Ambrose *et al.*, (1972) |
| Rat | 13-Week Feeding (5/sex/dose) (0, 300, 1000, 2000, and 4000 ppm or (m/f) 0/0, 23/28, 76/93, 151/184, and 318/364 mg/kg/day) | (m/f) = 23/28 mg/kg/day | (m/f) = 76/93 mg/kg/day | ↓ body weight (m and f), ↓ food consumption (m and f), and changes to hematologic parameters including Hct, Hb levels, and RBC counts (f) | Billington, (1992) |
| Rat | 2-Generation Reproduction; dietary exposure (30/sex/dose) (0, 60, 150, and 600 ppm or (m/f) 0/0, 4/5, 11/13, and 43/51 mg/kg/day) | Parental Systemic, and Reproductive: (m/f) = 11/13 mg/kg/day<br><br>Pup: $BMDL_{1SD}$ =18 mg/kg/day | Parental Systemic and Reproductive (m/f) = 43/51 mg/kg/day<br><br>Pup: $BMD_{1SD}$ = 25 mg/kg/day | *Parental Systemic LOEL*<br>↓ body weight (m and f), ↑ absolute and/or relative (to body or brain) spleen (m and f), kidneys (m), testes (m), adrenal gland (m and f), ovaries (f), brain (m and f), epididymis (m), and seminal vesicle/coagulating gland (m) weights, and an ↑ incidence and severity of splenic hemosiderosis (m and f).<br>*Reproductive LOEL*<br>↓ sperm counts (m)<br>*Pup LOEL*<br>Delay of balanopreputial separation (m)[a]. | Stump (1998) |
| Rat | 3-Generation Reproduction; Dietary exposure (20/sex/dose) (0, 100, 300, and 1000 ppm or 0, 5, 15, 50 mg/kg/day) | Parental Systemic, Reproductive, and Pup = 50 mg/kg/day | Parental Systemic, Reproductive, and Pup > 50 mg/kg/day | Parental Systemic, Reproductive, and Pup LOELs not determined | Borzelleca *et al.* (1966) |
| Rat | Developmental Toxicity; Oral Gavage; 10 doses (25 dams/dose) (0, 0.8, 4, 20, and 100 mg/kg/day) | Maternal and Developmental = 100 mg/kg/day | Maternal and Developmental > 100 mg/kg/day | No effects observed at any dose for either dams or fetuses | Gallo (1980); Ruckert (1999) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{1SD}$ = 5.0 mg/kg/day | $BMD_{1SD}$ = 7.8 mg/kg/day | ↑ metHb levels (f) (Week 13) | Bellringer (1994) |

**Table 32. Summary of Subchronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Oral Immunotoxicity; 29-day Feeding exposure (10/sex/dose) (0, 50, 200, and 600 ppm or (m/f) 0/0, 4/5, 16/19, and 48/56 mg/kg/day) | Systemic (m/f) = 16/19 mg/kg/day Immunotoxicity (m/f) = 48/56 mg/kg/day | Systemic (m/f) = 48/56 mg/kg/day Immunotoxicity (m/f) > 48/56 mg/kg/day | *Systemic LOEL* ↓ body weight and body weight gain (m and f), signs of anemia (f) | Padgett (2007) |
| Rat | 30-Day Feeding; 17-day treatment(10/sex/dose) (0, 300, 500, 700 ppm or (m/f) 0/0, 25/28, 41/41, and 57/67 mg/kg/day) | $BMDL_{1SD}$ = 14.4 mg/kg/day | $BMD_{1SD}$ = 17.2 mg/kg/day | ↑ metHB levels (m) (Day 21) | O'Neill (2002) |
| Mouse | 3-Month Feeding (10/sex/dose) (0, 25.0, 200.0, 1600.0, and 12800.0 ppm or (m/f) 0/0, 7/10, 49/78, 442/566, and 5325/6467 mg/kg/day) | (m/f) = 49/78 mg/kg/day | (m/f) = 442/566 mg/kg/day | ↑ liver and spleen weights and ↑ incidence of liver lesions (m and f) | McLaughlin (1983) |
| Mouse | 13-Week Feeding (10/sex/dose) (0, 400.0, 650.0, 900.0, and 1150.0 ppm or (m/f): 0/0, 71/98, 120/155, 166/238, and 200/266 mg/kg/day) | $BMDL_{1SD}$ = 3.0 mg/kg/day | $BMD_{1SD}$ = 4.6 mg/kg/day | ↑ metHb levels (m) (Week 13) | Tompkins (1993b) |
| Dog | 13-Week Feeding (2/sex/dose) (0, 1000, 5000, 10,000, and 20,000 or 0, 45, 225, 450, and 900 mg/kg/day | (m/f) < 45 mg/kg/day | (m/f) = 45 mg/kg/day | ↓ body weight and body weight gain (m and f), and changes to hematology (m) and serum biochemistry (m and f) | Tompkins (1992) |
| Dog | 8-Week Feeding (2/sex/dose) (0, 1600, 2800, and 4000 or (m/f) 0/0, 57/44, 93/99, and 114/81 mg/kg/day | (m/f) < 57/44 mg/kg/day | (m/f) = 57/44 mg/kg/day | ↑ metHb levels | Tompkins (1993a) |
| Dog | Chronic Feeding and Carcinogenicity; One-year dietary exposure (4/sex/dose) (0, 200, 600, and 3200 ppm or (m/f) 0/0, 5/6, 45/42, and 79/85 mg/kg/day). | (m/f) < 5/6 mg/kg/day | (m/f) = 5/6 mg/kg/day | ↑ metHb levels (m and f) (Week 12) | Tompkins (1993c) |
| Rabbit | Developmental Toxicity; Oral Gavage; 13 doses (20 does/dose) (0, 4, 20, and 100 mg/kg) | Maternal = 20 mg/kg/day Developmental = 100 mg/kg/day | Maternal = 100 mg/kg/day Developmental > 100 mg/kg/day | *Maternal LOEL* ↑ mortality and ↓ body weight change | Florek (1980); O'Neill (1993) |

**Table 32. Summary of Subchronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rabbit | 21-Day Dermal (5/sex/dose) (0, 250, 500, and 1000 mg/kg/day) | (m/f) = 1000 mg/kg/day | (m/f) >1000 mg/kg/day | No effects observed at any dose | Dykstra and Gardner (1991) |

[a]Subchronic PODs for putative propanil-mediated subchronic endocrine disruption.

### 3) Chronic Toxicity

A summary of chronic POD levels is provided in Table 33 and includes 5 studies that reported results for chronic exposures (~52 to 104 weeks) to propanil in the rat, mouse, and dog. Studies of the chronic inhalation and dermal toxicity of propanil were not available so oral studies were used to define the threshold of propanil toxicity for risk assessment purposes.

The lowest chronic, oral no effects level ($BMDL_{10}$ = 1.5 mg/kg/day) was from a 2-year chronic toxicity and oncogenicity study using rats at doses that ranged from 9 to 145 mg/kg/day (Bellringer, 1994). Increased incidences of splenic hemosiderosis (total) were observed in males at all dose levels by Week 104:

- Males: +24 to 62% ($p < 0.01$ or 0.001 at ≥ 9 mg/kg/day)

Additional, statistically significant dose-responsive signs of splenic toxicity in the same study included organ enlargement and increased absolute and relative spleen weights. Hemosiderin deposition was also observed in kidney proximal convoluted tubular epithelium in main group males and females with significance ($p < 0.001$) at (m/f) 88/38 mg/kg/day ($p < 0.001$). The changes to the above hematologic, splenic, and kidney parameters were consistent with the treatment related formation of metHb.

DPR obtained BMD results by modeling male total spleen hemosiderosis data using a log-logistic model and a 10% extra risk effect level ($BMD_{10}/BMDL_{10}$ = 2.3/1.5 mg/kg/day) (see BMD Outputs in Appendices). BMD results were also obtained for the following related endpoints in the same study (Table 33):

- Increased metHB levels (Week 104 (m)): $BMD_{1SD}/BMDL_{1SD}$ = 15.3/8.9 mg/kg/day)
- Spleen enlargement (Week 52 (m)): $BMD_{10}/BMDL_{10}$ = 36.0/18.9 mg/kg/day)
- Kidney hemosiderosis (Week 52 (m)): $BMD_{10}/BMDL_{10}$ = 8.4/5.9

Similar patterns of chronic splenic toxicity were also observed in the following chronic toxicity studies:

2-year chronic toxicity and carcinogenicity feeding study using mice (Tompkins, 1994):

- Increased metHb levels (Week 52 (f) $BMD_{1SD}/BMDL_{1SD}$ = 16.8/10.8 mg/kg/day)
- Increased spleen weights (m/f) (≥ 75/89 mg/kg/day)
- Increased Heinz Body counts (m) (≥ 75 mg/kg/day)
- Increased incidences of malignant lymphoma of the spleen (f) (174 mg/kg/day)

2-year chronic toxicity and carcinogenicity feeding study using mice (Weatherholz, 1983):

- Increased hemosiderin deposition in spleen (m/f) (≥ 26/32 mg/kg/day)

1-year chronic toxicity feeding study using dogs (Tompkins, 1993c):

- Changes to hematologic parameters (m/f) (≥ 5/6 mg/kg/day)
- Increased Heinz Body counts (m/f) (≥ 5/6 mg/kg/day)
- Increased Howell-Jolly Body counts (m/f) (≥ 5/6 mg/kg/day)
- Increased incidences of hemosiderosis of RE cells (m/f) (≥ 5/6 mg/kg/day)

The second lowest chronic, oral no effects level ($BMDL_{10}$ = 3.1 mg/kg/day) was from a 2-year chronic toxicity and oncogenicity study using rats and doses that ranged from 9 to 145 mg/kg/day (Bellringer, 1994). Increased incidence of pericholangitis (total) was observed at all dose levels:

- Males: +8-60% ($p < 0.001$ at ≥ 28 mg/kg/day)
- Females: +10-72% ($p < 0.01$ at ≥ 38 mg/kg/day)

The hepatotoxicity of propanil is supported by statistically significant and dose responsive increases in the total incidences of bile duct hyperplasia (m/f) (28/38 mg/kg/day) and granulomatous inflammation (m/f) (88/38 mg/kg/day). DPR obtained BMD results by modeling Week 104, male total liver pericholangitis data using a log-logistic model and a 10% extra risk effect level ($ED_{10}/BMDL_{10}$ = 7.3/3.1 mg/kg/day).

BMD results were also obtained for the following related endpoints in the same study (included in Table 33):

- Increased liver bile duct hyperplasia (Total (f): $BMD_{10}/BMDL_{10}$ = 9.6/4.9 mg/kg/day)
- Increased liver granulomatous inflammation (Total (f): $BMD_{10}/BMDL_{10}$ = 13.5/10.4 mg/kg/day)

Taken together, the above liver endpoints are consistent with a pattern of propanil toxicity to the liver that is initiated by the proximal hydrolysis of propanil and activation of 3,4-DCA by liver aryl acylamidase and CYP450 subsequently damaging to hepatocytes.

**Conclusion**

$BMDL_{10}$ = 1.5 mg/kg/day from the 2-year chronic feeding and carcinogenicity study in rats.

- Lowest chronic POD in database.
- Corresponding data was amenable to a robust, modeling approach.
- Increased splenic hemosiderosis with propanil treatment was consistent with propanil's best-characterized toxic mode of action.
- Supported by the incidences of spleen toxicity in 3 chronic studies using mice and dogs.
- Protective of systemic (including hematologic), developmental, and immunotoxic effects of propanil.

- 7-fold lower than the lowest chronic POD for putative propanil-mediated chronic endocrine disruption in the same study ($BMDL_{10}$ = 11.2 mg/kg/day; reduced secretions in seminal vesicles (Bellringer, 1994)).
- The $BMDL_{10}$ was based on one of the same study end-points used by US EPA as the threshold for chronic toxicity.

**Table 33. Summary of Chronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 3.1 mg/kg/day | $ED_{10}$ = 7.3 mg/kg/day | Toxicity to liver: ↑ pericholangitis (Total) (m) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 4.9 mg/kg/day | $BMD_{10}$ = 9.6 mg/kg/day | Toxicity to liver: ↑ bile duct hyperplasia (Total) (m) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 10.4 mg/kg/day | $BMD_{10}$ = 13.5 mg/kg/day | Toxicity to liver: ↑ granulomatous inflammation (Total) (f) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{1SD}$ = 8.9 mg/kg/day | $BMD_{1SD}$ = 15.3 mg/kg/day | ↑ metHb levels (Week 104) (m) | Bellringer (1994) |

**Table 33. Summary of Chronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 1.5 mg/kg/day | $BMD_{10}$ = 2.3 mg/kg/day | Toxicity to spleen: ↑ hemosiderosis (Total) (m) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 18.9 mg/kg/day | $BMD_{10}$ = 36.0 mg/kg/day | Toxicity to spleen: enlargement (Week 52) (m) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 5.9 mg/kg/day | $BMD_{10}$ = 8.4 mg/kg/day | Toxicity to kidney: ↑ hemosiderosis (Week 52) (m) | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{1SD}$ = 37.5 mg/kg/day | $BMD_{1SD}$ = 47.4 mg/kg/day | Toxicity to testes: ↑ relative weight (Week 52) (m) [a] | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 19.6 mg/kg/day | $BMD_{10}$ = 25.6 mg/kg/day | Toxicity to testes: ↑ focal interstitial hyperplasia (Total) (m) [a] | Bellringer (1994) |

**Table 33. Summary of Chronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 15.1 mg/kg/day | $BMD_{10}$ = 35.8 mg/kg/day | Toxicity to epididymides: ↑ incidence of absent spermatozoa (Total) (m) [a] | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 11.2 mg/kg/day | $BMD_{10}$ = 23.1 mg/kg/day | Toxicity to seminal vesicles: ↓ secretions (Total) (m) [a] | Bellringer (1994) |
| Rat | Chronic Feeding and Carcinogenicity; 2-year dietary exposure (50/sex/dose) (0, 200, 600, and 1800 ppm or (m/f) 9/11.5, 27.7/38.3, and 88/145 mg/kg/day) | $BMDL_{10}$ = 32.2 mg/kg/day | $BMD_{10}$ = 58.2 mg/kg/day | Toxicity to prostate gland: ↑ Atrophy (Total) (m) [a] | Bellringer (1994) |
| Mouse | Chronic Feeding and Carcinogenicity; Two-year dietary exposure (80/sex/dose) (0, 500, and 1000 ppm or (m/f) 75/89, and 150/174 mg/kg/day) | $LED_{1SD}$ = 5.2 mg/kg/day | $ED_{1SD}$ = 8.1 mg/kg/day | ↑ metHb levels (Week 104) (f) | Tompkins (1994) |
| Mouse | Chronic Feeding and Carcinogenicity; Two-year dietary exposure (66 (controls) or 80/sex/dose) 0, 0, 5, 30, 180 and 180 ppm or (m/f) 0/0, 0/0, 0.71/0.88, 4.39/5.35, 26.1/32.4, and 26.2/32.4 mg/kg/day). | (m/f) = 4/5 mg/kg/day | (m/f) = 26/32 mg/kg/day | ↑ incidence of hemosiderin deposition in the spleen (m and f) | Weatherholz (1983) |

**Table 33. Summary of Chronic POD Values for Propanil**

| Species | Exposure | NOEL/BMDL | LOEL/BMD | Toxic Effects at LOEL | References |
|---|---|---|---|---|---|
| Dog | Chronic Feeding; One-year dietary exposure (4/sex/dose) (0, 200, 600, and 3200 ppm or (m/f) 0/0, 5/6, 45/42, and 79/85 mg/kg/day). | (m/f) < 5/6 mg/kg/day | (m/f) 5/6 mg/kg/day | Changes to hematologic parameters including ↑ metHb levels, ↓ RBC counts, Hb levels, and hematocrit values, ↑ incidence of Heinz Bodies and hemosiderosis (m and f) | Tompkins (1993c) |
| Dog | Chronic Feeding; One-year dietary exposure (2/dose) (0, 100, 600, and 3000 or 4000 ppm or 0, 2.5, 15, and 75 or 100 mg/kg/day). | (m/f) = 15 mg/kg/day | (m/f) = 100 mg/kg/day | ↓ body weight and pathological changes to the kidneys (m and/or f) | Ambrose *et al.* (1972) |

[a]Chronic PODs for putative propanil-mediated chronic endocrine disruption.

**4) Oncogenicity Weight of Evidence**

Two tumor types were increased with dietary propanil treatment in the rat: benign testicular interstitial tumors and hepatocellular adenomas (Bellringer, 1994). Tumors that originate in the interstitial tissue are the most frequently observed spontaneous neoplasms in the rat testis. The testicular interstitium is primarily made up of perivascular Leydig cells whose main task is the LH and LH-releasing hormone (LHRH)-mediated production of testosterone (McConnell *et al.*, 1992). Disruption of testosterone signaling leading to increased pituitary LHRH or LH secretion is a suspected pathway of hyperplasia and neoplasia in the testicular interstitium (McConnell *et al.*, 1992). There was a significant dose-responsive increase in these tumors in "at-risk" males whether or not the top dose group (1800 ppm) was included in the analysis ($p < 0.001$ and $p = 0.043$, respectively). The incidence exceeded the maximum spontaneous incidence rates in male historical controls at ≥ 600 ppm.

Benign testicular interstitial tumors in the male rat were not considered for linear, low-dose extrapolation because these tumors likely resulted from propanil-mediated disruption of androgen signaling leading to increased pituitary LH secretion. DPR considered this to be a threshold effect with neoplastic consequences in target tissues. Several observations support an LH-dependent mode of action: (a) propanil weakly binds to the rat androgen receptor *in vitro* (McCarroll, 2012); (b) there was an increased incidence of testicular focal interstitial hyperplasia combined with absent epididymal spermatozoa, reduced secretions in seminal vesicles, and prostate atrophy in male rats in the same study; and (c) delayed balanopreputial separation was observed in male rat pups in a two-generation reproductive toxicity study (Stump, 1998). DPR concluded that these effects were likely mediated by propanil through disruption of the pituitary-testicular axis, with testicular tumors as a long term consequence.

Measurements of serum androgen and luteinizing hormone (LH) levels in response to propanil did not show changes that could be linked directly to the effects described above (Stump, 1998). However, the intrinsic pulsatility of androgen and LH levels creates a level of variability in these parameters that makes it difficult to detect subtle, treatment-related changes (Bartke *et al.*, 1973; Dong and Handelsman, 1989).

Further support for a threshold MOA comes from study data for linuron, an anilide herbicide with a similar molecular structure and modes of herbicidal and mammalian toxicity to propanil (USEPA, 2016). For example, linuron has receptor mediated anti-androgenic activity, induces tissue-level effects in the sex and accessory sex organs of male rats, and increases the incidence of benign testicular interstitial tumors (USEPA, 2015a). One study in particular clearly demonstrated an MOA for testicular interstitial cell tumors mediated by the anti-androgenic activity (Makris, 1991). Key events in the putative MOA included competitive antagonism by binding to the androgen receptor (AR) leading to hypersecretion of LH.

The PODs ($BMDL_{10}$) for the putative chronic endocrine effects described above range from 11.2 to 37.5 mg/kg/day while the POD for the most likely tumor precursor (testicular focal interstitial hyperplasia) is 19.6 mg/kg/day (Table 33). The lowest POD discussed above is 7.5 fold higher than the critical oral, chronic POD based on splenic hemosiderosis ($BMDL_{10}$ = 1.5 mg/kg/day). Taken together, DPR suggests that the critical oral chronic POD will be protective of effects mediated by the putative endocrine MOA.

The second type of tumor that was increased with dietary propanil treatment in the rat was the benign hepatocellular adenoma (Bellringer, 1994). The rodent liver is considered to be a common target site for xenobiotics because of its primary metabolism and detoxification functions (Thoolen *et al.*, 2010). Hepatocellular adenomas originate in hepatocytes that make up the lobular architecture of the liver parenchyma. These adenomas are considered to be benign and are relatively common in older rodents and in rodents treated with hepatotoxic xenobiotics with carcinogenic potential (Thoolen *et al.*, 2010). Hepatocellular adenomas can arise from toxicant-induced regenerative hyperplasia and progress to carcinomas although this is less common in rats than in mice (Thoolen *et al.*, 2010). A plausible path to propanil-induced regenerative hyperplasia may be initiated by proximal hydrolysis of propanil and activation of 3,4-DCA by liver aryl acylamidase and CYP450 (Williams and Jacobson, 1966). A significantly ($p < 0.05$) increased incidence of adenomas was noted for the terminal necropsy data at 1800 ppm that exceeded the maximum spontaneous incidence rates in female historical controls. The increased incidence of benign hepatocellular adenomas in female rats in the high dose group appeared to be the result of propanil treatment (Table 15). This effect was not considered suitable for low-dose, linear extrapolation because it lacked a clear and consistent dose response and statistical significance (Fisher's Exact Test) in any dose group. Additionally, there were no hepatocellular carcinomas in the female high dose group and no clear treatment-related increases in hepatocellular adenomas or carcinomas in male rats.

Two neoplastic findings were significantly increased with propanil treatment in the mouse: malignant lymphomas and hepatocellular adenomas (Tompkins, 1994). Lymphomas localized in the spleen are common in CD-1 mice (Frith *et al.*, 1993; Ward, 2006). The most common forms develop from B-cells (follicular center cell (FCC)) and B and/or T-cells (lymphoblastic) (Frith *et al.*, 1993; Ward, 2006). Lymphomas may be induced with exposures to retroviruses, radiation, and environmental chemicals and their rate of spontaneous incidence increases with age (Frith *et al.*, 1993; Ward, 2006). DPR suggests that propanil-mediated splenic lymphoma in the mouse may initiate with the accumulation of scavenged erythrocytes, thereby leading to splenic enlargement, hyperplasia, and hemosiderin accumulation. Hemosiderin iron-catalyzed free radical reactions (e.g., lipid peroxidation, DNA strand breaks, and protein degradation) could then lead to oncogenesis (Bus and Popp, 1987).

An increased incidence of malignant lymphoma was observed in female mice and was considered to result from treatment with propanil by the study authors (Tompkins, 1994). While malignant lymphoma localized in the spleen showed a significant dose response in these sub-groups (Peto trend test: $p < 0.01$), DPR's analyses focused on the incidences of lymphoma in all tissues because it was inclusive of all of the animals with this form of cancer. Incidences of malignant lymphoma in all tissues were significantly increased ($p < 0.05$) in high dose group females (1000 ppm). However, this effect was only apparent at the high dose and was not considered to be suitable for low-dose, linear extrapolation.

As stated above for rats, hepatocellular adenomas originate in hepatocytes that make up the lobular architecture of the liver parenchyma. These adenomas are considered to be benign, and are relatively common in older rodents and in rodents treated with hepatotoxic xenobiotics with carcinogenic potential (Thoolen *et al.*, 2010). Hepatocellular adenomas in mice can arise from toxicant-induced regenerative hyperplasia and progress to carcinomas (Thoolen *et al.*, 2010). Significant and dose responsive increases ($p < 0.05$) in the total incidences of hepatocellular adenoma in the liver were observed in high dose group males found dead or killed in extremis (1000 ppm) (Tompkins, 1994).

The increased incidence of hepatocellular adenomas in male mice appeared to result from propanil treatment. However, DPR did not consider this effect to be suitable for low-dose, linear extrapolation because it failed to reach statistical significance for pairwise comparisons at any dose level or for a dose responsive trend in Cochran-Armitage and Poly 3 Tests (Table 16). Additionally, there were no consistent treatment-related increases in hepatocellular carcinomas in male or female mice.

#### 5) Summary of Critical PODs for Risk Assessment

All proposed final, critical POD values for propanil are found in Table 34, below. The values from the US EPA 2003 re-registration document are provided for comparison.

**Table 34. Summary of Critical PODs for Propanil**

| | DPR | | | USEPA | | |
|---|---|---|---|---|---|---|
| **Exposure Route and Duration** | **Critical Endpoint and Study** | **PODs[a] (mg/kg/day)** | **RfDs (mg/kg/day)** | **Critical Endpoint and Study** | **LOELs (mg/kg/day)** | **RfDs (mg/kg/day)** |
| Acute/All Routes | Increased metHB levels (m) (Days 5) (O'Neill, 2002) | $BMDL_{1SD}$ = 14.1 | 0.05 UFtot = 300[b] | No effects resulting from a single exposure identified in any study | c | NA |
| Subchronic/ All Routes | Increased metHb levels (m) (week 13) (Bellringer, 1994) | $BMDL_{1SD}$ = 5 | 0.02 UFtot = 300[b] | Increased metHb levels (m and f rats) (week 13) (Bellringer, 1994) | Incidental Short Term: (1-30 days) and Intermediate Term (1-6 months): LOAEL = 9 | Occupational (dermal and inhalation): 0.03 UFtot = 300[d] Residential (oral, dermal, and inhalation): 0.009 UFtot =1000[e] |
| Chronic/All Routes | Hemosiderosis of spleen (m) (Bellringer, 1994) | $BMDL_{1SD}$ = 1.5 | 0.005 UFtot = 300[b] | Increased metHb levels and spleen weights (f) and incidence of small seminal vesicles and prostates (m) (Bellringer, 1994) | LOAEL = 9 | 0.009 UFtot = 1000[e] |

[a]As defined by US EPA (2012), a point of departure (POD) is the dose-response point that marks the starting point for low-dose extrapolation, and generally corresponds to a select, estimated, low-level of response. In this Risk Characterization Document (RCD), the critical PODs for propanil are based on hematologic toxicity and are defined as an increased methemoglobin (metHB) level by one standard deviation compared to control levels or as a 10% increased incidence of hemosiderosis in the spleen.
[b]Reference Dose (RfD): For propanil, the uncertainty factors (UF) used here are 10 for interspecies sensitivity and 10 for intraspecies variability and 3 for potentially enhanced sensitivity to metHb formation in infants and subpopulations with hereditary enzymatic deficiencies. Total UF (UFtot) = 300; RfD = (PoD ÷ UF of 300).
[c] US EPA did not establish an acute POD or an acute RfD because their assessment did not find "appropriate effects attributable to a single exposure (dose)" in any of the toxicity studies for propanil (USEPA, 2003)
[d]10x for inter-species extrapolation, 10x for intra-species variability and 3x for uncertainty associated with the lack of a NOAEL.
[e]10x for inter-species extrapolation, 10x for intra-species variability and 10x for data base uncertainty plus uncertainty associated with the lack of a NOAEL.

## B) Exposure Assessment

Human exposure to propanil could result from the consumption of food and/or water with pesticide residues (i.e., dietary exposures) or activities related to the agricultural production of rice (i.e., occupational and bystander exposures). The latter category includes exposures of airborne propanil to residential bystanders. The risks posed by all of the above exposure scenarios are evaluated in this document, alone and in aggregate. Exposures from residential uses of propanil are not expected, as there are no currently no other approved uses of this AI in California.

### 1) Dietary and Drinking Water Exposure

#### *(i) Introduction*

DPR conducts acute and chronic dietary exposure assessments to evaluate the risk of human exposure to pesticide residues in food in California (Bronzan and Jones, 1989). At this time, the only type of dietary exposure assessment conducted by DPR is for total dietary exposure. These analyses are performed per DPR guidance, using tolerances or residue levels in all label-approved commodities as well as residue levels in drinking water (DPR, 2009).

Dietary exposure is a product of food consumption and the corresponding residue concentration of a given pesticide. The total dietary exposure for an individual during a defined period of time (e.g., a day) is the sum of dietary exposures for all foods (in various forms and as ingredients in food items) consumed within that time-period:

Exposure = $\sum_{i=1}^{n}(\text{residue}_i \text{ x consumption}_i \text{ of foods})$ (number of foods items in the diet).

Data on the amount of the pesticide residue on food and food consumption provide dietary exposure estimates for various population subgroups based on age, gender, ethnicity, season, and pregnancy/lactation status.

For estimating acute exposure, the highest and mean residue values at or below the tolerance are considered for unblended and blended foods, respectively. Alternately, randomized distributions of residue values may also be considered when more refined estimates are needed. Mean residue values are considered for estimating chronic exposures. In practice, the selection of residue data for more a refined analysis will depend, in part, on what data is available. Acute exposure is calculated on a per-user basis that entails including only the survey days where at least one commodity with potential pesticide residues is consumed in the distribution of exposures. Chronic exposure to pesticides is calculated using per-capita, mean consumption estimates that include the entire population (DPR, 2009).

The acute and chronic dietary exposure assessments for propanil were conducted for all combined food uses and included drinking water. As of October 2016, there were 24 established tolerances for residues of propanil on all possible grain crops (i.e., rice) and animal commodities (USGPO, 2016). As of October 2016, there were 14 active products containing between 40 and 81% propanil approved for use in California (DPR, 2016a).

#### *(ii) Consumption Data and Dietary Exposure*

Tier 1, 2, and 3 acute and chronic dietary exposure assessments were performed using Dietary Exposure Evaluation Model software (DEEM™-FCID ver. 3.16; Durango Software, LLC). This version of DEEM™-FCID used the February 2012 US EPA/USDA FCID recipe set and National Health and Nutrition Examination Survey (NHANES) 2-day food consumption survey data for 2003 through 2008. Estimates of dietary exposure and risk were calculated for the US population and 12 select subgroups. The subgroups were defined by age, gender and ethnicity, as well as concerns for special vulnerabilities related to development (e.g., all infants, nursing and non-nursing infants, and children). DEEM™-FCID's acute module was also used to generate a Critical Exposure Commodity (CEC) analysis to identify the foods that contribute most to dietary exposure.

Acute exposure estimates for deterministic and probabilistic risk assessments used one-day consumption data for all commodities with propanil tolerances and drinking water. In the former case, the consumption of each commodity was multiplied by a single residue value (point estimate) and the combined results for each individual in a population subgroup were then summed while in in latter case, select, randomized distributions of residue values were used. Chronic exposure estimates were calculated in a way similar to those for acute, deterministic estimates. In each case, the food consumption data of each population subgroup was multiplied by an average or individual residue value. Estimates for both acute and chronic exposures were expressed as μg propanil residue per kg body weight per day.

***(iii) Exposure to Propanil from Food and Water***

Propanil residue species of toxicological significance include the parent molecule and metabolites based on a 3,4-DCA moiety. US EPA tolerances for propanil are based on residue analytical methods that quantify hydrolyzed and released ("convertible to") 3,4-DCA as propanil equivalents (USGPO, 2016).

***(iv) Residue Data Sources***

The propanil residue data used in the dietary exposure assessment described here were from three sources: data from field trial residue studies originally submitted by registrants to support product registration were used for foods based on rice; data from feeding studies were used to estimate residues in poultry and ruminant-based foods; and, DPR surface water monitoring data were used to as a surrogate for residues in drinking water. While data from the USDA Pesticide Data Program (PDP) is a preferred source of residue data for dietary risk assessment, DPR could not use it for the dietary risk assessment of propanil. The multi-residue analytical methods used to quantify propanil residues in rice and drinking water for the PDP (i.e., QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) and associated detection methods) quantified and reported propanil parent residues but not all residues convertible to 3,4-DCA (USDA, 2014). DPR concluded that the use of the above PDP data would result in underestimates of acute and dietary exposures to propanil.

***(v) Anticipated Rice Residues***

Registrant-sponsored field trial studies were conducted in support of setting tolerances for propanil and its metabolites convertible to 3,4-DCA (Young *et al.*, 1992b; Young *et al.*, 1992a; Young *et al.*, 1992c; Ehn, 2004). Rice crops were treated at various label rates including the maximum (4 to 8 lbs. AI/acre (A)). Data from the measurement of 31 rough rice grain samples grown in California fields during the 1990 and 2002 growing seasons were used to calculate average anticipated residue values using 1-times or 0.5-times the analytical limit of detection (LOD) for non-detects (NDs). Average residue levels were used for acute and chronic exposure assessment of all rice-based foods (DPR, 2009). The resulting anticipated rice residue values used for this risk assessment are summarized in Table 35. For comparison, the anticipated rice residue level used by US EPA for estimating chronic dietary exposure was 0.36 ppm (Kinard, 2002).

**Table 35. Summary of Anticipated Propanil Residue Levels in Rough Rice Grain**

| Reference | Application | Range of Detects (ppm Propanil eqv.) (n) | LOD/Q[a] (ppm Propanil eqv.) | Maximum Level (ppm Propanil eqv.) | Average Level (1 X LOD) (ppm Propanil eqv.) | Average Level (1/2 X LOD) (ppm Propanil eqv.) |
|---|---|---|---|---|---|---|
| Ehn (2004) | SuperWham CA! 6 or 8 lbs. AI/A | 0.053 [b] (1) | 0.05 [b] | 2.43 | 0.43 | 0.42 |
| Young *et al.* (1992b) | Propanil EC at 4 lbs. AI/A | 0.014 to 0.11[b] (6) | 0.014 [b] | | | |
| Young *et al.* (1992a) | Propanil EC at 4 +4 lbs. AI/A | 0.12 to 0.46 [b] (6) | 0.014 [b] | | | |
| Young *et al.* (1992c) | Propanil EC at 6 lbs. AI/A | 0.73 to 2.43 [b] (6) | 0.014 [b] | | | |

[a]Limit of Detection/Quantification: LOD/LOQ
[b]Original data reported as 3,4-DCA and converted to propanil equivalents (eqv.) as follows: ppm propanil = (ppm 3,4-DCA) X 1.35 where 1.35 = ratio of MW propanil (218.1 g/mol) over MW 3,4-DCA (162.0 g/mol)

### *(vi) Estimate for Percentage of California Rice Crop Treated*

The average percentage of the California rice crop treated with propanil was estimated for the years 2010 through 2015 (75%) using acres treated data queried from the DPR Pesticide Use Reporting (PUR) database and acres harvested data from the United States Department of Agriculture (USDA) National Agricultural Statistics Service (USDA, 2017; DPR, 2017 ). Annual percentages were calculated using the following formula (DPR, 2009) (Table 36):

Percent Crop Treated (PCT) (%) = (Acres Treated with Propanil (acres)/(Acres Harvested (acres))X 100%

For comparison, the PCT value for rice that was used by US EPA for estimating chronic dietary exposure was 70% (Kinard, 2002).

**Table 36. Data Used to Estimate the Percentage California Rice Crop Treated**

| Year | Acres Treated with Propanil | Acres Harvested | PCT (%) |
|---|---|---|---|
| 2015 | 318104.93 | 426000.00 | 75 |
| 2014 | 345985.29 | 442000.00 | 78 |
| 2013 | 438514.98 | 562000.00 | 78 |
| 2012 | 415329.37 | 557000.00 | 75 |
| 2011 | 428345.42 | 580000.00 | 74 |
| 2010 | 393400.73 | 553000.00 | 71 |
| **Avg** | | 75 | |

### *(vii) Anticipated Milk, Meat, Poultry, Egg, and Crayfish Residues*

The anticipated residues of propanil and its metabolites convertible to 3,4-DCA in milk, meat, poultry, and egg were identical to those used for the chronic dietary exposure assessment performed by US EPA and based on ruminant and poultry feeding studies and a crayfish residue study (Kinard, 2002).

### *(viii) Anticipated Drinking Water Residues*

The surrogates for residues of propanil and its metabolites convertible to 3,4-DCA in drinking water were based on DPR surface water monitoring data for the years 2000 through 2015 (DPR, 2016c). Maximum surrogate residue levels were identified for propanil and 3,4-DCA and summed for Acute Tier 1 and 2 exposure assessment while a distribution of propanil residue values (detects and 0.5-times the LOD for NDs) was used for Acute Tier 3 exposure assessment. Summed average surrogate anticipated residue values for propanil and 3,4-DCA were also calculated using 0.5-times the LOD for NDs and used for Chronic exposure assessment (DPR, 2009). Maximum surrogate and average residue levels of propanil and 3,4-DCA in groundwater were also calculated for comparison to California groundwater monitoring data collected between 2001 and 2015 (DPR, 2016b). DPR surface water data was selected over both the DPR ground water monitoring data and the US EPA modeled residues for exposure assessment as a surrogate for high-end drinking water residue level for California. These residue values are summarized in Table 37.

**Table 37. Summary of Surrogate Anticipated Propanil Residue Levels in Drinking Water**

| Reference | Source | Sample Dates (n) | Range of Detects (ppb/n) | Analyte | Range of LOD/Q[a] (ppb) (n) | Analyte | Maximum Level (ppb Propanil eqv.) | Average Level (1/2 X LOD) (ppb Propanil eqv.) |
|---|---|---|---|---|---|---|---|---|
| DPR (2016c) | Surface Water | 2005 to 2012 (107) | 0 (0) | 3,4-DCA | 4.00E-3 to 1.82e-2 | 3,4-DCA | 2.46E-2 [b] | 3.52E-3 [b] |
| DPR (2016c) | Surface Water | 2000 to 2015 (1956) | 4.30E-3 to 47 (150) | propanil | 4.00E-3 to 5 | propanil | 47 | 1.52E-1 |
| | | | | | | **Sum** | 47 | 1.56E-1 |
| DPR (2016b) | Ground Water | 2004 to 2011 (1887) | 1.00E-3 to 5.41E-1 (99) | 3,4-DCA | 4.00E-3 to 6.00E-3 | 3,4-DCA | 7.30E-1 [b] | 4.69E-3 [b] |
| DPR (2016b) | Ground Water | 2001, 2005 to 2011, and 2013 to 2015 (826) | 9.7E-2 (1) | propanil | 6.00E-3 to 5.00E-2 | propanil | 9.70E-2 | 9.35E-3 |
| | | | | | | **Sum** | 8.27E-1 | 1.40E-2 |

[a]Limit of Detection/Quantification: LOD/LOQ

[b] Original data reported as 3,4-DCA and converted to propanil equivalent (eqv.) as follows: ppm propanil = (ppm 3,4-DCA) X 1.35 where 1.35 = ratio of MW propanil (218.1 g/mol) over MW 3,4-DCA (162.0 g/mol)

### 2) Summary of Residue Data

The anticipated residues of for propanil and its metabolites convertible to 3,4-DCA used for the dietary risk assessment described in this document are summarized in Table 38. The processing adjustment factors used by US EPA for estimating chronic dietary exposure were also applied here (Kinard, 2002).

**Table 38. Summary of Anticipated Propanil Residue Levels in All Foods**

| Commodity | Data Source | % Crop Treated (PCT) | Processing Factor | Acute Tier 1: Tolerance (ppm) | Acute Tier 2: Residues (ppm) | Acute Tier 3 and Chronic Tier 3 Residues (ppm) |
|---|---|---|---|---|---|---|
| Beef, fat | a | 1 | 1 | 0.1 | 0.081 | 0.081 |
| Beef, fat-baby food | a | 1 | 1 | 0.1 | 0.081 | 0.081 |
| Beef, kidney | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Beef, liver | a | 1 | 1 | 1 | 0.018 | 0.018 |
| Beef, liver-baby food | a | 1 | 1 | 1 | 0.018 | 0.018 |
| Beef, meat | a | 1 | 1 | 0.05 | 0.003 | 0.003 |
| Beef, meat byproducts | a | 1 | 1 | 1 | 0.003 | 0.003 |
| Beef, meat byproducts-baby food | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Beef, meat, dried | a | 1 | 1.92 | 1 | 0.003 | 0.003 |
| Beef, meat-baby food | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Chicken, fat | a | 1 | 1 | 0.05 | 0.007 | 0.007 |
| Chicken, fat-baby food | a | 1 | 1 | 0.05 | 0.007 | 0.007 |
| Chicken, liver | a | 1 | 1 | 0.5 | 0.031 | 0.031 |
| Chicken, meat | a | 1 | 1 | 0.1 | 0.01 | 0.01 |
| Chicken, meat byproducts | a | 1 | 1 | 0.5 | 0.031 | 0.031 |
| Chicken, meat byproducts-baby food | a | 1 | 1 | 0.5 | 0.031 | 0.031 |
| Chicken, meat-baby food | a | 1 | 1 | 0.1 | 0.01 | 0.01 |
| Chicken, skin | a | 1 | 1 | 0.5 | 0.007 | 0.007 |
| Chicken, skin-baby food | a | 1 | 1 | 0.5 | 0.031 | 0.031 |
| Egg, white | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Egg, white (solids)-baby food | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Egg, whole | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Egg, whole-baby food | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Egg, yolk | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Egg, yolk-baby food | a | 1 | 1 | 0.3 | 0.028 | 0.028 |
| Fish-shellfish, crustacean | a | 1 | 1 | 0.05 | 0.03 | 0.03 |
| Goat, fat | a | 1 | 1 | 0.1 | 0.081 | 0.081 |
| Goat, kidney | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Goat, liver | a | 1 | 1 | 1 | 0.018 | 0.018 |
| Goat, meat | a | 1 | 1 | 0.05 | 0.003 | 0.003 |
| Goat, meat byproducts | a | 1 | 1 | 1 | 0.044 | 0.044 |

**Table 38. Summary of Anticipated Propanil Residue Levels in All Foods**

| Commodity | Data Source | % Crop Treated (PCT) | Processing Factor | Acute Tier 1: Tolerance (ppm) | Acute Tier 2: Residues (ppm) | Acute Tier 3 and Chronic Tier 3 Residues (ppm) |
|---|---|---|---|---|---|---|
| Horse, meat | a | 1 | 1 | 0.05 | 0.003 | 0.003 |
| Milk, fat | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, fat-baby food/infant formula | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, nonfat solids | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, nonfat solids-baby food/in | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, sugar (lactose)-baby food/ | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, water | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Milk, water-baby food/infant formula | a | 1 | 1 | 0.05 | 0.0013 | 0.0013 |
| Pork, fat | a | 1 | 1 | 0.1 | 0.3 | 0.3 |
| Pork, fat-baby food | a | 1 | 1 | 0.1 | 0.3 | 0.3 |
| Pork, kidney | a | 1 | 1 | 1 | 0.16 | 0.16 |
| Pork, liver | a | 1 | 1 | 1 | 0.065 | 0.065 |
| Pork, meat | a | 1 | 1 | 0.05 | 0.01 | 0.01 |
| Pork, meat byproducts | a | 1 | 1 | 1 | 0.16 | 0.16 |
| Pork, meat byproducts-baby food | a | 1 | 1 | 1 | 0.16 | 0.16 |
| Pork, meat-baby food | a | 1 | 1 | 0.05 | 0.01 | 0.01 |
| Pork, skin | a | 1 | 1 | 1 | 0.3 | 0.3 |
| Poultry, other, fat | a | 1 | 1 | 0.05 | 0.007 | 0.007 |
| Poultry, other, liver | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Poultry, other, meat | a | 1 | 1 | 0.1 | 0.01 | 0.01 |
| Poultry, other, meat byproducts | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Poultry, other, skin | a | 1 | 1 | 0.5 | 0.007 | 0.007 |
| Rabbit, meat | a | 1 | 1 | NA | 0.003 | 0.003 |
| Rice, bran | b | 0.75[f] | 4.6 | 40 | 0.43[d] | 0.42[e] |
| Rice, bran-baby food | b | 0.75[f] | 4.6 | 40 | 0.43[d] | 0.42[e] |
| Rice, brown | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Rice, brown-baby food | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Rice, flour | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Rice, flour-baby food | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Rice, white | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Rice, white-baby food | b | 0.75[f] | 1 | 10 | 0.43[d] | 0.42[e] |
| Sheep, fat | a | 1 | 1 | 0.1 | 0.081 | 0.081 |

**Table 38. Summary of Anticipated Propanil Residue Levels in All Foods**

| Commodity | Data Source | % Crop Treated (PCT) | Processing Factor | Acute Tier 1: Tolerance (ppm) | Acute Tier 2: Residues (ppm) | Acute Tier 3 and Chronic Tier 3 Residues (ppm) |
|---|---|---|---|---|---|---|
| Sheep, fat-baby food | a | 1 | 1 | 0.1 | 0.081 | 0.081 |
| Sheep, kidney | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Sheep, liver | a | 1 | 1 | 1 | 0.018 | 0.018 |
| Sheep, meat | a | 1 | 1 | 0.05 | 0.003 | 0.003 |
| Sheep, meat byproducts | a | 1 | 1 | 1 | 0.044 | 0.044 |
| Sheep, meat-baby food | a | 1 | 1 | 0.05 | 0.003 | 0.003 |
| Turkey, fat | a | 1 | 1 | 0.05 | 0.007 | 0.007 |
| Turkey, fat-baby food | a | 1 | 1 | 0.05 | 0.007 | 0.007 |
| Turkey, liver | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Turkey, liver-baby food | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Turkey, meat | a | 1 | 1 | 0.1 | 0.01 | 0.01 |
| Turkey, meat byproducts | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Turkey, meat byproducts-baby food | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Turkey, meat-baby food | a | 1 | 1 | 0.1 | 0.01 | 0.01 |
| Turkey, skin | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Turkey, skin-baby food | a | 1 | 1 | 1 | 0.031 | 0.031 |
| Drinking Water | c | 1 | 1 | 0.047[f] | 0.047[f] | 1.56E-4[g,h] |

a) Kinard (2002)
b) Young *et al.* (1992b); Young *et al.* (1992a); Young *et al.* (1992c); Ehn (2004)
c) DPR (2016c)
d) Average rice residues (with 1-times the LOD for NDs ) used for Acute Tier 2 exposure.
e) Average rice residues (with 0.5-times the LOD for NDs ) used for Acute Tier 3 and Chronic Tier 2 exposures.
f) Maximum summed propanil and 3,4-DCA surface water residues used for Acute Tiers 1 and 2 exposures.
g) Average summed propanil and 3,4-DCA surface water residues (with 0.5-times the LOD for NDs ) used for Chronic Tier 2 exposure.
h) A distribution of individual propanil residue values (with 0.5-time the LOD for NDs) was used for Acute Tier 3 exposure.

### 3) Acute Dietary Exposure

The acute dietary exposure of propanil was estimated using a tiered approach for the selection of appropriate anticipated residue values per DPR guidance (DPR, 2009). The Tiers 1 and 2 are deterministic and use increasingly refined point estimates that include tolerances and upper-bound or average residue levels. Tier 3 is a further refined, Monte Carlo analysis-based probabilistic approach that uses select distributions of residues levels and provides a probability distribution for exposure.

DPR uses two exposure thresholds to determine whether or not a higher tier of assessment is needed (DPR, 2009). Margin of exposure (MOE), defined as the ratio of the critical POD over the exposure, is compared to the corresponding health protection level to make this determination. If the lowest acute MOE is within either 10-fold of the target MOE level at the 95$^{th}$ percentile exposure or 5-fold of the target MOE level at the 99$^{th}$ percentile exposure, the next tier of assessment is indicated. The target MOE level for propanil is 300, so the thresholds for the next tier of assessment would be 3000 or 1500 at the 95$^{th}$ or 99$^{th}$ percentile exposures, respectively. These thresholds are used because they can accommodate exposure from other potential routes. The 5- and 10-fold distance from the target MOE level also reduces the likelihood that dietary exposure will be a major contributor to aggregate risk.

### *(i) Acute Exposure Assessment*

The acute dietary exposure of the US population and select subgroups to propanil was assessed using deterministic and mixed deterministic and probabilistic approaches (Tiers 1, 2, and 3).

**Tier 1 Point Estimate Assessment**

For this analysis, propanil residues in all foods were set at tolerance levels. The sum of the maximum detected levels of propanil and 3,4-DCA from DPR surface water monitoring data were used as a surrogate for direct and indirect drinking water exposure. No processing factors were applied for this analysis.

This Tier 1 analysis produced propanil exposures that resulted in corresponding MOE levels below 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, for all population subgroups. Based on above results, a Tier 2 point estimate assessment was performed.

**Tier 2 Point Estimate Assessment**

This model assumes that (a) all foods consumed in a given day contain the highest reported or estimated residue level at or below the tolerance, (b) pesticide levels below the LOD are equal to the LOD for single and blended commodities, (c) all crops are treated with the pesticide (PCT = 1), and (d) in cases where residue concentrations vary from the time of sampling to consumption, processing factors are applied. (DPR, 2009). The anticipated residue data described above and summarized in Table 38 were considered to adequately to reflect upper-end propanil exposures required for an acute, Tier 2 point estimate exposure assessment. Rice was considered to be a blended food so an average residue level (with 1-times the LOD for NDs) was used for all foods based on rice and the sum of the maximum detected levels of propanil and 3,4-DCA from DPR surface water monitoring data were used as a surrogate for all direct and indirect drinking water exposures.

This Tier 2 analysis produced propanil exposures that resulted in corresponding MOE levels below 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, for the “Non-Nursing Infants” and “All Infants” population subgroups. Based on above results, a Tier 3 assessment was performed.

**Tier 3 Mixed Point and Probabilistic Assessment**

This model assumes that (a) all foods consumed in a given day contain either the average reported residue level or a randomized residue distribution at or below the tolerance, (b) pesticide levels below the LOD

are equal to 0.5-times the LOD for single or blended commodities (respectively), (c) a PCT is used where applicable, and (d) in cases where residue concentrations vary from the time of sampling to consumption, processing factors are applied (DPR, 2009). The anticipated residue data described above and summarized in Table 38 were considered to adequately to reflect upper-end propanil exposures required for an acute, Tier 3 probabilistic exposure assessment. Rice was considered to be a blended food, so an average residue level (with 0.5-times the LOD for NDs) was used for all foods based on rice and a California-specific PCT value (0.75) was also applied. A distribution of detected levels of propanil and 0.5-times the LOD for NDs from DPR surface water monitoring data was used as a surrogate for all direct and indirect drinking water exposures.

This Tier 3 analysis produced propanil exposures that ranged from 0.4 to 2 µg/kg/day and from 0.7 to 3 µg/kg/day for the 95$^{th}$ and 99$^{th}$ percentiles, respectively (Table 39). These exposures resulted in corresponding MOE levels above 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, for all population subgroups (Table 43). The population subgroups with the highest exposures at the 95$^{th}$ and 99$^{th}$ percentiles were "Non-Nursing Infants" and "All Infants".

**Table 39. User Exposures for Acute Tier 3 Dietary Exposure Assessment: All Commodities and DPR Surface Water Data**

| | Exposure (µg/kg/day) | | |
|---|---|---|---|
| **Population Subgroup** | **95$^{th}$ Percentile** | **99$^{th}$ Percentile** | **99.9$^{th}$ Percentile** |
| Total US Population | 0.55 | 1.09 | 2.37 |
| Hispanic | 0.72 | 1.28 | 2.47 |
| Non-Hispanic White | 0.44 | 0.83 | 1.82 |
| Non-Hispanic Black | 0.57 | 1.11 | 2.14 |
| Non-Hispanic Other | 1.23 | 1.98 | 3.41 |
| Nursing Infants | 1.35 | 2.25 | 5.51 |
| Non-Nursing Infants | **1.75** | **3.24** | **7.34** |
| All Infants | **1.56** | **2.99** | **6.56** |
| Females 13-50 years old | 0.43 | 0.79 | 1.44 |
| Children 1-2 years old | 1.19 | 2.40 | 4.76 |
| Children 3-5 years old | 1.08 | 1.83 | 2.72 |
| Children 6-12 years old | 0.68 | 1.16 | 2.25 |
| Adults 50-99 years old | 0.36 | 0.67 | 1.34 |

Highest values in **bold**.

The contributions of critical commodities are summarized in (Table 40). The acute Critical Exposure Commodity (CEC) identified rice (all sources) as making substantial (>5%) contributions to the overall acute dietary exposure for all of the population subgroups evaluated. Pork fat was the only other significant contributor to acute dietary propanil exposures. The main forms of rice consumed were white rice and rice flour in baby food with exposure contributions ranging from 46 to 71% and 36 to 84%, respectively.

**Table 40. Acute Tier 3 Dietary Exposure Assessment: Critical Commodity Contributions**

| | | Contribution (%) | | |
|---|---|---|---|---|
| **Population Subgroup** | **Rice** | **Main Rice Form (%)** | **Water (indirect and direct)** | **Pork Fat** |
| Total US Population | 80.36 | White (48.19) | < 5 | < 5 |
| Hispanic | 77.32 | White (52.44) | < 5 | < 5 |
| Non-Hispanic White | 74.91 | Flour-Baby food (36.11) | < 5 | 5.91 |
| Non-Hispanic Black | 74.69 | White (45.64) | < 5 | < 5 |
| Non-Hispanic Other | 88.61 | White (65.66) | < 5 | < 5 |
| Nursing Infants | 92.68 | Flour-Baby food (70.37) | < 5 | < 5 |
| Non-Nursing Infants | 94.72 | Flour-Baby food (84.46) | < 5 | < 5 |
| All Infants | 94.14 | Flour-Baby food (80.49) | < 5 | < 5 |
| Females 13-50 years old | 79.30 | White (73.63) | < 5 | < 5 |
| Children 1-2 years old | 83.33 | White (49.04) | < 5 | < 5 |
| Children 3-5 years old | 79.20 | White (55.21) | < 5 | < 5 |
| Children 6-12 years old | 80.40 | White (68.13) | < 5 | 5.75 |
| Adults 50-99 years old | 70.84 | White (70.84) | < 5 | 6.35 |

Highest values in **bold**.

### 4) Chronic Dietary Exposure

Chronic dietary exposure assessments use a single value to represent the residue concentration for each selected food and food form. This residue concentration for each food and food form is then multiplied by the average consumption of each population subgroup to calculate the exposure contribution for that food. Total exposure is then sum of individual food exposure contributions. It is DPR practice to use the following standard assumptions when assessing chronic dietary exposure (DPR, 2009): (a) the commodities that could contain propanil residues contain them at average levels and (b) the population average daily consumption distribution reflects the longitudinal consumption patterns of individuals.

The average anticipated residue data described above and summarized in Table 38 were considered to adequately to reflect average propanil exposures required for a chronic, point estimate exposure assessment. As described above in detail, average anticipated residues for rice-based foods and surrogate drinking water values were calculated using field trial and surface water monitoring data, respectively with 0.5-times the LOD value for NDs. The California-specific PCT (0.75) was applied to rice-based foods.

**Chronic Deterministic Exposure Assessment**

This analysis produced estimated chronic propanil exposures that ranged from 0.11 (“Adults 50-99 years”) to 0.44 µg/kg/day (“Non-Nursing Infants”) (Table 41).

**Table 41. User Exposures for Chronic Dietary Exposure Assessment: All Commodities and DPR Surface Water Data**

| Population Subgroup | (µg/kg/day) |
|---|---|
| Total US Population | 0.16 |
| Hispanic | 0.21 |
| Non-Hispanic White | 0.13 |
| Non-Hispanic Black | 0.16 |
| Non-Hispanic Other | 0.35 |
| Nursing Infants | 0.23 |
| Non-Nursing Infants | **0.44** |
| All Infants | **0.37** |
| Females of childbearing age (13-50 years old) | 0.12 |
| Children 1-2 years old | 0.39 |
| Children 3-5 years old | 0.32 |
| Children 6-12 years old | 0.20 |
| Adults 50-99 years old | 0.11 |

Highest values in **bold**.

### 5) Occupational Exposure

The complete human exposure assessment for propanil can be found in Appendix C of this document. In it, the reader will find detailed estimates for acute, seasonal, annual, and lifetime occupational exposures for herbicide handler and field worker scenarios as well as a complete description of the methods used (e.g. input data, formulae, assumptions, etc.). Herbicide handler exposures were estimated using generic surrogate data from Pesticide Handlers Exposure Database (PHED) while field worker exposures were estimated using application rates.

### 6) Exposure to the Residential Bystanders from Spray Drift

An assessment of short-term (daily) inhalation and dermal exposure to residential bystanders from propanil in spray drift can be found in Appendix C. The residential bystander spray drift exposure assessment includes estimates for aerial (fixed and rotary winged aircraft) and ground boom application scenarios as well as a complete description of the methods used (e.g., input data, formulae, assumptions, etc.). Residential bystander exposures were estimated using AGDISP and AgDRIFT computer models.

### 7) Aggregate Exposure

Exposures were not aggregated. Rather, aggregate risks were calculated using acute dietary, occupational, and residential bystander MOEs.

## C) Risk Characterization

The process of risk characterization involves calculating a margin of exposure (MOE) for each exposure scenario. The MOE is calculated by dividing the critical POD for a specific exposure duration and route by an estimate of human exposure.

MOE = POD (mg/kg/day) / Exposure (mg/kg/day)

All of the critical PODs for propanil were based on oral toxicity studies (Table 42). The dietary exposure assessment is reported herein. The occupational exposure assessment is summarized in this RCD, and the full exposure assessment can be found in Appendix C.

The acute, subchronic and chronic PODs and RfDs used to characterize risk from exposure to propanil were derived from studies using animal models and not humans. As a result, an MOE of 300 was considered prudent to protect humans from propanil toxicity. This MOE was the product of a UF of 10 for interspecies sensitivity, a UF of 10 for intraspecies variability and a UF of 3x for potentially enhanced sensitivity to metHb formation in infants and subpopulations with hereditary enzymatic deficiencies (Kabra *et al.*, 1998; NAS, 2000; Knobeloch and Proctor, 2001).

**Table 42. Summary of Critical PODs for Propanil**

| Exposure Route and Duration | Critical Endpoint and Study | PODs (mg/kg/day) | RfDs (mg/kg/day) |
|---|---|---|---|
| Acute/All Routes | Increased metHB levels (m) (Days 5) (O'Neill, 2002) | $BMDL_{1SD}$[b] = 14.1 | 0.05 UFtot = 300[a] |
| Subchronic/ All Routes | Increased metHb levels (m) (week 13) (Bellringer, 1994) | $BMDL_{1SD}$[b] = 5 | 0.02 UFtot = 300[a] |
| Chronic/All Routes | Hemosiderosis of spleen (m) (week 104) (Bellringer, 1994) | $BMDL_{10}$[b] = 1.5 | 0.005 UFtot = 300[a] |

[a]Reference Dose (RfD): For propanil, the uncertainty factors (UF) used here are 10 for interspecies sensitivity and 10 for intraspecies variability and 3 for potentially enhanced sensitivity to metHb formation in infants and subpopulations with hereditary enzymatic deficiencies. Total UF (UFtot) = 300; RfD = (PoD ÷ UF of 300).
[b]Benchmark Dose Lower Confidence Limit (BMDL): a value representing a 95% lower bound of the BMD and a point of departure (POD) for the observed effect; subscripts indicates an effect threshold based on data for concurrent controls (1SD = 1 standard deviation; 10 = 10% extra risk).

### 1) Risk from Dietary Exposure

#### *(i) Acute Dietary Risk*

**Tier 1 Point Estimate Assessment**

For this analysis, propanil residues in all foods were set at tolerance levels and the sum of the maximum detected levels of propanil and 3,4-DCA from DPR surface water monitoring data were used as a surrogate for direct and indirect drinking water. The acute POD (14.1 mg/kg/day) was used to calculate MOE values. As stated previously, these exposures resulted in corresponding MOE levels below 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, and a more refined Tier 2 analysis was performed.

**Tier 2 Point Estimate Assessment**

For this analysis, estimated residue levels were used for all food except those based on rice. An average residue level was used for foods based on rice and the sum of the maximum detected levels of propanil and 3,4-DCA from DPR surface water monitoring data were used as a surrogate for all direct and indirect drinking water sources. The acute POD (14.1 mg/kg/day) was used to calculate MOE values. The resulting exposures resulted in MOE levels above 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, so a more refined Tier 3 analysis was performed.

**Tier 3 Point Estimate and Probabilistic Assessment**

For this analysis, estimated residue levels were used for all food except those based on rice. An average residue level was used for foods based on rice and the distribution of detected levels of propanil from DPR surface water monitoring data was used as a surrogate for all direct and indirect drinking water sources. The acute POD (14.1 mg/kg/day) was used to calculate MOE values. The corresponding MOEs ranged from 8040 to 39339 at the 95$^{th}$ percentile and 4351 to 21140 at the 99$^{th}$ (Table 43. The "Non-nursing Infants" and "All Infants" subpopulations were identified as the most highly exposed. The resulting exposures resulted in MOE levels above 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles for all subpopulations.

**Table 43. User Margins of Exposure for Acute Tier 3 Dietary Exposure Assessment: All Commodities and DPR Surface Water Data**

| | Acute MOE | | |
|---|---|---|---|
| **Population Subgroup** | **95$^{th}$ Percentile** | **99$^{th}$ Percentile** | **99.9$^{th}$ Percentile** |
| Total US Population | 25677 | 12981 | 5953 |
| Hispanic | 19624 | 11035 | 5719 |
| Non-Hispanic White | 31908 | 16964 | 7766 |
| Non-Hispanic Black | 24944 | 12721 | 6591 |
| Non-Hispanic Other | 11498 | 7106 | 4130 |
| Nursing Infants | 10477 | 6254 | 2558 |
| Non-Nursing Infants | **8040** | **4351** | **1922** |
| All Infants | **9044** | **4709** | **2150** |
| Females 13-50 years old | 33092 | 17830 | 9821 |
| Children 1-2 years old | 11822 | 5864 | 2965 |
| Children 3-5 years old | 13041 | 7686 | 5191 |
| Children 6-12 years old | 20864 | 12151 | 6271 |
| Adults 50-99 years old | 39339 | 21140 | 10520 |

Lowest values in **bold**.

### *(ii) Chronic Dietary Risk*

For this analysis, all foods consumed in a given day were assumed to contain the average reported residue level at or below the tolerance. The sum of the average detected levels of propanil and 3,4-DCA from DPR surface water monitoring data were used as a surrogate for direct and indirect drinking water. The chronic POD (1.5 mg/kg/day) was used to calculate MOE values. The corresponding MOEs ranged from 3446 to 13945 corresponding to 0.0.03 and 0.01% of the chronic POD (1.5 mg/kg/day) (Table 44). The "Non-nursing Infants" and "All Infants" subpopulations were identified as the most highly exposed. All of the estimated exposures resulted in MOE levels greater than 10-times the target MOE level.

**Table 44. User Margins of Exposure for Chronic Dietary Exposure Assessment: All Commodities and DPR Surface Water Data**

| Population Subgroup | Chronic MOE | % of POD |
|---|---|---|
| Total US Population | 9527 | 0.01% |
| Hispanic | 7009 | 0.01% |
| Non-Hispanic White | 11420 | 0.01% |
| Non-Hispanic Black | 9243 | 0.01% |
| Non-Hispanic Other | 4302 | 0.02% |
| Nursing Infants | **6521** | **0.02%** |
| Non-Nursing Infants | **3446** | **0.03%** |
| All Infants | 4034 | 0.02% |
| Females 13-50 years old | 12706 | 0.01% |
| Children 1-2 years old | 3889 | 0.03% |
| Children 3-5 years old | 4682 | 0.02% |
| Children 6-12 years old | 7492 | 0.01% |
| Adults 50-99 years old | 13945 | 0.01% |

Lowest values in **bold**.

### 2) Risk from Occupational Exposure

The acute, seasonal, and annual exposure estimates in the occupational exposure assessment for propanil (Appendix C) were used to calculate the MOEs reported in this RCD.

#### *(i) Acute/Short-Term Risk*

The MOEs for acute/short-term occupational exposure scenarios for herbicide handlers and field workers are summarized in Tables 45 and 46. The acute POD (14.1 mg/kg/day) was used to calculate all MOE values. All of the acute MOEs for herbicide handler/applicator scenarios (1 to 15) were lower than the target MOE (300) (Table 45). The handler job category with the lowest MOE was the mixer/loader (M/L) for aerial applications. The acute MOEs for scouting (15) and weeding (233) were both lower than the target MOE (300) (Table 46).

#### *(ii) Seasonal and Annual Risk*

The MOEs for seasonal and annual occupational exposure scenarios for herbicide handlers and field workers are summarized in Tables 45 and 46. The subchronic and chronic PODs (5 and 1.5 mg/kg/day) were used to calculate seasonal and annual MOE values, respectively. All of the seasonal and annual MOEs (1 to 74 and 2 to 133, respectively) for herbicide handler/applicator scenarios were lower than the target MOE (300) (Table 45). As above, the handler job category with the lowest seasonal and annual MOE was the mixer/loader (M/L) for aerial applications. The seasonal and annual MOEs for scouting (11 and 20) and the seasonal and MOE for weeding were also lower than the target MOE (300) (Table 46).

**Table 45. Estimates of Short-, Intermediate- and Long-Term Risk (MOEs) from Exposure to Propanil for Herbicide Handlers**

| Job Category [a] | Formulation[b] | Use Rate[c] | Acres/Day[d] | Acute ADD[e] | SADD[f] | AADD[g] |
|---|---|---|---|---|---|---|
| | | (lb AI/A or gal) | (A/day) | MOE | MOE | MOE |
| Ground Boom, M/L | DF | Rice=6.0 (max) | 200 (max) | 5 | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 24 | 43 |
| Aerial, M/L | DF | Rice=6.0 (max) | 720 | 1 | | |
| | | Rice=3.0 (typical) | 720 | | 3 | 5 |
| Ground Boom, M/L | L (AC, FC, suspension) | Rice=6.0 (max) | 200 (max) | 2 | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 10 | 18 |
| Aerial, M/L | L (AC, FC, suspension) | Rice=6.0 (max) | 720 | 1 | | |
| | | Rice=3.0 (typical) | 720 | | 1 | 2 |
| Ground Boom, A | DF, AC, FC, suspension | Rice=6.0 (max) | 200 (max) | 15 | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 74 | 133 |
| Aerial, A | DF, AC, FC, suspension | Rice=6.0 (max) | 720 | 11 | | |
| | | Rice=3.0 (typical) | 720 | | 22 | 39 |
| Flagger [i] | DF | Rice=6.0 (max) | 350 | 8 | | |
| | | Rice=3.0 (typical) | 350 | | 16 | 28 |

Exposure data used for MOE calculations was from Table 6 of the Human Exposure Assessment for Propanil (see Appendix C). Values < 300 are shaded.

Table 6 Legend; (reproduced from Appendix C).

a The exposure scenarios are based on the product labels. M/L = mixer/loader; A = applicator.

b FM = Formulation; DF = Dry Flowable; AC = Aqueous Concentrate; FC = Flowable concentrate.

c The maximum use rates based on the currently registered product labels are used to estimate short-term exposure; typical application rate based on RED (U.S. EPA, 2003 and 2006) and the most recent five years California use data (DPR. 2016) are used to estimate long-term exposure. AI = Active ingredient; A = Acre.

d Maximum and typical (average) daily acres to be treated in each scenario based on the RED (U.S. EPA, 2003 and 2006). Based on California regulation (Title 3, California Code of Regulations, Section 6462. Propanil), the maximum treated area by aircraft within each county per day is 720 acres.

e Acute Absorbed Daily Dosage (Acute ADD). Acute ADD = (short-term dermal exposure rate [µg/lb AI handled] x dermal absorption rate + short-term inhalation exposure rate [µg/lb AI handled] x inhalation absorption rate) x max use rate x max daily treated acres ÷ body weight. Calculation assumptions include:

- The 90% upper confidence limit of the 95$^{th}$ percentile short-term exposure estimate based on HHAB guidance document (Beauvais *et. al*., 2007), the multipliers from Powell (2007).
- Dermal absorption rate = 50 % (default dermal absorption rate based on HHA practice);
- Inhalation absorption is assumed to be 100% (default inhalation absorption rate based on HHA practice (Frank, 2008);
- Body weight = 70 kg for both male and female (U.S. EPA, 1997).
- Maximum application rate based on product labels, 6 lb AI/acre
- Maximum daily treated acres based on the RED (U.S. EPA, 2003 and 2006), 200 acres for ground application. For aerial application, US EPA used 3200 acres for maximum estimate, however, based on California propanil regulation (Title 3, California Code of Regulations, Section 6462. Propanil), the maximum aerial daily acre is 720 acres/day per county in California.

f Seasonal Average Daily Dosage (SADD). Seasonal ADD = (long-term dermal exposure rate [µg/lb AI handled] x dermal absorption rate + long-term inhalation exposure rate [µg/lb AI handled] x inhalation absorption rate) x typical use rate x typical daily treated acres ÷ body weight. Calculation assumptions include:

- The 90% upper confidence limit of the arithmetic mean long-term exposure estimate based on HHAB guidance document (Beauvais *et. al*. (2007); multipliers from Powell (2007).
- Dermal absorption rate = 50 % (default dermal absorption rate based on HHA practice);
- Inhalation absorption is assumed to be 100% (default inhalation absorption rate based on HHA practice);
- Body weight = 70 kg for both male and female (U.S. EPA, 1997).
- Typical (average) application rate based on RED (U.S. EPA, 2003 and 2006) and recent five years PUR data (DPR, 2016a), 3 lb AI/acre
- Typical (average) daily treated acres based on RED (U.S. EPA, 2003 and 2006), 80 acres for ground application. Based on California regulation (Title 3, California Code of Regulations, Section 6462. Propanil), propanil aerial application is allowed up to 720 acres/day per county.

g Annual Average Daily Dosage (AADD) = SADD x annual use months per year/12 months in a year. The estimated high-use season for handler was based on the California Pesticide Use Reporting Database (DPR, 2016a, see text and Figure 4).

h Lifetime Annual Daily Dosage = AADD x 40 years of work in a lifetime/75 years in a lifetime.

i Based on Worker Protection Standard (WPS) [40 CFR 170.240 (d) (4-6)],"Persons occupying an enclosed cockpit may substitute a long-sleeved shirt, long pants, shoes, and socks for labeling-specified personal protective equipment." The pilot is not required to wear gloves and eyewear.

j Most product labels include the language: “Human flagging is prohibited.” However, three DUET 60 product labels do not prohibit the use of a flagger. To protect all legal handlers, flagger exposure was evaluated in this exposure assessment.

**Table 46. Estimates of Short-, Intermediate- and Long-Term Risk (MOEs) from Exposure to Propanil for Rice Field Workers**

| Task [a] | Acute ADD[b] | Ave. DFR[c] | TC [d] | SADD [e] | Exposure Months [f] | AADD [g] |
|---|---|---|---|---|---|---|
| | MOE | ($mg/cm^2$) | ($cm^2/hr$) | MOE | | MOE |
| Scouting | 15 | 7.24 | 1100 | 11 | 2 | 20 |
| Weeding | 233 | 7.24 | 70 | 173 | 2 | 311 |

Exposure data used for MOE calculations was from Table 8 of the Human Exposure Assessment for Propanil (see Appendix C). Values < 300 are shaded.

Table 8 Legend; (reproduced from Appendix C).

a Based on product labels, propanil can only be used on rice in California. Scouting is assumed to be the scenario with the highest exposure. Therefore, scouting exposure will cover other activities such as harvesting (mechanical). Weeding (hand) is to be the assumed the scenario with the highest exposure covering all weeding methods (mechanical).

b Acute Absorbed Daily Dosage (ADD) is from Table 7.

c Average DFR. According to HHA practice, the DFR value at the assumed average reentry interval of expiration of REI plus 7 days. Based on U.S. EPA (2012), if chemical-specific DFR unavailable, 10% per day is used as default residue dissipation to calculate the average DFR of propanil. The DFR on the average REI was estimated based on a log-linear regression model (Edmiston et al., 2002).

d TC (transfer coefficient) values are from the Agricultural Default Transfer Coefficients (U.S. EPA, 2013).

e Seasonal Average Daily Dosage (SADD) = average DFR * TC * work hours/day (the work hours were assumed 8 hr/day) * 50% dermal absorption (default dermal absorption based on HHA practice) ÷ 70 kg body weight (U.S. EPA, 1997).

f The annual exposure months for field workers are determined by application periods based on the PUR database (Figure 5 and text).

g Annual Average Daily Dosage (AADD) = SADD * annual exposure months /12 months in a year.

h Lifetime Average Daily Dosage (LADD) = AADD * (40 years of work in a lifetime) / (75 years in a lifetime).

### 3) Residential Bystander Risk

#### *(i) Residential Bystander Risk from Aerial Applications*

The MOEs for short-term daily exposure to propanil for residential bystanders from aerial and ground boom application drift scenarios are summarized in Tables 47 and 48. The acute POD (14.1 mg/kg/day) was used to calculate all MOE values. Adult dermal MOEs exceeded the health protective target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 and 25 feet, respectively while adult inhalation MOEs exceeded the health protective target for all aerial application scenarios. Child dermal MOEs exceeded the health protective target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 feet while all child inhalation and oral MOEs exceeded the health protective target for all aerial application scenarios.

#### *(i) Residential Bystander Risk from Ground Boom Applications*

The MOEs for short-term daily exposure to propanil for residential bystanders from ground boom application drift scenarios are summarized in Table 49. The acute POD (14.1 mg/kg/day) was used to calculate all MOE values. All adult and child dermal, inhalation, and oral MOEs exceeded the target of 300. The lowest MOEs observed were for dermal exposure in adults (0 feet/MOE = 572) and children (0 feet/MOE = 390).

**Table 47. Estimates of Short-Term Risk (MOEs) from Drift Exposure to Propanil for Residential Bystanders: Fixed-Wing Aerial Application Method**

| Downwind Distance (ft) | Adult | | Child (1-2 years) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Dermal | Inhalation | Oral | | |
| | Dermal | Inhalation | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 120 | 1461 | 82 | 502 | 1989 | 64091 | N/A |
| 25 | 218 | 2046 | 149 | 863 | 3634 | 117500 | N/A |
| 50 | 297 | 2461 | 203 | 1034 | 4947 | 156667 | N/A |
| 100 | 513 | 3205 | 350 | 1373 | 8545 | 282000 | N/A |
| 250 | 945 | 3341 | 645 | 1461 | 15667 | 470000 | N/A |
| 500 | 1430 | 4700 | 976 | 2003 | 23898 | 705000 | N/A |
| 1000 | 2587 | 9658 | 1767 | 4040 | 42727 | 1410000 | N/A |

Exposure data used for MOE calculations was from Table 9b of the Human Exposure Assessment for Propanil (see Appendix C). Values < 300 are shaded.

**Table 48. Estimates of Short-Term Risk (MOEs) from Drift Exposure to Propanil for Residential Bystanders: Rotary Aerial Application Method**

| Downwind Distance (ft) | Adult | | Child (1-2 years) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Dermal | Inhalation | Oral | | |
| | Dermal | Inhalation | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 72 | 1040 | 49 | 340 | 1192 | 39167 | N/A |
| 25 | 238 | 2086 | 163 | 790 | 3972 | 128182 | N/A |
| 50 | 412 | 2787 | 281 | 1105 | 6845 | 235000 | N/A |
| 100 | 793 | 3821 | 541 | 1579 | 13178 | 470000 | N/A |
| 250 | 1875 | 5802 | 1278 | 2414 | 31333 | 1410000 | N/A |
| 500 | 3019 | 9400 | 2061 | 3917 | 50357 | 1410000 | N/A |
| 1000 | 6052 | 20143 | 4123 | 8393 | 100714 | NA | N/A |

Exposure data used for MOE calculations was from Table 9c of the Human Exposure Assessment for Propanil (see Appendix C). Values < 300 are shaded.

**Table 49. Estimates of Short-Term Risk (MOEs) from Drift Exposure to Propanil for Residential Bystanders: Ground Boom Application Method**

| Downwind Distance (ft) | Adult | | Child (1-2 years) | | | | |
|---|---|---|---|---|---|---|---|
| | | | Dermal | Inhalation | Oral | | |
| | Dermal | Inhalation | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 25 | 572 | 2046 | 390 | 863 | 19054 | 705000 | N/A |
| 50 | 863 | 2461 | 589 | 1034 | 28776 | 1410000 | N/A |
| 75 | 1157 | 2781 | 789 | 1180 | 38108 | 1410000 | N/A |
| 100 | 1469 | 3205 | 1002 | 1373 | 48621 | 1410000 | N/A |
| 150 | 2014 | 3249 | 1373 | 1402 | 67143 | 1410000 | N/A |
| 200 | 2587 | 3294 | 1767 | 1430 | 88125 | 1410000 | N/A |
| 250 | 3197 | 3341 | 2183 | 1461 | 108462 | N/A | N/A |
| 300 | 3884 | 3543 | 2650 | 1544 | 128182 | N/A | N/A |

Exposure data used for MOE calculations was from Table 9a of the Human Exposure Assessment for Propanil (see Appendix C) Values < 300 are shaded.

### 4) Aggregate Risk

Aggregate exposure is defined as the exposure to a single chemical (i.e., a pesticide) through multiple pathways and routes (USEPA, 2001). Relevant pathways facilitate the transport of a pesticide into a human body and in this RCD include food, drinking water, air, and those related to agricultural applications. The relevant routes are oral, dermal, and inhalation. Exposures by different routes are then combined (aggregated) when exposure durations and toxic effects of the pesticide correspond. Propanil residues have been detected in food, drinking water, and air so multiple possible exposure scenarios by all routes were predicted for residential bystanders and for agricultural workers. The aggregate exposures for propanil that were considered in this RCD included the following (Table 50): (a) occupational exposures to workers (dermal and inhalation routes) with contributions from dietary sources

(oral route) and (b) non-occupational exposures to residential bystanders from dietary sources (oral route) and from spray drift (oral, dermal, and inhalation routes). Aggregate MOEs were estimated using the following formulae:

- Aggregate MOE for Workers = $1/(1/MOE_O + 1/MOE_F)$
- Aggregate MOE for Residential Bystanders: Adult = $1/(1/MOE_D + 1/MOE_I + 1/MOE_F)$
- Aggregate MOE for Residential Bystanders: Child = $1/(1/MOE_D + 1/MOE_I + 1/MOE_C + 1/MOE_F)$

**Exposure Route Abbreviations:**
O: combined occupation exposure (i.e., ADD)
D: dermal exposure from drift.
I: inhalation exposure from drift.
F: oral exposure from food and water
C: cumulative deposition from drift (AHM + AOM + ASI) where:
AHM: hand-to-mouth exposure from drift
AOM: object-to-mouth exposure from drift.
ASI: soil ingestion exposure from drift.

In every case, MOE aggregation was conducted in a sequential, additive manner in order to obtain information on the relative contribution of each component.

**Table 50. Summary of Aggregated Exposure Components of Propanil to Agricultural Workers and Residential Bystanders**

| Type | Subpopulation | Duration | POD | Occupational Exposure Scenarios | Drift Exposure Scenarios | Dietary Exposure |
|---|---|---|---|---|---|---|
| Workers | Females of childbearing age (13 to 50 years old) | Short-term Daily (Acute) | Acute: 14.2 mg/kg/day | Herbicide handlers and field workers (O) | NA | Acute Tier 3 food and water (95th percentile exposure) (F) |
| Residential Bystander: Adult | Females of childbearing age (13 to 50 years old) | Short-term Daily (Acute) | Acute: 14.2 mg/kg/day | N/A | Dermal and inhalation from aerial (fixed and rotary winged aircraft) and ground (ground boom) applications (D and I) | Acute Tier 3 food and water (95th percentile exposure) (F) |
| Residential Bystander: Child | Children (1 to 2 years old) | Short-term Daily (Acute) | Acute: 14.2 mg/kg/day | N/A | Dermal, inhalation, and oral (cumulative deposition) from aerial (fixed and rotary winged aircraft) and ground (ground boom) applications (D, I, and C) | Acute Tier 3 food and water (95th percentile exposure) (F) |

### *(i) Aggregate Risk for Workers*

Acute/short-term occupational, residential bystander, and dietary MOEs were aggregated using the corresponding formula and method described above (Table 51). The aggregate MOEs for herbicide handlers and field workers were less than health protective target (300) for all application scenarios. In the above cases, the occupational MOE component was the majority contributor of exposure risk.

### *(ii) Aggregate Risk for Residential Bystanders*

Acute/short-term residential bystander, and dietary MOEs were aggregated using the corresponding formula and method described above (Tables 52-55). The aggregate MOEs for adults (females of childbearing age, 13 to 50 years old) exceeded the health protective target (300) for fixed wing and rotary aerial scenarios at downwind distances greater than 50 and 25 feet, respectively and for ground boom scenarios at all distances (Tables 52 and 53). The aggregate MOEs for children (1 to 2 years old) exceeded the health protective target (300) for all aerial and ground boom applications at downwind distances greater than 50 feet and all ground boom scenarios at downwind distances greater than 25 feet (Tables 54 and 55). In all the above cases, the relative contribution of dietary MOE component increased with down-wind distance.

**Table 51. Estimates of Short-Term, Aggregate Risk (MOEs) from Exposures to Propanil for Workers**

| Job Category or Task | Formulation, Use Rate and Acres per Day | Exposure Route | MOE |
|---|---|---|---|
| Ground boom, M/L | DF, Rice = 6.0 (max), 200 (max) | O | 5 |
| | | O + F | 5 |
| Aerial, M/L | DF, Rice = 6.0 (max), 720 | O | 1 |
| | | O + F | 1 |
| Ground boom, M/L | L (AC, FC, suspension), Rice = 6.0 (max), 200 (max) | O | 2 |
| | | O + F | 2 |
| Aerial, M/L | L (AC, FC, suspension), Rice = 6.0 (max), 720 | O | 1 |
| | | O + F | 1 |
| Ground boom, A | DF, AC, FC, suspension, Rice = 6.0 (max), 200 (max) | O | 15 |
| | | O + F | 15 |
| Aerial, A | DF, AC, FC, suspension, Rice = 6.0 (max), 720 | O | 11 |
| | | O + F | 11 |
| Flagger | DF, Rice = 6.0 (max), 350 | O | 8 |
| | | O + F | 8 |
| Scouting | N/A | O | 15 |
| | | O + F | 15 |
| Weeding | N/A | O | 233 |
| | | O + F | 231 |

Values < 300 are shaded.
Exposure Route Abbreviations:
O: combined occupation exposure (i.e., ADD)
F: oral exposure from food and water

**Table 52. Estimates of Short-Term, Aggregate Risk (MOEs) from Exposures to Propanil in Residential Bystanders in Aerial Application Scenarios: Females of Childbearing Age (13 to 50 years old)**

| Drift Scenario | Exposure Route | Downwind Distance (ft) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **0** | **25** | **50** | **100** | **250** | **500** | **1000** |
| Fixed Wing Aerial Application | D | 120 | 218 | 297 | 513 | 945 | 1430 | 2587 |
| | D + I | 111 | 197 | 265 | 442 | 737 | 1096 | 2041 |
| | D + I + F | 110 | 196 | 263 | 436 | 721 | 1061 | 1922 |
| Rotary Aerial Application | D | 72 | 238 | 412 | 793 | 1875 | 3019 | 6052 |
| | D + I | 67 | 214 | 359 | 657 | 1417 | 2285 | 4653 |
| | D + I + F | 67 | 213 | 355 | 644 | 1359 | 2138 | 4080 |

Values < 300 are shaded.
Exposure Route Abbreviations:
D: dermal exposure from drift.
I: inhalation exposure from drift.
F: oral exposure from food and water

**Table 53. Estimates of Short-Term, Aggregate Risk (MOEs) from Exposures to Propanil in Residential Bystanders in Ground Boom Application Scenarios: Females of Childbearing Age (13 to 50 years old)**

| Drift Scenario | Exposure Route | Downwind Distance (ft) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **25** | **50** | **75** | **100** | **150** | **200** | **250** | **300** |
| Ground Boom | D | 572 | 863 | 1157 | 1469 | 2014 | 2587 | 3197 | 3884 |
| | D + I | 447 | 639 | 817 | 1007 | 1243 | 1449 | 1634 | 1853 |
| | D + I + F | 441 | 627 | 797 | 977 | 1198 | 1388 | 1557 | 1755 |

Values < 300 are shaded.
Exposure Route Abbreviations:
D: dermal exposure from drift.
I: inhalation exposure from drift.
F: oral exposure from food and water

**Table 54. Estimates of Short-Term, Aggregate Risk (MOEs) from Exposures to Propanil in Residential Bystanders in Aerial Application Scenarios: Children (1 to 2 years old)**

| Drift Scenario | Exposure Route | Downwind Distance (ft) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **0** | **25** | **50** | **100** | **250** | **500** | **1000** |
| Fixed Wing Aerial Application | D | 82 | 149 | 203 | 350 | 645 | 976 | 1767 |
| | D + I | 70 | 127 | 169 | 279 | 447 | 656 | 1229 |
| | D + I + C | 68 | 123 | 164 | 270 | 435 | 638 | 1194 |
| | D + I + C + F | 67 | 121 | 161 | 264 | 419 | 605 | 1084 |
| Rotary Aerial Application | D | 49 | 163 | 281 | 541 | 1278 | 2061 | 4123 |
| | D + I | 43 | 135 | 224 | 403 | 836 | 1351 | 2765 |
| | D + I + C | 41 | 130 | 217 | 391 | 814 | 1314 | NA |
| | D + I + C + F | 41 | 129 | 213 | 378 | 761 | 1183 | NA |

Values < 300 are shaded.
Exposure Route Abbreviations:
D: dermal exposure from drift.
I: inhalation exposure from drift.
C: cumulative deposition from drift. This includes oral hand-to-mouth, object-to-mouth, and soil ingestion.
F: oral exposure from food and water

**Table 55. Estimates of Short-Term, Aggregate Risk (MOEs) from Exposures to Propanil in Residential Bystanders in Ground Boom Application Scenarios: Children (1 to 2 years old)**

| Drift Scenario | Exposure Route | Downwind Distance (ft) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | **25** | **50** | **75** | **100** | **150** | **200** | **250** | **300** |
| Ground Boom | D | 390 | 589 | 789 | 1002 | 1373 | 1767 | 2183 | 2650 |
| | D + I | 269 | 375 | 473 | 579 | 694 | 790 | 875 | 976 |
| | D + I + C | 265 | 370 | 467 | 572 | 686 | 783 | NA | NA |
| | D + I + C + F | 259 | 359 | 449 | 546 | 649 | 734 | NA | NA |

Values < 300 are shaded.

Exposure Route Abbreviations:

D: dermal exposure from drift.

C: cumulative deposition from drift. This includes oral hand-to-mouth, object-to-mouth, and soil ingestion.

F: oral exposure from food and water

## D) Risk Appraisal

### 1) Introduction

Potential risks from dietary, occupational, residential bystander, and aggregate exposures to propanil were evaluated for this risk assessment. All evaluations of exposure and risk have limitations in their basic assumptions and in the data on which they are based. These limitations contribute to uncertainties in the estimates of human risk. Assumptions and data extrapolations are used wherever the available data are not sufficient to identify a hazard, characterize a dose response, or assess an exposure. These uncertainties extend to uncertainty factors or MOEs used to characterize risk. The specific areas of uncertainty associated with the risk assessment for propanil are discussed in the following sections.

### 2) Hazard Identification

While the most appropriate toxicity data for the human hazard identification of propanil would be from human studies, such data were not available. However, toxicity data from studies using laboratory animals were available and considered adequate for this purpose. All of the critical PODs used to assess the risk from propanil exposure by oral, dermal, and inhalation routes were derived from experimental results in which laboratory animals were dosed orally.

#### *(i) Acute Oral Toxicity*

A $BMDL_{1SD}$ of 14.1 mg/kg/day from a 30-day feeding study in rats was selected as the critical POD to evaluate the risk for acute oral, dermal, and inhalation exposure to propanil (O'Neill, 2002). In this study, the rats received propanil in the diet for 17 days and after that, basal diet without propanil for 13 days. The study included a comprehensive toxicologic evaluation and reported effects (clinical signs, changes to hematologic parameters, etc.) that were consistent with those reported in other studies of propanil toxicity. Increased metHb levels were observed after 1 day of propanil treatment and at every time-point thereafter. This effect persisted even after propanil was removed from the diet at day 17. The day 1 data on metHb levels did not produce acceptable BMD models. However, day 5 metHb concentration data in male rats established a $BMDL_{1SD}$ of 14.1 mg/kg/day that approximated an acute exposure regimen. During treatment day 5, statistically significant ($p<0.01$) and dose responsive increases in metHb levels (m/f: +67 to 200%/+117 to 450%) were observed at all dose levels (m /f: $\geq$ 25/28 mg/kg/day). These hematologic effects were supported by related hematology effects in other feeding studies with acute, subchronic, and chronic durations and were consistent with propanil's best-characterized toxic MOA. Taken together, these results support the use of this endpoint to develop a threshold for acute toxicity.

A study NOEL could not be determined for metHb levels because the effect was observed at all dose levels. In this case, the traditional approach would be to scale the LOEL to an ENEL by dividing the LOEL with a rationally-derived, but essentially arbitrary, UF. A UF of 3 or 10 for could be used for the conversion of a LOEL to a NOEL based on a subjective assignment of severity and carries uncertainty. In the above case, a BMD approach was preferred because it was the more robust option, based on the use of data from multiple treatment levels that incorporates information about the magnitude, variation, and pattern of dose response. The greatest uncertainty associated with the BMD approach is with the selection of the BMR. The metHb data modeled was continuous. Since there was no absolute or relative cutoff that could be used to directly relate elevated metHB levels to threshold toxicity in the rat or in the human, 1

SD was selected as the BMR per the US EPA guidance recommendation for continuous data (USEPA, 2012a). While there are uncertainties associated with the BMD approach related to model fit and selection, they are, in large part, mitigated by the intrinsic robustness of using magnitude and variation information from multiple data points and through the use of best-practices suggested in guidance documents (Reed *et al.*, 2004b; Reed *et al.*, 2004a; USEPA, 2012a).

The lowest acute $BMDL_{1SD}$ was 8.9 mg/kg/day from a chronic feeding study using rats. This POD was based on decrements of body weight gain during the first week of treatment. Decrements in body weight and body weight gain are regarded as clinical signs related to general health. Such changes were reported for propanil in several studies, including those with non-dietary exposure routes. However, in each study body weight measurements were made after at least one week of treatment. Therefore, any corresponding effects could not be considered as strictly acute. In contrast, blood metHb levels rose after a single day of exposure and were persistent over the duration of study, consistent with the hematologic MOA. Therefore, the higher POD of 14.1 mg/kg/day based on increased metHb levels in rats after 5 days of treatment was selected to characterize the acute risk from exposure to propanil.

DPR determined that data from inhalation and dermal studies with acute end-points were insufficient for evaluating propanil's toxicity by these routes. In each case, the dose-levels and corresponding end-points lacked the sensitivity necessary to identify the threshold of toxicity. Consequently, default bioavailability factors of 100% for inhalation exposures and 50% for dermal exposures were used with oral PODs to estimate risk. While there are uncertainties associated with the use of default bioavailability factors, they are unlikely to underestimate the relative internal exposure of propanil.

#### *(ii) Subchronic Oral Toxicity*

A $BMDL_{1SD}$ of 5.0 mg/kg/day from a 2-year chronic toxicity study in rats (Bellringer, 1994) was selected as the critical POD for evaluating subchronic oral, inhalation, and dermal exposures to propanil. This study included a comprehensive toxicologic evaluation, as well as subchronic endpoints. The POD was based on a dose-dependent rise in blood metHb in male animals observed after 13 weeks of exposure (+7 to 84%; $\geq$ 10 mg/kg/day) although this effect was also observed in females (+34 to 107%; $\geq$ 14 mg/kg/day).

Dose responsive changes for several related hematologic parameters were also noted including decreased red cell counts, decreased Hb levels, and decreased PCV values. All of these effects were consistent with the formation of metHb and the onset of hemolytic anemia. These results were supported by hematologic effects in other acute, subchronic, and chronic feeding studies and were consistent with propanil's best-characterized toxic MOA. Taken together, these considerations support the use of increased metHb levels to develop the critical subchronic POD. As with the acute POD, a study NOEL was not established, necessitating the BMD approach. The benefits and uncertainties associated with a BMD approach are identical to those previously discussed above for the acute POD.

The lowest subchronic $BMDL_{1SD}$ was 3 mg/kg/day from a subchronic feeding study using rats and based on metHb levels (Tompkins, 1993b). The decision to use a higher POD was based on the choice to use a POD with a similar magnitude but with a more robust data set, resulting in a model that better described the observed dose response (i.e. less model dependence).

There were no subchronic inhalation studies and the one subchronic dermal toxicity study with relevant end-points was of limited value because any effects reported may have been confounded by treatment-independent protozoan infections in the experimental animals (Margalitch and Ackerman, 1990 ). Default bioavailability factors of 100% for inhalation exposures and 50% for dermal exposures were therefore used with the subchronic, oral $BMDL_{1SD}$ of 5.0 mg/kg/day. While there are uncertainties associated with the use of default bioavailability factors, their use is unlikely to underestimate the relative internal exposure, and by extension, risk from propanil.

***(iii) Chronic Oral, Dermal, and Inhalation Toxicity***

A $BMDL_{10}$ of 1.5 mg/kg/day from a chronic toxicity study in rats based on incidence of splenic hemosiderosis in male animals (Bellringer, 1994) was selected as the critical POD for evaluating chronic oral, inhalation, and dermal exposures to propanil. This study included a comprehensive toxicologic evaluation (e.g., clinical signs, food intake, body weight, blood chemistry and hematology, etc.). The incidence of splenic hemosiderosis in males increased in all dose groups (+24 to +62%). Other signs of splenic toxicity included organ enlargement and increased absolute and relative spleen weights. Hemosiderin deposition was also observed in kidney proximal convoluted tubular epithelium in satellite group males and females (week 52) at all dose levels. All of the hematologic, splenic, and renal changes were consistent with the formation of metHb. As a NOEL was not observed (the effect occurred at all dose levels) a BMD approach was appropriate. The benefits and uncertainties associated with a BMD approach are identical to those previously discussed above for the acute POD. Quantal BMD algorithms were used to model splenic hemosiderosis data with a 10% extra risk level. The decision to use a BMR set to 10% extra risk was in part based on the recommendation to use a "standard reporting level" for quantal data in the US EPA Benchmark Dose Technical Guidance document when comparing BMDL values across endpoints (the lower 95% confidence interval of the BMD) (USEPA, 2012a). DPR's current best practices for the selection BMR levels also require careful consideration of effect incidence levels, effect severity, and group size based on recommendation given in our corresponding guidance (Reed *et al.*, 2004b). The resulting $BMDL_{10}$ (1.5 mg/kg/day) was the lowest POD for any other effect based on splenic, hematologic, or liver toxicity. The acute, subchronic, and chronic PODs used for this risk assessment are all based on an MOA that includes the formation of metHb. When taken together, these determinations suggest that longer exposures lead to increasingly severe effects.

There were no chronic inhalation or dermal toxicity studies for propanil, necessitating the use of the critical oral POD with default bioavailability factors of 100% for inhalation exposures and 50% for dermal exposures. Once again, although there are uncertainties associated with the use of these factors, they are unlikely to underestimate the relative internal exposure of propanil.

***(iv) Genotoxicity***

The results from tests evaluating the genotoxicity of propanil were negative in assays for gene mutation, DNA damage (induction of UDS), mitotic recombination, and chromosomal aberration (Simmon, 1979; Shirasu *et al.*, 1980; O'Neill *et al.*, 1983; Kruszewski *et al.*, 1984; Gudi and Krsmanovic, 2001; San and Reece, 2001). Positive results were observed in an *in vitro* assay for DNA damage (increased zone of inhibition using a repair deficient strain of Bacillus subtilis with no metabolic activation (Simmon, 1979) and in an *in vivo* somatic mutation and recombination test (Drosophila wing spot assay), using larval

strains with standard and high p450 capacities (Kaya *et al.*, 2000). Positive results were also observed in an *in vivo* study evaluating the clastogenicity of 3,4-DCA (Eissa *et al.*, 2012). DPR suggest that this study provides compelling evidence that propanil may have genotoxic activity mediated by its metabolite, 3,4-DCA.

#### *(v) Oncogenicity Weight of Evidence*

A more complete discussion of this topic appears in the Hazard Identification section. A summary of key points relevant to risk appraisal follows.

Two tumor types were significantly increased with dietary propanil treatment in the rat: benign testicular interstitial tumors and hepatocellular adenomas (Bellringer, 1994). Tumors that originate in the interstitial tissue are the most frequently observed spontaneous neoplasms in the rat testis. The interstitium is primarily made up of perivascular Leydig cells whose main task is the production of testosterone in response to stimulation by pituitary LH-- (McConnell *et al.*, 1992). Disruption of testosterone signaling leading to increased pituitary LH secretion is a suspected pathway to hyperplasia and neoplasia in the testicular interstitium (McConnell *et al.*, 1992).

The second type of tumor that increased with dietary propanil in the rat was the benign hepatocellular adenoma (Bellringer, 1994). The rodent liver is a common target organ for xenobiotics because of its primary metabolism and detoxification functions (Thoolen *et al.*, 2010). Hepatocellular adenomas originate in hepatocytes that make up the lobular architecture of the liver parenchyma. They are benign, common in older rodents, and often arise from regenerative hyperplasia following exposures to hepatotoxic xenobiotics (Thoolen *et al.*, 2010). Although they occasionally progress to carcinomas, this outcome is less common in rats than in mice (Thoolen *et al.*, 2010). A path to propanil-induced regenerative hyperplasia might be initiated by proximal hydrolysis and activation of 3,4-DCA by liver aryl acylamidase and CYP450 (Williams and Jacobson, 1966).

The appearance of two types of cancer were significantly increased following propanil dosing in mice: malignant lymphomas and hepatocellular adenomas (Tompkins, 1994). Lymphomas localized to the spleen are common in CD-1 mice most often developing from B-cells (follicular center cell (FCC)) and B and/or T-cells (lymphoblastic) (Frith *et al.*, 1993; Ward, 2006). Lymphomas may be induced with exposures to retroviruses, radiation, and environmental chemicals and their rate of spontaneous incidence increases with age (Frith *et al.*, 1993; Ward, 2006). DPR concluded that the increased incidence of propanil-mediated splenic lymphoma in mice may begin with the accumulation of scavenged erythrocytes leading to splenic enlargement, hyperplasia, and hemosiderin accumulation. Hemosiderin iron-catalyzed free radical reactions (e.g., lipid peroxidation, DNA strand breaks, and protein degradation) might then induce oncogenesis (Bus and Popp, 1987).

As for the rat, the hepatocellular adenomas observed in mice originate in hepatocytes that make up the lobular architecture of the liver parenchyma, are usually considered benign, and are relatively common in older rodents and in those treated with hepatotoxic xenobiotics (Thoolen *et al.*, 2010). Hepatocellular adenomas in mice can arise from toxicant-induced regenerative hyperplasia and progress to carcinomas (Thoolen *et al.*, 2010).

Altogether, the chronic rodent studies showed that propanil induced three types of tumors: 1) liver tumors in female rats and male mice, 2) malignant lymphoma in female mice, and 3) testicular tumors in male rats. For the first two type of tumors (liver and lymphoma), DPR assumed that a genotoxic mode of action of propanil was operative. This assumption was based on the available *in vivo* evidence for genotoxictity of the metabolite 3,4-DCA. When a threshold mode of action for these tumors is not known and there is evidence of genotoxicity, a linear extrapolation approach should be considered to calculate cancer potency. However, neither of these tumors were amenable to linear extrapolation analysis because they were a high-dose effect.

The third tumor type, testicular tumors in rats, showed the most sensitivity to propanil. For these tumors, DPR assumed propanil induction via threshold MOA. This MOA involves propanil-mediated disruption of androgen signaling, which in turn leads to sustained hyper-secretion of LH by the pituitary and the development of testicular focal interstitial hyperplasia, a known precursor to the observed testicular tumors. Accordingly, DPR established PODs for upstream effects (increased testis weight, testicular hyperplasia, absent epididymal spermatozoa, and reduced secretions in seminal vesicles) to protect against the development of testicular tumors. It should be noted that the critical chronic POD of 1.5 mg/kg/day for hematologic effects was over 7-fold lower than the lowest PoD of endocrine effects and thus was considered to be protective of all chronic and subchronic effects, including the development of testicular tumors.

***(vi) Immunotoxicity***

In published literature studies, propanil and its metabolites have been demonstrated to adversely affect components of both the innate and adaptive immune responses through suppression or enhancement depending on the exposure and the specific response being measured (Barnett and Gandy, 1989; Barnett *et al.*, 1992; Zhao *et al.*, 1995; Cuff *et al.*, 1996; Xie *et al.*, 1997a; Xie *et al.*, 1997b; Zhao *et al.*, 1998; Watson *et al.*, 2000; Frost *et al.*, 2001; de la Rosa *et al.*, 2003; Brundage *et al.*, 2004; de la Rosa *et al.*, 2005; Salazar *et al.*, 2005; Salazar *et al.*, 2006; Corsini *et al.*, 2007; Ustyugova *et al.*, 2007; Salazar *et al.*, 2008). Furthermore, there is evidence for endocrine system-mediated immunotoxicity that is not mediated by the direct or indirect disruption of steroid hormone signaling at the levels of steroid receptor binding and steroid synthesis (Salazar *et al.*, 2006). The relevance of these observations to human health is underscored by the results of a prospective population-based study of male agricultural workers that correlated quantifiable levels of 3,4-DCA in urine (as a marker for exposure) with increased levels of plasma IL-6 and decreased levels of IL-10 and IFN in exposed cohorts (Corsini *et al.*, 2007).

The lowest immunotoxicity-based POD suitable for assessing the risk of propanil exposure to human health is a NOEL established in a guideline 29-day immunotoxicity study of 48 mg/kg/day in male rats (Padgett, 2007). This NOEL is approximately ten-fold higher than the critical subchronic oral POD ($BMDL_{1SD}$ = 5.0 mg/kg-day) based on metHb levels. Based on their relative values, the latter POD is considered to be protective of the immuntoxicity of propanil.

***(vii) Reproductive and Developmental Toxicities***

The NOELs were the identical for parental, systemic, reproductive, and pup toxicities in 2 and 3-generation reproduction studies (1 each) with dietary exposure and using rats (Borzelleca *et al.*, 1966; Stump, 1998). A POD for pup toxicity ($BMDL_{1SD}$ = 18 mg/kg/day) based on the delayed completion of balanopreputial separation was also derived (Stump, 1998). The lowest POD for reproductive toxicity ($BMDL_{1SD}$ = 11.2 mg/kg/day) was based on decreased seminal vesicle secretions in male rats from a 2-year chronic toxicity and carcinogenicity study (Bellringer, 1994). Other PODs based on male reproductive endpoints ranged from 15.1 mg/kg/day (absent epididymal spermatozoa) to 37.5 mg/kg/day (increased testicular weight). While there is potential evidence of reproductive and pup toxicity for propanil, there is no evidence to suggest increased pre or post-natal sensitivity. Further, the critical POD levels based on metHb levels (acute and subchronic) and splenic hemosiderin (chronic) should be protective against these effects.

#### *(viii) Endocrine Disruption*

Propanil has been shown to have a weak affinity for the rat AR in an *in vitro* rat prostate competitive binding assay (McCarroll, 2012). While propanil's affinity for the AR receptor was 6000-fold less than that for testosterone and 51-fold less than that for hydroxyflutamide, evidence suggests that propanil may act via an endocrine MOA to disrupt the pituitary-testicular axis *in situ*. There is also evidence for endocrine system-mediated toxicity of propanil that is not a function of direct or indirect disruption of steroid hormone signaling at the levels of steroid receptor and steroid synthesis (Salazar *et al.*, 2006).

Direct toxicological evidence for endocrine disruptor activity comes from two studies. In the first, a 2-generation reproductive toxicity study (Stump, 1998), male and female rat pups treated with propanil developed more slowly in the completion of balanopreputial separation and vaginal perforation compared to controls. In the same study, organs rich in endocrine hormone receptors were affected. Effects included increased testes (m), adrenal gland (m and f), ovary (f), brain (m and f), epididymis (m), and seminal vesicle/coagulating gland (m) weights and decreased testicular sperm counts effects. In the second, a 2-year rat chronic toxicity and carcinogenicity study (Bellringer, 1994), there was an increased incidence of testicular focal interstitial hyperplasia combined with absent epididymal spermatozoa, reduced secretions in seminal vesicles, and prostate atrophy in male rats in the same study. Other effects indicated by thickening of the cervix and uterus and enlarged adrenal glands in females. DPR suggests that all of these effects were likely mediated by propanil through disruption of the pituitary-gonadal axis and testicular tumors in males may represent one long-term consequence.

The PODs for the putative endocrine effects described above are 18 mg/kg/day ($BMDL_{1SD}$) for subchronic effects and range from 11.2 to 37.5 mg/kg/day ($BMDL_{10}$) for chronic effects. The subchronic POD is 3.6-fold higher that than the critical oral, subchronic POD based on metHb level ($BMDL_{1SD}$ = 5 mg/kg/day) while the lowest chronic POD is 7.5 fold higher that than the critical oral, chronic POD based on splenic hemosiderosis ($BMDL_{10}$ = 1.5 mg/kg/day). Based on these comparisons, DPR suggests that the critical oral, subchronic, and chronic PODs will be protective of effects mediated by the putative endocrine MOA.

### *(ix) Issues Related to Metabolites, Contaminants, and Co-Formulated AIs*

***3,4-DCA***

The only scenarios likely to involve direct, toxicologically-relevant exposures to 3,4-DCA are those corresponding to dietary intake. Occupational and bystander exposures by dermal, inhalation, and cumulative deposition routes are likely to be entirely in the form of propanil parent. Based on the above, the following paragraphs will focus on the risk posed by dietary exposure.

The PODs used for estimating risks from acute and chronic dietary exposures to propanil were based on registrant submitted studies using propanil as the test article. The data for 3,4-DCA included in the toxicity profile for comparison were based on studies summarized in an EU regulatory document (ECB, 2006a). While the 3,4-DCA data were limited and often precluded the direct comparison of threshold toxicities of the parent and metabolite in comparable endpoints, all relevant possibilities were considered.

In the consensus metabolic scheme for propanil in mammals, one molecule of propanil is converted to one molecule of 3,4-DCA following aryl acylamidase hydrolysis. A mass-based POD for 3,4-DCA must be converted to a mass-based POD for propanil-equivalents using a conversion factor based on the ratio of corresponding molecular weights to calculate dietary risk because these are the units for the propanil residue data used to estimate dietary exposures. This conversion is also a prerequisite for directly comparing PODs for 3,4-DCA and propanil.

Note that there were no acute or chronic PODs for 3,4-DCA to compare to the critical acute and chronic oral PODs for propanil. The NOEL for the 21-day dermal propanil exposure study resulted in a NOEL value significantly higher than the LOEL in the corresponding study with 3,4-DCA. However, DPR did not use the study results because of a concomitant protozoan infection in the animals, thereby impacting quality of the study's data (Margalitch and Ackerman, 1990 ).

The lowest oral $LD_{50}$ value for 3,4-DCA (530 mg/kg) corresponds to an estimated $LD_{50}$ of 716 mg propanil equivalents/kg (= 530 mg 3,4-DCA/kg) x (1.35 or 218.1 g/mol propanil/162.0 g/mol 3,4-DCA). This estimated $LD_{50}$ is only 8% lower than the lowest corresponding oral $LD_{50}$ value for propanil (779 mg/kg).

The maternal and developmental NOELs for 3,4-DCA from a developmental toxicity study in rats were 5 and 25 mg/kg/day, respectively, corresponding to 7 and 34 mg propanil equivalents/kg/day. The converted maternal 3,4-DCA NOEL is 30% higher than the corresponding critical oral subchronic POD for propanil based on metHb levels in rats ($BMDL_{1SD}$ = 5 mg propanil/kg/day). The 3,4-DCA developmental NOEL is also higher than the POD for propanil based on a delay of balanopreputial separation in male rats ($BMDL_{1SD}$ = 18 mg propanil/kg/day), whether or not it is converted to propanil equivalents.

DPR suggests that the use of critical acute and chronic PODs based on the toxicity of propanil parent will be protective for acute and chronic dietary exposures to propanil residues convertible to 3,4-DCA without the application of an additional UF. Based on the lack of directly comparable data for 3,4-DCA, there remains a possibility that the use of propanil-based PODs may lead to an underestimation of dietary risk.

***TCAB***

The minimum and maximum reported levels of TCAB in technical propanil were 0.1 ppm (1 x $10^{-5}$ %) and 2900 ppm (0.29%), respectively (Bunce, Corke et al. 1979; Hill, Rollen et al. 1981; Di Muccio, Camoni et al. 1984; Singh and Bingley 1991; van Birgelen, Hebert et al. 1999). It follows that a propanil dose equivalent to the subchronic or chronic oral PODs ($BMDL_{1SD}$ = 5 mg/kg/day or $BMDL_{10}$ = 1.5 mg/kg/day, respectively) could have a maximal estimated doses of ≤ 0.015 or ≤ 0.0045 mg/kg/day TCAB, respectively (TCAB mg/kg/day = POD mg/kg/day x 0.29% x 1/100%). The estimated maximum TCAB level based on the subchronic POD for propanil is approximately 7-fold less than the values for the lowest corresponding oral, subchronic, reproductive, developmental, and endocrine disruption LOELs for TCAB (0.1 mg/kg/day) (van Birgelen, 1998a; van Birgelen *et al.*, 1999; NTP, 2010) and the estimated maximum TCAB level based on the chronic POD for propanil is approximately 700-fold less than the values for the lowest corresponding chronic TCAB LOEL (3 mg/kg/day) (NTP, 2010). This suggests that the critical PODs for propanil parent will be protective of the dietary intake of the parent molecule and its metabolite TCAB for non-oncogenic effects.

DPR contends that there is clear evidence for a genotoxic MOA for oncogenicity for TCAB. While an assessment of the cancer risk posed by exposures to TCAB alone or in mixtures with species directly related to propanil should be given consideration, it is beyond the scope of the current risk assessment for propanil.

***TCAOB***

The highest reported levels of TCAOB in technical propanil were < 0.05 ppm (5 x $10^{-6}$ %), which were approximately 58,000-fold lower than the highest levels reported for TCAB (Bunce *et al.*, 1979; Hill *et al.*, 1981; Di Muccio *et al.*, 1984; Singh and Bingley, 1991; van Birgelen *et al.*, 1999). They suggest maximal estimated doses of ≤ 2.5 x $10^{-7}$ mg/kg/day for TCAOB at propanil doses equivalent to its subchronic oral PODs ($BMDL_{1SD}$ = 5 mg/kg/day; TCAB mg/kg/day = POD mg/kg/day x (5 x $10^{-6}$ %) x 1/100%). This estimated maximum TCAOB level is thus approximately 400,000-fold less than the value for the lowest corresponding oral, subchronic, reproductive, developmental, and endocrine disruption LOEL (0.1 mg/kg/day). This suggests that the critical PODs for propanil parent will be protective against the dietary exposure of both the parent molecule and its metabolite TCAOB.

***BSM and BSM***

In California, some propanil formulations also contain the herbicidal AIs bensulfuron methyl (BSM) and halosulfuron methyl (HSM) (NPIRS, 2012). The characterization of risk from exposures to mixtures containing propanil and BSM or HSM is beyond the scope of this assessment. Nevertheless, co-exposure to these chemicals is likely and presents an additional layer of toxicologic uncertainty. The development of newer technologies and methods (e.g., *in vitro* methods like those in ToxCast) may be needed to gain a greater understanding of the toxicity of mixtures of this type.

**3) Exposure Assessment**

The principle uncertainties associated with exposure assessment fall into three main categories: (a) parameter uncertainty, (b) model uncertainty, and (c) scenario uncertainty.

***(i) Dietary Exposure Assessment***

### i(a) Parameter Uncertainty

Sources of parameter uncertainty associated with the dietary exposure assessment of propanil include the availability, quality, and applicability of food and water residue data and errors in sampling or reporting within the DEEM$^{TM}$-FCID consumption database.

***Anticipated Rice Residue Data***

The only currently approved use for propanil in California is for the protection of rice crops. While USDA PDP was established to provide residue data that are applicable to risk assessments, this was not the case for propanil residues in rice grain because the PDP relies on multi-residue QuEChERS (Quick, Easy, Cheap, Effective, Rugged, and Safe) methods to quantify and report propanil parent residues but not residues convertible to 3,4-DCA (USDA, 2014). Registrant-sponsored field trial studies that were conducted in support of setting tolerances for propanil and its metabolites convertible to 3,4-DCA were used instead (Young *et al.*, 1992b; Young *et al.*, 1992a; Young *et al.*, 1992c; Ehn, 2004). The decision to use field trial data for estimating dietary exposure is supported by the US EPA (USEPA, 2003). The field trial data used reflected relevant use patterns and environmental conditions relevant to California, as only California data was included. While variations in weather patterns (i.e., precipitation levels, air temperature, etc.) add uncertainty to the relevance of field-trial residue levels, the availability of data for propanil and its metabolites convertible to 3,4-DCA provides a measure of confidence that, in that respect, residues and risk are less likely to have been underestimated. Further, both DPR and US EPA used anticipated residue data for rough rice grain (i.e., the grain including the hull), a form of rice grain that has a higher level of residue than unpolished (ie. brown) or polished (i.e. white) rice grains. Maximum anticipated residue levels for acute exposure assessment while average anticipated residue values were also calculated using 1 and 0.5-times the analytical limit of detection (LOD) for non-detects acute (blended foods) for chronic exposure assessment (DPR, 2009).

***Anticipated Drinking Water Residue Data***

The surrogate anticipated residues of propanil and its metabolites convertible to 3,4-DCA in drinking water used for this risk assessment were based on DPR surface water monitoring data for the years 2000 through 2015 (DPR, 2016c). The Environmental Monitoring Branch of DPR routinely samples irrigation ditch water and field outflows for pesticide contamination. These surface water sources are not used for drinking water in California. Rice growers in California are required to hold water from pesticide-treated rice crops on their fields for seven days following propanil applications (UCCE, 2015). This practice was adopted as a primary method to reduce the concentrations of pesticide residues. In the case of propanil, the hold provides time for the actions of known degradation pathways that include photolysis, uptake by plants, sorption to soil, and microbial metabolism (Kanawi *et al.*, 2016). Following release, this water may eventually flow into tributaries, surface water bodies, and ground water reservoirs while the degradative processes continue. This risk assessment used concentrations of propanil alone and with 3,4-DCA found in near-field surface water through the DPR Surface Water Protection Program because they were considered as a high-end surrogate for finished drinking water, and therefore represent high-end estimates of potential exposure. Maximum anticipated residue levels were identified for propanil and 3,4-DCA and summed for acute Tier 1 and 2 exposure assessments while average anticipated residue values were also calculated using 0.5-times the analytical limit of detection (LOD) for non-detects and summed

for chronic exposure assessment (DPR, 2009). A distribution of propanil residue values (detects and 0.5-times the LOD for NDs) was used for the acute Tier 3 analysis. Anticipated maximum and average residue levels of Propanil and 3,4-DCA in groundwater were also calculated using groundwater monitoring data collected between 2001 and 2015 (DPR, 2016b). DPR surface water data was selected over DPR ground water data to calculate surrogate drinking water values because they represented the highest potential exposures for any of the sources of drinking water evaluated. Neither surface water nor groundwater data were an exact match for peak residue levels in finished water . In choosing to estimate dietary exposures based on surface water monitoring data, DPR acknowledges that the resulting analysis likely represents high-end or worst-case for California drinking water exposures. The estimated values for drinking water are shown in Table 56. The US EPA modeling-based residue estimates for propanil and 3,4-DCA in ground and surface water are included for comparison (Abdel-Saheb, 2001).

**Table 56. Summary of Anticipated Propanil Residue Levels in Drinking Water**

| Reference | Source | Sample Dates (n) | Range of Detects (ppb/n) | Analyte | Range of LOD/Q (ppb) | Analyte | Maximum Level (ppb Propanil eqv.) | Average Level (1/2 X LOD) (ppb Propanil eqv.) |
|---|---|---|---|---|---|---|---|---|
| (DPR, 2016c) | Surface Water | 2005 to 2012 (107) | 0 (0) | 3,4-DCA | 4.00E-3 to 1.82e-2 | 3,4-DCA | 2.46E-2 [a] | 3.52E-3 [a] |
| (DPR, 2016c) | Surface Water | 2000 to 2015 (1956) | 4.30E-3 to 47 (150) | propanil | 4.00E-3 to 5 | propanil | 47 | 1.52E-1 |
| | | | | | | **Sum** | 47 | 1.56E-1 |
| (DPR, 2016b) | Ground Water | 2004 to 2011 (1887) | 1.00E-3 to 5.41E-1 (99) | 3,4-DCA | 4.00E-3 to 6.00E-3 | 3,4-DCA | 7.30E-1 [a] | 4.69E-3 [a] |
| (DPR, 2016b) | Ground Water | 2001, 2005 to 2011, and 2013 to 2015 (826) | 9.7E-2 (1) | propanil | 6.00E-3 to 5.00E-2 | propanil | 9.70E-2 | 9.35E-3 |
| | | | | | | **Sum** | 8.27E-1 | 1.40E-2 |
| **US EPA Modeled Estimates** | | | | | | | | |
| **Reference** | **Source** | | | | | **Analyte** | **Peak (ppb Propanil eqv.)** | **Long-Term Average (ppb Propanil eqv.)** |
| (Abdel-Saheb, 2001) | Surface Water (California only) | | | | | 3,4-DCA | 143.1 [a] | 8.37 [a] |
| (Abdel-Saheb, 2001) | Surface Water (California only) | | | | | propanil | 7.0E-1 | 2.0E-2 |
| | | | | | | **Sum** | 144 | 8.39 |
| (Abdel-Saheb, 2001) | Ground Water | | | | | 3,4-DCA | 4.78E-1 [a] | 4.78E-1 [a] |
| (Abdel-Saheb, 2001) | Ground Water | | | | | propanil | 1.0E-3 | 1.0E-3 |
| | | | | | | **Sum** | 4.79E-4 | 4.79E-4 |

a Original data reported as 3,4-DCA and converted to propanil eqv. as follows: ppm propanil = (ppm 3,4-DCA) X 1.35 where 1.35 = ratio of MW PRN (218.1 g/mol) over MW 3,4-DCA (162.0 g/mol)

### *Other Anticipated Residues*

The anticipated residues of propanil and its metabolites convertible to 3,4-DCA in milk, meat, poultry, and egg were identical to those used for the chronic dietary exposure assessment performed by US EPA and based on ruminant and poultry feeding studies and a crayfish residue study (Kinard, 2002). Based on the dose or exposure levels used in the corresponding studies, these anticipated residue data are likely to reflect high-end exposures.

### *3,4-DCA Residue Considerations*

The levels of 3,4-DCA residues used to estimate levels of propanil equivalents in surface water may include residues from the structurally similar herbicides, linuron and diuron (DaSilva, 2016). At present it is not possible to quantify 3,4-DCA residues based on their source. While this may result in an overestimate of risk, it may also more accurately replicate real-world exposures to 3,4-DCA from drinking water.

***Cumulative Toxicity***

As is the case for propanil, 3,4-DCA is both a metabolite and degradant of linuron and diuron. Based on the weight of evidence, DPR agrees with the US EPA's position in 2003 that is summarized as follows:

> 3,4-DCA is also a metabolite of two other pesticides, linuron and diuron. However, the MARC (Metabolism Assessment Review Committee) does not recommend aggregating residues of 3,4-DCA for the propanil, linuron and diuron risk assessments. 3,4-DCA is a degradate of these three pesticides; however, it is only a significant residue of concern for propanil. 3,4-DCA is not a residue of concern per se for linuron or diuron (<1%). The analytical method for quantifying residues of concern from linuron and diuron converts all residues to 3,4-DCA as a convenience, but 3,4-DCA was not a significant residue in any metabolism or hydrolysis study. Therefore, the MARC recommended that all residues convertible to 3,4-DCA would be included in the tolerance expression for linuron and diuron because no validated enforcement method was available for the quantification of individual components of the residues of concern. (USEPA, 2003) (pg. 10).

***Consumption Data***

Acute and chronic dietary exposure assessments were performed using Dietary Exposure Evaluation Model software (DEEM™-FCID ver. 3.16; Durango Software, LLC). This version of DEEM™-FCID used the February 2012 US EPA/USDA FCID recipe set and National Health and Nutrition Examination Survey (NHANES) 2-day food consumption survey data for 2003 through 2008. Uncertainties in this approach can arise due to subgroup or regional underrepresentation, reporting errors, changes in culinary habits over the consumption period, and changing demographics. Additional uncertainty arises from the assumption that propanil exposures only result from the consumption of foods based on commodities with tolerances for propanil. That is, no illegal uses of propanil in food crops were included in this analysis.

### i(b) Scenario and Model Uncertainty

***Acute Dietary Exposure***

A Tier 1 and 2 point-estimate analyses were run using commodities with residue levels set to corresponding tolerances or up to and including their tolerances and that included surface water monitoring data. In both cases, the resulting exposures corresponded to MOE levels below 3000 and 1500 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively, for several subgroups. A more refined Tier 3 analysis was subsequently performed. Although there are uncertainties associated with this approach, the assumptions are conservative as it is unlikely that all of the commodities consumed in a given day will contain propanil residues at the highest legally-allowed level. The refined, acute Tier 3 probabilistic analysis used maximum or average (with 0.5 LOD for blended foods) field trial residue data for rice-based

commodities, anticipated residues for meat, milk, eggs and crayfish, and a probabilistic distribution of surface water monitoring data. Additional refinements included factors to account for residue concentration with processing. The resulting exposures resulted in MOE levels above 3000 and 1500 at the 95th and 99th percentiles, respectively, so analyses with further refinements were not performed.

***Chronic Dietary Exposure***

A chronic Tier 1 analysis was not performed based on the unlikeliness of a scenario where all foods based on propanil treated commodities contain residues at tolerance-level. A refined, chronic point-estimate analysis was therefore conducted. This analysis used average (with 0.5 LOD) field trial residue data for rice-based commodities, anticipated residues for meat, milk, eggs and crayfish, surface water monitoring data. Additional refinements included factors to account for residue concentration with processing, and the PCT for rice. The resulting exposures resulted in MOE levels at or above 3460, so analyses with further refinements were not performed.

The DEEM chronic module uses the NHANES two-day average food consumption data to calculate the average, per capita, chronic dietary exposure. The per capita consumption includes individuals who consume rice (users) as well as those that are non-consumers. Because the consumption database showed that about 19% of the US population do not consume rice, we performed a sensitivity analysis to assess the impact of non-consumers on the overall chronic exposure. For this analysis, we used the same input data from the chronic residue file but in the DEEM acute module that allows the exposure to be estimated rice users only. For most subpopulations, the exposure estimates were essentially the same when the non-users were excluded. However, the user-only exposure for Nursing Infants and All Infants increased by 24% and 7 %, respectively, indicating that for rice the mean per capita consumption rate underestimated the mean user-only consumption rate. Regardless, the corresponding per user MOEs for both subpopulations were over 10 fold greater than the target MOE (300) and, as such, did not indicate a health concern.

***(ii) Occupational and Residential Bystander Exposure Assessment***

The risk appraisal sections for the occupational and residential bystander exposure assessments of propanil are in the Human Exposure Assessment for Propanil (Appendix C).

**4) Risk Characterization**

An MOE of 300 assumes that humans are 10-times more sensitive to a toxicant's action than the laboratory animals used to obtain the critical end-point data and that the human variation in this sensitivity could vary as much as 30-fold. As such, an MOE of 300 was considered by DPR to be a health-protective benchmark for propanil based on consideration of the weight-of-evidence for the critical PODs used, their corresponding MOAs, and their relationships to other end-points of concern. The uncertainties intrinsic to risk characterization are associated with the development of the component data (i.e critical PODs, UFs, and exposures) are discussed in the Risk Appraisal sections found earlier in this document as well as in the Human Exposure Assessment for Propanil (see Appendix C).

# V Conclusions

The health risk assessment of propanil was conducted for the general population for agricultural workers and for residential bystanders. The general population was represented by the total US population and 12 population subgroups that included adults, females of childbearing age, infants, and children. Workers included herbicide handlers and rice field workers while residential bystanders included adults (females of childbearing age, 13 to 50 years old) and children (1 to 2 years old). The following exposure scenarios were evaluated: (a) acute and chronic dietary; (b) acute/short-term, seasonal and annual, combined route (dermal and inhalation) occupational; (c) acute/short-term residential bystander, combined route (dermal, inhalation, and oral in children). Aggregate exposures risks were also estimated for workers (females of childbearing age, 13 to 50 years old) the residential bystanders (females of childbearing age, 13 to 50 years old and children 1 to 2 years old). Aggregate risks for workers included dietary and occupational MOEs while aggregate risks for residential bystanders also included spray drift MOEs. An MOE of 300 was used because it was considered to be health-protective for the critical PODs used.

Dietary Risk

All acute MOEs were greater than 8000 and 4300 at the 95$^{th}$ and 99$^{th}$ percentiles, respectively and all chronic MOEs were greater than 3000.

Occupational Risk

All acute and seasonal MOEs were less than 300 for all handler/applicator and field worker groups. Annual MOEs were below 300 for all handler/applicator groups and field scout groups.

Residential Bystander Risk

Adult (females of childbearing age, 13 to 50 years old) dermal MOEs exceeded the health protective target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 and 25 feet, respectively while adult inhalation MOEs exceeded the health protective target for all aerial application scenarios. Child (1 to 2 years old) dermal MOEs exceeded the health protective target (300) for fixed-wing and rotary aerial application scenarios at downwind distances greater than 50 feet while all child inhalation and oral MOEs exceeded the health protective target for all aerial application scenarios.All adult and child dermal, inhalation, and oral MOEs exceeded the target of 300 for ground boom application scenarios.

Aggregate Risk

Workers: The aggregate MOEs for herbicide handlers and field workers were less than health protective target (300) for all application scenarios. In the above cases, the occupational MOE component was the majority contributor of exposure risk.

Residential Bystanders: The aggregate MOEs for adults (females of childbearing age, 13 to 50 years old) exceeded the health protective target (300) for fixed wing and rotary aerial scenarios at downwind distances greater than 50 and 25 feet, respectively and for ground boom scenarios at all distances. The aggregate MOEs for children (1 to 2 years old) exceeded the health protective target (300) for all aerial and ground boom applications at downwind distances greater than 50 feet and all ground boom scenarios greater than 25 feet. In all the above cases, the relative contribution of spray drift MOE components decreased with down-wind distance.

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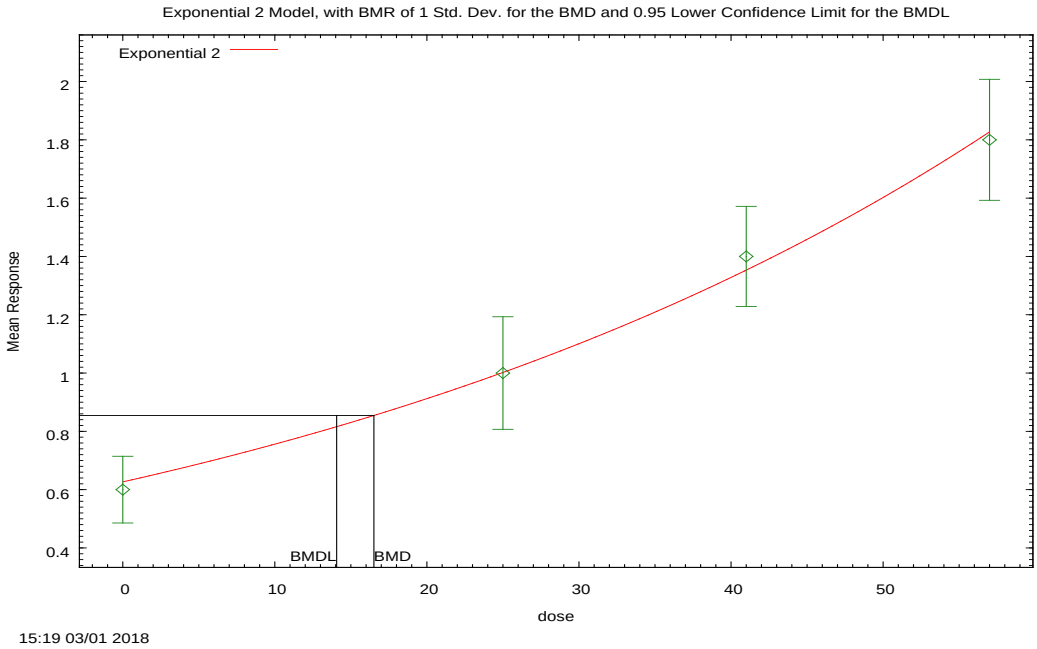
Zhao, W., Schafer, R., Cuff, C. F., Gandy, J., and Barnett, J. B. 1995. Changes in primary and secondary lymphoid organ T-cell subpopulations resulting from acute in vivo exposure to propanil. *Journal of toxicology and environmental health* 46:171-181.

# VII Appendices

## A) BMDS Outputs

### 1) Acute or Short-Term: Day 5 metHb Levels (Male Rat) (4 pages)




```
 ======================================================================
        Exponential Model. (Version: 1.10;  Date: 01/12/2015)
        Input Data File: H:/plohstroh/Documents/Propanil RCD/Study
Review/Subchronic Studies/MRID45829301 BMD/exp_MRID 45829301 M Day 5
metHb rev. 01 Mar 18_Exp-ConstantVariance-BMR1Std-Up.(d)
        Gnuplot Plotting File:
                                        Thu Mar 01 15:19:41 2018
 ======================================================================

 BMDS Model Run
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   The form of the response function by Model:
      Model 2:     Y[dose] = a * exp{sign * b * dose}
      Model 3:     Y[dose] = a * exp{sign * (b * dose)^d}
      Model 4:     Y[dose] = a * [c-(c-1) * exp{-b * dose}]
      Model 5:     Y[dose] = a * [c-(c-1) * exp{-(b * dose)^d}]

    Note: Y[dose] is the median response for exposure = dose;
          sign = +1 for increasing trend in data;
          sign = -1 for decreasing trend.

      Model 2 is nested within Models 3 and 4.
      Model 3 is nested within Model 5.
      Model 4 is nested within Model 5.


   Dependent variable = Mean
   Independent variable = Dose
   Data are assumed to be distributed: normally
   Variance Model: exp(lnalpha +rho *ln(Y[dose]))
   rho is set to 0.
```

A constant variance model is fit.

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

MLE solution provided: Exact

Initial Parameter Values

| Variable | Model 2 | |
|---|---|---|
| lnalpha | -2.97638 | |
| rho | 0 | Specified |
| a | 0.608245 | |
| b | 0.0195537 | |
| c | 0 | Specified |
| d | 1 | Specified |

Parameter Estimates

| Variable | Model 2 | Std. Err. |
|---|---|---|
| lnalpha | -2.95853 | 0.000377957 |
| a | 0.626638 | 0.051186 |
| b | 0.0187752 | 0.00175455 |

Table of Stats From Input Data

| Dose | N | Obs Mean | Obs Std Dev |
|---|---|---|---|
| 0 | 10 | 0.6 | 0.16 |
| 25 | 10 | 1 | 0.27 |
| 41 | 10 | 1.4 | 0.24 |
| 57 | 9 | 1.8 | 0.27 |

Estimated Values of Interest

| Dose | Est Mean | Est Std | Scaled Residual |
|---|---|---|---|
| 0 | 0.6266 | 0.2278 | -0.3698 |
| 25 | 1.002 | 0.2278 | -0.02769 |
| 41 | 1.353 | 0.2278 | 0.6511 |
| 57 | 1.827 | 0.2278 | -0.3585 |

Other models for which likelihoods are calculated:

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + log(mean(i)) * rho)

Model R: Yij = Mu + e(i)
Var{e(ij)} = Sigma^2

Likelihoods of Interest

| Model | Log(likelihood) | DF | AIC |
|---|---|---|---|
| A1 | 38.53945 | 5 | -67.07891 |
| A2 | 40.08474 | 8 | -64.16949 |
| A3 | 38.53945 | 5 | -67.07891 |
| R | 7.796781 | 2 | -11.59356 |
| 2 | 38.19138 | 3 | -70.38277 |

Additive constant for all log-likelihoods = -35.84. This constant added to the
above values gives the log-likelihood including the term that does not depend on the model parameters.

Explanation of Tests

Test 1: Does response and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A2 vs. A1)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does Model 2 fit the data? (A3 vs. 2)

Tests of Interest

| Test | -2*log(Likelihood Ratio) | D. F. | p-value |
|---|---|---|---|
| Test 1 | 64.58 | 6 | < 0.0001 |
| Test 2 | 3.091 | 3 | 0.3779 |
| Test 3 | 3.091 | 3 | 0.3779 |
| Test 4 | 0.6961 | 2 | 0.706 |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose

levels, it seems appropriate to model the data.

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here.

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here.

The p-value for Test 4 is greater than .1. Model 2 seems to adequately describe the data.

Benchmark Dose Computations:

Specified Effect = 1.000000

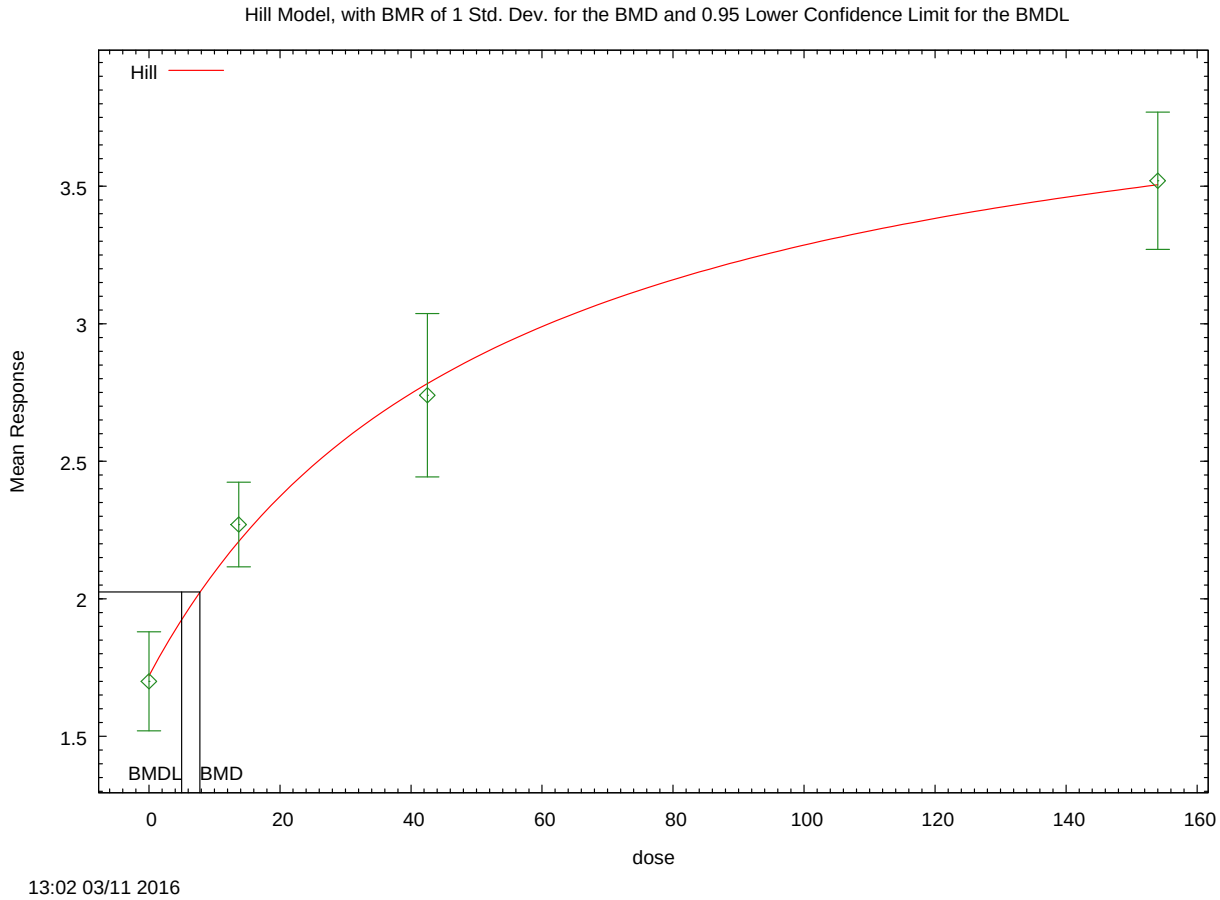
Risk Type = Estimated standard deviations from control

Confidence Level = 0.950000

BMD = 16.5154

BMDL = 14.0659

**2) Subchronic: Week 13 metHB Levels (Female Rat) (4 pages)**




```
 ======================================================================
        Hill Model. (Version: 2.17;  Date: 01/28/2013)
        Input Data File: H:/plohstroh/Documents/Propanil RCD/Study Review/274-
0018/274 0018 BMD/hil_274 0018 Female metHb Week 13_Opt.(d)
        Gnuplot Plotting File:  H:/plohstroh/Documents/Propanil RCD/Study Review/274-
0018/274 0018 BMD/hil_274 0018 Female metHb Week 13_Opt.plt
                                              Fri Mar 11 13:02:54 2016
 ======================================================================

 BMDS Model Run
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   The form of the response function is:

   Y[dose] = intercept + v*dose^n/(k^n + dose^n)


   Dependent variable = Mean
   Independent variable = Dose
   rho is set to 0
   Power parameter restricted to be greater than 1
   A constant variance model is fit

   Total number of dose groups = 4
   Total number of records with missing values = 0
```

Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

| | | |
|---|---|---|
| alpha = | 0.101079 | |
| rho = | 0 | Specified |
| intercept = | 1.7 | |
| v = | 1.82 | |
| n = | 0.30112 | |
| k = | 50.466 | |

Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s) -rho -n
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix )

| | alpha | intercept | v | k |
|---|---|---|---|---|
| alpha | 1 | -6.2e-008 | 1.5e-007 | 1.2e-007 |
| intercept | -6.2e-008 | 1 | 0.0026 | 0.55 |
| v | 1.5e-007 | 0.0026 | 1 | 0.77 |
| k | 1.2e-007 | 0.55 | 0.77 | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval Lower Conf. Limit | Upper Conf. Limit |
|---|---|---|---|---|
| alpha | 0.0922048 | 0.0208803 | 0.0512802 | 0.133129 |
| intercept | 1.72122 | 0.0933674 | 1.53823 | 1.90422 |
| v | 2.413 | 0.272093 | 1.87971 | 2.9463 |
| n | 1 | NA | | |
| k | 53.9431 | 18.5571 | 17.5718 | 90.3144 |

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

| Dose | N | Obs Mean | Est Mean | Obs Std Dev | Est Std Dev | Scaled Res. |
|---|---|---|---|---|---|---|
| 0 | 10 | 1.7 | 1.72 | 0.252 | 0.304 | -0.221 |
| 13.7 | 9 | 2.27 | 2.21 | 0.2 | 0.304 | 0.593 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 42.5 | 10 | 2.74 | 2.78 | 0.415 | 0.304 | -0.464 |
| 154 | 10 | 3.52 | 3.51 | 0.349 | 0.304 | 0.122 |

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2
Model A3 uses any fixed variance parameters that were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

| Model | Log(likelihood) | # Param's | AIC |
|---|---|---|---|
| A1 | 27.301269 | 5 | -44.602537 |
| A2 | 30.200236 | 8 | -44.400471 |
| A3 | 27.301269 | 5 | -44.602537 |
| fitted | 26.982996 | 4 | -45.965993 |
| R | -7.640911 | 2 | 19.281822 |

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels? (A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

| Test | -2*log(Likelihood Ratio) | Test df | p-value |
|---|---|---|---|
| Test 1 | 75.6823 | 6 | <.0001 |
| Test 2 | 5.79793 | 3 | 0.1219 |
| Test 3 | 5.79793 | 3 | 0.1219 |
| Test 4 | 0.636544 | 1 | 0.425 |

The p-value for Test 1 is less than .05. There appears to be a difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is greater than .1. A homogeneous variance model appears to be appropriate here

The p-value for Test 3 is greater than .1. The modeled variance appears to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems

to adequately describe the data

Benchmark Dose Computation

Specified effect = 1

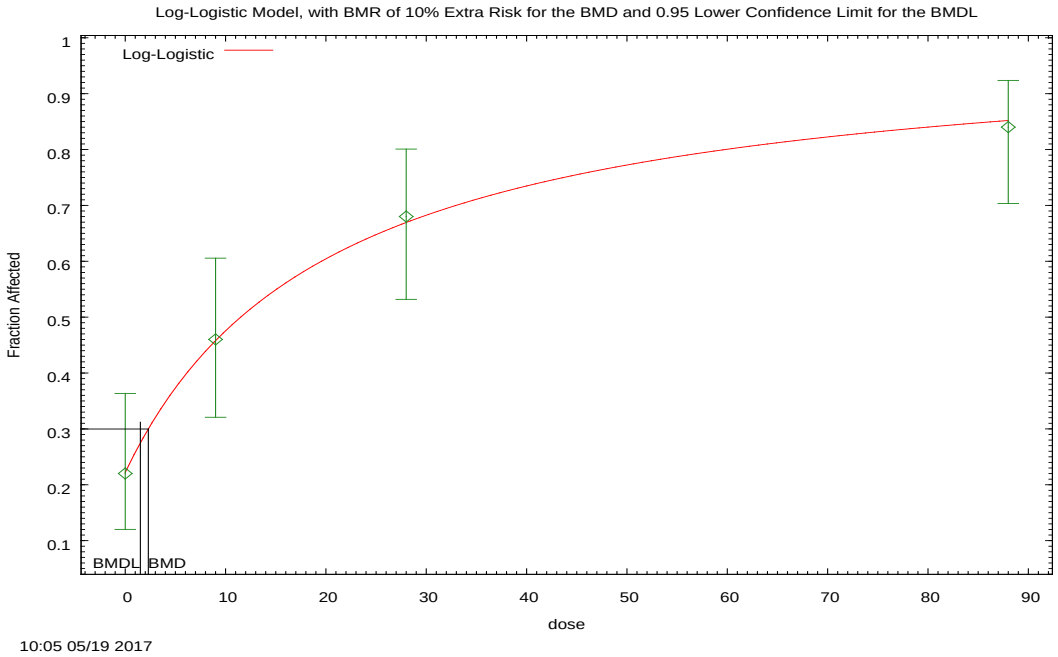
Risk Type = Estimated standard deviations from the control mean

Confidence level = 0.95

BMD = 7.7654

BMDL = 4.99478

**3) Chronic Oral: Total Splenic Hemosiderosis (3 pages)**




```
 ========================================================================
        Logistic Model. (Version: 2.14; Date: 2/28/2013)
        Input Data File: H:/plohstroh/Documents/Propanil RCD/Study
Review/274-0018/274 0018 BMD/lnl_274 0018 Male Spleen HemoSid Main
All_Lnl-BMR10-Restrict.(d)
        Gnuplot Plotting File:  H:/plohstroh/Documents/Propanil RCD/Study
Review/274-0018/274 0018 BMD/lnl_274 0018 Male Spleen HemoSid Main
All_Lnl-BMR10-Restrict.plt
                                        Fri May 19 10:05:46 2017
 ========================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background+(1-background)/[1+EXP(-intercept-
slope*Log(dose))]


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 4
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial Parameter Values
background = 0.22
intercept = -3.05603
slope = 1

Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s) -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix )

| | background | intercept |
|---|---|---|
| background | 1 | -0.55 |
| intercept | -0.55 | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval Lower Conf. Limit | Upper Conf. Limit |
|---|---|---|---|---|
| background | 0.221825 | 0.0569941 | 0.110119 | 0.333532 |
| intercept | -3.0312 | 0.272975 | -3.56622 | -2.49618 |
| slope | 1 | NA | | |

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---|---|---|---|---|---|
| Full model | -114.17 | 4 | | | |
| Fitted model | -114.211 | 2 | 0.0824752 | 2 | 0.9596 |
| Reduced model | -137.628 | 1 | 46.9164 | 3 | <.0001 |

AIC: 232.422

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.2218 | 11.091 | 11.000 | 50.000 | -0.031 |
| 9.0000 | 0.4575 | 22.873 | 23.000 | 50.000 | 0.036 |
| 28.0000 | 0.6690 | 33.452 | 34.000 | 50.000 | 0.165 |
| 88.0000 | 0.8517 | 42.584 | 42.000 | 50.000 | -0.232 |

Chi^2 = 0.08 d.f. = 2 P-value = 0.9591

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2.30246

BMDL = 1.50793

## B) DEEM FCID Outputs

### 1) Acute Tier 3 (18 pages)

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""

Summary calculations--per capita:

| | 95th Percentile Exposure | 95th Percentile MOE | 99th Percentile Exposure | 99th Percentile MOE | 99.9th Percentile Exposure | 99.9th Percentile MOE |
|---|---|---|---|---|---|---|
| Total US Population: | | | | | | |
| | 0.000549 | 25691 | 0.001086 | 12989 | 0.002368 | 5954 |
| Hispanic: | | | | | | |
| | 0.000718 | 19639 | 0.001276 | 11047 | 0.002464 | 5723 |
| Non-Hisp-White: | | | | | | |
| | 0.000441 | 31940 | 0.000830 | 16981 | 0.001815 | 7768 |
| Non-Hisp-Black: | | | | | | |
| | 0.000565 | 24957 | 0.001108 | 12726 | 0.002139 | 6592 |
| Non-Hisp-Other: | | | | | | |
| | 0.001226 | 11500 | 0.001984 | 7107 | 0.003414 | 4130 |
| Nursing Infants: | | | | | | |
| | 0.001322 | 10664 | 0.001723 | 8183 | 0.005500 | 2563 |
| Non-Nursing Infants: | | | | | | |
| | 0.001750 | 8056 | 0.003235 | 4357 | 0.007334 | 1922 |
| All Infants: | | | | | | |
| | 0.001503 | 9382 | 0.002807 | 5023 | 0.006535 | 2157 |
| Female 13-50: | | | | | | |
| | 0.000426 | 33093 | 0.000791 | 17831 | 0.001436 | 9821 |
| Children 1-2: | | | | | | |
| | 0.001193 | 11822 | 0.002404 | 5866 | 0.004755 | 2965 |
| Children 3-5: | | | | | | |
| | 0.001081 | 13041 | 0.001834 | 7686 | 0.002716 | 5191 |
| Children 6-12: | | | | | | |
| | 0.000676 | 20866 | 0.001160 | 12152 | 0.002247 | 6276 |
| Adults 50-99: | | | | | | |
| | 0.000358 | 39341 | 0.000667 | 21140 | 0.001340 | 10520 |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""

Summary calculations--users:

| | 95th Percentile Exposure | 95th Percentile MOE | 99th Percentile Exposure | 99th Percentile MOE | 99.9th Percentile Exposure | 99.9th Percentile MOE |
|---|---|---|---|---|---|---|
| Total US Population: | | | | | | |
| | 0.000549 | 25677 | 0.001086 | 12981 | 0.002368 | 5953 |
| Hispanic: | | | | | | |
| | 0.000719 | 19624 | 0.001278 | 11035 | 0.002465 | 5719 |
| Non-Hisp-White: | | | | | | |
| | 0.000442 | 31908 | 0.000831 | 16964 | 0.001816 | 7766 |
| Non-Hisp-Black: | | | | | | |
| | 0.000565 | 24944 | 0.001108 | 12721 | 0.002139 | 6591 |
| Non-Hisp-Other: | | | | | | |
| | 0.001226 | 11498 | 0.001984 | 7106 | 0.003414 | 4130 |
| Nursing Infants: | | | | | | |
| | 0.001346 | 10477 | 0.002254 | 6254 | 0.005512 | 2558 |
| Non-Nursing Infants: | | | | | | |
| | 0.001754 | 8040 | 0.003240 | 4351 | 0.007335 | 1922 |
| All Infants: | | | | | | |
| | 0.001559 | 9044 | 0.002994 | 4709 | 0.006557 | 2150 |
| Female 13-50: | | | | | | |
| | 0.000426 | 33092 | 0.000791 | 17830 | 0.001436 | 9821 |
| Children 1-2: | | | | | | |
| | 0.001193 | 11822 | 0.002404 | 5864 | 0.004755 | 2965 |
| Children 3-5: | | | | | | |
| | 0.001081 | 13041 | 0.001834 | 7686 | 0.002716 | 5191 |
| Children 6-12: | | | | | | |
| | 0.000676 | 20864 | 0.001160 | 12151 | 0.002248 | 6271 |
| Adults 50-99: | | | | | | |
| | 0.000358 | 39339 | 0.000667 | 21140 | 0.001340 | 10520 |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""

Total US Population — Daily Exposure Analysis /a (mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000157 | 0.000157 |
| Standard Deviation | 0.000230 | 0.000231 |
| Margin of Exposure 2/ | 89,703 | 89,572 |

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000018 | 770,006 | 90.00 | 0.000371 | 38,001 |
| 20.00 | 0.000031 | 453,545 | 95.00 | 0.000549 | 25,677 |
| 30.00 | 0.000044 | 316,950 | 97.50 | 0.000755 | 18,663 |
| 40.00 | 0.000060 | 233,067 | 99.00 | 0.001086 | 12,981 |
| 50.00 | 0.000081 | 173,211 | 99.50 | 0.001385 | 10,180 |
| 60.00 | 0.000111 | 127,540 | 99.75 | 0.001707 | 8,261 |
| 70.00 | 0.000155 | 91,257 | 99.90 | 0.002368 | 5,953 |
| 80.00 | 0.000226 | 62,512 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000018 | 777,738 | 90.00 | 0.000371 | 38,037 |
| 20.00 | 0.000031 | 455,679 | 95.00 | 0.000549 | 25,691 |
| 30.00 | 0.000044 | 317,863 | 97.50 | 0.000755 | 18,671 |
| 40.00 | 0.000060 | 233,770 | 99.00 | 0.001086 | 12,989 |
| 50.00 | 0.000081 | 173,522 | 99.50 | 0.001384 | 10,185 |
| 60.00 | 0.000110 | 127,752 | 99.75 | 0.001706 | 8,263 |
| 70.00 | 0.000154 | 91,410 | 99.90 | 0.002368 | 5,954 |
| 80.00 | 0.000225 | 62,600 | | | |

a/ Analysis based on all two-day participant records in NHANES 2003-2008 2-Day with 2 days of valid drinking water records.
2/ Margin of Exposure = NOEL/ Dietary Exposure.

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Hispanic

Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000214 | 0.000214 |
| Standard Deviation | 0.000268 | 0.000268 |
| Margin of Exposure | 65,939 | 65,812 |

Percent of Person-Days that are User-Days = 99.81%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000025 | 568,663 | 90.00 | 0.000489 | 28,855 |
| 20.00 | 0.000044 | 323,757 | 95.00 | 0.000719 | 19,624 |
| 30.00 | 0.000064 | 220,338 | 97.50 | 0.000946 | 14,901 |
| 40.00 | 0.000091 | 154,309 | 99.00 | 0.001278 | 11,035 |
| 50.00 | 0.000127 | 110,839 | 99.50 | 0.001503 | 9,383 |
| 60.00 | 0.000172 | 82,130 | 99.75 | 0.001797 | 7,844 |
| 70.00 | 0.000236 | 59,848 | 99.90 | 0.002465 | 5,719 |
| 80.00 | 0.000325 | 43,431 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000024 | 576,079 | 90.00 | 0.000488 | 28,875 |
| 20.00 | 0.000043 | 326,139 | 95.00 | 0.000718 | 19,639 |
| 30.00 | 0.000064 | 221,330 | 97.50 | 0.000945 | 14,915 |
| 40.00 | 0.000091 | 154,961 | 99.00 | 0.001276 | 11,047 |
| 50.00 | 0.000127 | 111,251 | 99.50 | 0.001502 | 9,387 |
| 60.00 | 0.000171 | 82,371 | 99.75 | 0.001797 | 7,846 |
| 70.00 | 0.000235 | 59,978 | 99.90 | 0.002464 | 5,723 |
| 80.00 | 0.000324 | 43,506 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Non-Hisp-White

Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000131 | 0.000131 |
| Standard Deviation | 0.000186 | 0.000186 |
| Margin of Exposure | 107,500 | 107,358 |

Percent of Person-Days that are User-Days = 99.87%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000018 | 803,178 | 90.00 | 0.000303 | 46,470 |
| 20.00 | 0.000029 | 482,853 | 95.00 | 0.000442 | 31,908 |
| 30.00 | 0.000041 | 341,165 | 97.50 | 0.000605 | 23,310 |
| 40.00 | 0.000055 | 256,755 | 99.00 | 0.000831 | 16,964 |
| 50.00 | 0.000073 | 193,781 | 99.50 | 0.001038 | 13,578 |
| 60.00 | 0.000097 | 145,996 | 99.75 | 0.001325 | 10,643 |
| 70.00 | 0.000131 | 107,353 | 99.90 | 0.001816 | 7,766 |
| 80.00 | 0.000190 | 74,162 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000017 | 809,925 | 90.00 | 0.000303 | 46,506 |
| 20.00 | 0.000029 | 485,107 | 95.00 | 0.000441 | 31,940 |
| 30.00 | 0.000041 | 342,208 | 97.50 | 0.000604 | 23,328 |
| 40.00 | 0.000055 | 257,332 | 99.00 | 0.000830 | 16,981 |
| 50.00 | 0.000073 | 194,189 | 99.50 | 0.001038 | 13,584 |
| 60.00 | 0.000096 | 146,234 | 99.75 | 0.001325 | 10,644 |
| 70.00 | 0.000131 | 107,486 | 99.90 | 0.001815 | 7,768 |
| 80.00 | 0.000190 | 74,220 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Non-Hisp-Black
---

Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000161 | 0.000162 |
| Standard Deviation | 0.000231 | 0.000232 |
| Margin of Exposure | 87,329 | 87,202 |

Percent of Person-Days that are User-Days = 99.85%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000016 | 872,173 | 90.00 | 0.000385 | 36,621 |
| 20.00 | 0.000030 | 475,866 | 95.00 | 0.000565 | 24,944 |
| 30.00 | 0.000044 | 322,869 | 97.50 | 0.000769 | 18,339 |
| 40.00 | 0.000061 | 230,669 | 99.00 | 0.001108 | 12,721 |
| 50.00 | 0.000084 | 167,753 | 99.50 | 0.001389 | 10,153 |
| 60.00 | 0.000117 | 120,573 | 99.75 | 0.001673 | 8,426 |
| 70.00 | 0.000166 | 84,895 | 99.90 | 0.002139 | 6,591 |
| 80.00 | 0.000238 | 59,335 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000016 | 880,184 | 90.00 | 0.000385 | 36,655 |
| 20.00 | 0.000029 | 478,788 | 95.00 | 0.000565 | 24,957 |
| 30.00 | 0.000044 | 323,999 | 97.50 | 0.000768 | 18,347 |
| 40.00 | 0.000061 | 231,399 | 99.00 | 0.001108 | 12,726 |
| 50.00 | 0.000084 | 168,122 | 99.50 | 0.001388 | 10,156 |
| 60.00 | 0.000117 | 120,792 | 99.75 | 0.001673 | 8,429 |
| 70.00 | 0.000166 | 85,000 | 99.90 | 0.002139 | 6,592 |
| 80.00 | 0.000237 | 59,391 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Non-Hisp-Other

Daily Exposure Analysis (mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000349 | 0.000349 |
| Standard Deviation | 0.000444 | 0.000444 |
| Margin of Exposure | 40,443 | 40,361 |

Percent of Person-Days that are User-Days = 99.80%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000024 | 596,182 | 90.00 | 0.000874 | 16,131 |
| 20.00 | 0.000044 | 322,612 | 95.00 | 0.001226 | 11,498 |
| 30.00 | 0.000072 | 196,583 | 97.50 | 0.001636 | 8,618 |
| 40.00 | 0.000113 | 125,216 | 99.00 | 0.001984 | 7,106 |
| 50.00 | 0.000173 | 81,658 | 99.50 | 0.002494 | 5,652 |
| 60.00 | 0.000276 | 51,171 | 99.75 | 0.002746 | 5,135 |
| 70.00 | 0.000410 | 34,351 | 99.90 | 0.003414 | 4,130 |
| 80.00 | 0.000583 | 24,201 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000023 | 602,799 | 90.00 | 0.000874 | 16,141 |
| 20.00 | 0.000043 | 324,548 | 95.00 | 0.001226 | 11,500 |
| 30.00 | 0.000071 | 198,030 | 97.50 | 0.001635 | 8,622 |
| 40.00 | 0.000112 | 125,688 | 99.00 | 0.001984 | 7,107 |
| 50.00 | 0.000172 | 82,189 | 99.50 | 0.002494 | 5,653 |
| 60.00 | 0.000274 | 51,372 | 99.75 | 0.002745 | 5,136 |
| 70.00 | 0.000409 | 34,515 | 99.90 | 0.003414 | 4,130 |
| 80.00 | 0.000581 | 24,278 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""

Nursing Infants — Daily Exposure Analysis (mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000230 | 0.000322 |
| Standard Deviation | 0.000471 | 0.000530 |
| Margin of Exposure | 61,332 | 43,839 |

Percent of Person-Days that are User-Days = 71.48%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000002 | >1,000,000 | 90.00 | 0.000999 | 14,118 |
| 20.00 | 0.000003 | >1,000,000 | 95.00 | 0.001346 | 10,477 |
| 30.00 | 0.000010 | >1,000,000 | 97.50 | 0.001556 | 9,060 |
| 40.00 | 0.000025 | 561,930 | 99.00 | 0.002254 | 6,254 |
| 50.00 | 0.000083 | 170,087 | 99.50 | 0.002590 | 5,443 |
| 60.00 | 0.000173 | 81,582 | 99.75 | 0.003488 | 4,042 |
| 70.00 | 0.000338 | 41,746 | 99.90 | 0.005512 | 2,558 |
| 80.00 | 0.000511 | 27,578 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000000 | >1,000,000 | 90.00 | 0.000800 | 17,625 |
| 20.00 | 0.000000 | >1,000,000 | 95.00 | 0.001322 | 10,664 |
| 30.00 | 0.000000 | >1,000,000 | 97.50 | 0.001496 | 9,428 |
| 40.00 | 0.000002 | >1,000,000 | 99.00 | 0.001723 | 8,183 |
| 50.00 | 0.000010 | >1,000,000 | 99.50 | 0.002481 | 5,683 |
| 60.00 | 0.000040 | 352,964 | 99.75 | 0.003350 | 4,208 |
| 70.00 | 0.000160 | 87,942 | 99.90 | 0.005500 | 2,563 |
| 80.00 | 0.000351 | 40,208 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Non-Nursing Infants

| Daily Exposure Analysis (mg/kg body-weight/day) | per Capita | per User |
|---|---|---|
| Mean | 0.000435 | 0.000436 |
| Standard Deviation | 0.000721 | 0.000722 |
| Margin of Exposure | 32,436 | 32,304 |

Percent of Person-Days that are User-Days = 99.59%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000010 | >1,000,000 | 90.00 | 0.001089 | 12,953 |
| 20.00 | 0.000019 | 753,279 | 95.00 | 0.001754 | 8,040 |
| 30.00 | 0.000040 | 355,306 | 97.50 | 0.002508 | 5,622 |
| 40.00 | 0.000099 | 142,325 | 99.00 | 0.003240 | 4,351 |
| 50.00 | 0.000192 | 73,285 | 99.50 | 0.004818 | 2,926 |
| 60.00 | 0.000288 | 48,920 | 99.75 | 0.005884 | 2,396 |
| 70.00 | 0.000451 | 31,245 | 99.90 | 0.007335 | 1,922 |
| 80.00 | 0.000678 | 20,793 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000009 | >1,000,000 | 90.00 | 0.001086 | 12,980 |
| 20.00 | 0.000018 | 765,947 | 95.00 | 0.001750 | 8,056 |
| 30.00 | 0.000037 | 377,807 | 97.50 | 0.002507 | 5,624 |
| 40.00 | 0.000097 | 145,436 | 99.00 | 0.003235 | 4,357 |
| 50.00 | 0.000191 | 73,843 | 99.50 | 0.004817 | 2,927 |
| 60.00 | 0.000287 | 49,158 | 99.75 | 0.005870 | 2,401 |
| 70.00 | 0.000449 | 31,392 | 99.90 | 0.007334 | 1,922 |
| 80.00 | 0.000676 | 20,852 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""

All Infants — Daily Exposure Analysis (mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000371 | 0.000409 |
| Standard Deviation | 0.000661 | 0.000682 |
| Margin of Exposure | 37,960 | 34,509 |

Percent of Person-Days that are User-Days = 90.91%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000004 | >1,000,000 | 90.00 | 0.001057 | 13,333 |
| 20.00 | 0.000015 | 943,363 | 95.00 | 0.001559 | 9,044 |
| 30.00 | 0.000026 | 536,816 | 97.50 | 0.002286 | 6,167 |
| 40.00 | 0.000077 | 182,910 | 99.00 | 0.002994 | 4,709 |
| 50.00 | 0.000170 | 82,979 | 99.50 | 0.004313 | 3,269 |
| 60.00 | 0.000275 | 51,286 | 99.75 | 0.005800 | 2,431 |
| 70.00 | 0.000420 | 33,544 | 99.90 | 0.006557 | 2,150 |
| 80.00 | 0.000652 | 21,630 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000000 | >1,000,000 | 90.00 | 0.000998 | 14,132 |
| 20.00 | 0.000006 | >1,000,000 | 95.00 | 0.001503 | 9,382 |
| 30.00 | 0.000018 | 795,033 | 97.50 | 0.002138 | 6,594 |
| 40.00 | 0.000042 | 332,177 | 99.00 | 0.002807 | 5,023 |
| 50.00 | 0.000124 | 113,643 | 99.50 | 0.004289 | 3,287 |
| 60.00 | 0.000227 | 62,026 | 99.75 | 0.005516 | 2,556 |
| 70.00 | 0.000364 | 38,731 | 99.90 | 0.006535 | 2,157 |
| 80.00 | 0.000584 | 24,147 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Female 13-50

| Daily Exposure Analysis (mg/kg body-weight/day) | per Capita | per User |
|---|---|---|
| Mean | 0.000118 | 0.000118 |
| Standard Deviation | 0.000162 | 0.000162 |
| Margin of Exposure | 119,597 | 119,583 |

Percent of Person-Days that are User-Days = 99.99%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000014 | 989,182 | 90.00 | 0.000290 | 48,539 |
| 20.00 | 0.000024 | 583,675 | 95.00 | 0.000426 | 33,092 |
| 30.00 | 0.000033 | 421,143 | 97.50 | 0.000572 | 24,641 |
| 40.00 | 0.000045 | 312,437 | 99.00 | 0.000791 | 17,830 |
| 50.00 | 0.000059 | 237,144 | 99.50 | 0.000960 | 14,690 |
| 60.00 | 0.000081 | 173,693 | 99.75 | 0.001198 | 11,773 |
| 70.00 | 0.000114 | 124,201 | 99.90 | 0.001436 | 9,821 |
| 80.00 | 0.000173 | 81,692 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000014 | 989,896 | 90.00 | 0.000290 | 48,543 |
| 20.00 | 0.000024 | 583,871 | 95.00 | 0.000426 | 33,093 |
| 30.00 | 0.000033 | 421,248 | 97.50 | 0.000572 | 24,641 |
| 40.00 | 0.000045 | 312,491 | 99.00 | 0.000791 | 17,831 |
| 50.00 | 0.000059 | 237,187 | 99.50 | 0.000960 | 14,694 |
| 60.00 | 0.000081 | 173,721 | 99.75 | 0.001198 | 11,773 |
| 70.00 | 0.000114 | 124,215 | 99.90 | 0.001436 | 9,821 |
| 80.00 | 0.000173 | 81,698 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Children 1-2

Daily Exposure Analysis (mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000386 | 0.000386 |
| Standard Deviation | 0.000464 | 0.000464 |
| Margin of Exposure | 36,522 | 36,514 |

Percent of Person-Days that are User-Days = 99.98%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000068 | 208,141 | 90.00 | 0.000866 | 16,273 |
| 20.00 | 0.000109 | 129,646 | 95.00 | 0.001193 | 11,822 |
| 30.00 | 0.000142 | 99,291 | 97.50 | 0.001662 | 8,483 |
| 40.00 | 0.000184 | 76,711 | 99.00 | 0.002404 | 5,864 |
| 50.00 | 0.000234 | 60,238 | 99.50 | 0.002796 | 5,042 |
| 60.00 | 0.000299 | 47,209 | 99.75 | 0.003422 | 4,120 |
| 70.00 | 0.000395 | 35,680 | 99.90 | 0.004755 | 2,965 |
| 80.00 | 0.000562 | 25,102 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000068 | 208,307 | 90.00 | 0.000866 | 16,276 |
| 20.00 | 0.000109 | 129,701 | 95.00 | 0.001193 | 11,822 |
| 30.00 | 0.000142 | 99,317 | 97.50 | 0.001662 | 8,483 |
| 40.00 | 0.000184 | 76,729 | 99.00 | 0.002404 | 5,866 |
| 50.00 | 0.000234 | 60,249 | 99.50 | 0.002796 | 5,042 |
| 60.00 | 0.000299 | 47,219 | 99.75 | 0.003422 | 4,120 |
| 70.00 | 0.000395 | 35,683 | 99.90 | 0.004755 | 2,965 |
| 80.00 | 0.000562 | 25,105 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Children 3-5 Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000320 | 0.000320 |
| Standard Deviation | 0.000372 | 0.000372 |
| Margin of Exposure | 44,004 | 44,004 |

Percent of Person-Days that are User-Days = 100.00%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000057 | 245,916 | 90.00 | 0.000775 | 18,193 |
| 20.00 | 0.000083 | 169,344 | 95.00 | 0.001081 | 13,041 |
| 30.00 | 0.000111 | 126,961 | 97.50 | 0.001346 | 10,477 |
| 40.00 | 0.000144 | 98,216 | 99.00 | 0.001834 | 7,686 |
| 50.00 | 0.000187 | 75,584 | 99.50 | 0.002494 | 5,654 |
| 60.00 | 0.000245 | 57,459 | 99.75 | 0.002556 | 5,515 |
| 70.00 | 0.000321 | 43,897 | 99.90 | 0.002716 | 5,191 |
| 80.00 | 0.000467 | 30,219 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000057 | 245,916 | 90.00 | 0.000775 | 18,193 |
| 20.00 | 0.000083 | 169,344 | 95.00 | 0.001081 | 13,041 |
| 30.00 | 0.000111 | 126,961 | 97.50 | 0.001346 | 10,477 |
| 40.00 | 0.000144 | 98,216 | 99.00 | 0.001834 | 7,686 |
| 50.00 | 0.000187 | 75,584 | 99.50 | 0.002494 | 5,654 |
| 60.00 | 0.000245 | 57,459 | 99.75 | 0.002556 | 5,515 |
| 70.00 | 0.000321 | 43,897 | 99.90 | 0.002716 | 5,191 |
| 80.00 | 0.000467 | 30,219 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Children 6-12 Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000200 | 0.000200 |
| Standard Deviation | 0.000251 | 0.000251 |
| Margin of Exposure | 70,543 | 70,522 |

Percent of Person-Days that are User-Days = 99.97%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000034 | 414,840 | 90.00 | 0.000471 | 29,939 |
| 20.00 | 0.000054 | 261,608 | 95.00 | 0.000676 | 20,864 |
| 30.00 | 0.000070 | 200,206 | 97.50 | 0.000871 | 16,186 |
| 40.00 | 0.000090 | 156,250 | 99.00 | 0.001160 | 12,151 |
| 50.00 | 0.000116 | 121,808 | 99.50 | 0.001500 | 9,402 |
| 60.00 | 0.000148 | 94,993 | 99.75 | 0.001923 | 7,331 |
| 70.00 | 0.000198 | 71,371 | 99.90 | 0.002248 | 6,271 |
| 80.00 | 0.000280 | 50,350 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000034 | 415,728 | 90.00 | 0.000471 | 29,944 |
| 20.00 | 0.000054 | 261,775 | 95.00 | 0.000676 | 20,866 |
| 30.00 | 0.000070 | 200,297 | 97.50 | 0.000871 | 16,190 |
| 40.00 | 0.000090 | 156,329 | 99.00 | 0.001160 | 12,152 |
| 50.00 | 0.000116 | 121,845 | 99.50 | 0.001498 | 9,412 |
| 60.00 | 0.000148 | 95,015 | 99.75 | 0.001923 | 7,331 |
| 70.00 | 0.000197 | 71,396 | 99.90 | 0.002247 | 6,276 |
| 80.00 | 0.000280 | 50,362 | | | |

US EPA Ver. 3.18, 03-08-d
DEEM-FCID ACUTE Analysis for PROPANIL NHANES 2003-2008 2-Day
Residue file: PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Adjustment factor #2 used.
Analysis Date: 03-14-2018/14:29:31 Residue file dated: 03-14-2018/14:12:19
NOEL (Acute) = 14.100000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
MC iterations = 500; MC list in residue file; MC seed = 10; RNG = MS VB
Run Comment: ""
==========

Adults 50-99 Daily Exposure Analysis
(mg/kg body-weight/day)

| | per Capita | per User |
|---|---|---|
| Mean | 0.000107 | 0.000107 |
| Standard Deviation | 0.000143 | 0.000143 |
| Margin of Exposure | 131,341 | 131,322 |

Percent of Person-Days that are User-Days = 99.99%

Estimated percentile of user-days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000015 | 911,180 | 90.00 | 0.000248 | 56,850 |
| 20.00 | 0.000026 | 547,978 | 95.00 | 0.000358 | 39,339 |
| 30.00 | 0.000036 | 392,842 | 97.50 | 0.000478 | 29,470 |
| 40.00 | 0.000046 | 303,835 | 99.00 | 0.000667 | 21,140 |
| 50.00 | 0.000060 | 233,726 | 99.50 | 0.000837 | 16,839 |
| 60.00 | 0.000079 | 177,998 | 99.75 | 0.001076 | 13,103 |
| 70.00 | 0.000107 | 131,852 | 99.90 | 0.001340 | 10,520 |
| 80.00 | 0.000157 | 89,576 | | | |

Estimated percentile of per-capita days falling below calculated exposure in mg/kg body-wt/day with Margin of Exposure (MOE)

| Percentile | Exposure | MOE | Percentile | Exposure | MOE |
|---|---|---|---|---|---|
| 10.00 | 0.000015 | 912,011 | 90.00 | 0.000248 | 56,854 |
| 20.00 | 0.000026 | 548,248 | 95.00 | 0.000358 | 39,341 |
| 30.00 | 0.000036 | 392,940 | 97.50 | 0.000478 | 29,472 |
| 40.00 | 0.000046 | 303,902 | 99.00 | 0.000667 | 21,140 |
| 50.00 | 0.000060 | 233,783 | 99.50 | 0.000837 | 16,840 |
| 60.00 | 0.000079 | 178,026 | 99.75 | 0.001076 | 13,103 |
| 70.00 | 0.000107 | 131,874 | 99.90 | 0.001340 | 10,520 |
| 80.00 | 0.000157 | 89,591 | | | |

Filename: H:\plohstroh\Documents\Propanil RCD\Dietary RA\DEEM Files\DEEM Residue\PRN Acute Tier 3 24 Oct 17 rev 14 Mar 18.R08
Chemical: Propanil
RfD(Chronic): 0 mg/kg bw/day  NOEL(Chronic): 0 mg/kg bw/day
RfD(Acute): 0 mg/kg bw/day  NOEL(Acute):  14.1 mg/kg bw/day
Date created/last modified: 03-14-2018/14:12:19  Program ver. 3.16, 03-08-d

RDL indices and parameters for Monte Carlo Analysis:

| Index # | Dist Code | Parameter #1 | Param #2 | Param #3 | Comment |
|---|---|---|---|---|---|
| 1 | 6 | Water PRN.rdf | | | |

| EPA Code | Crop Grp | Commodity Name | Def Res (ppm) | Adj.Factors #1 | #2 | RDLComment Pntr |
|---|---|---|---|---|---|---|
| 3100047000 | 31 | Beef, fat | 0.081000 | 1.000 | 1.000 | EPA |
| 3100047001 | 31 | Beef, fat-babyfood | 0.081000 | 1.000 | 1.000 | EPA |
| 3100048000 | 31 | Beef, kidney | 0.044000 | 1.000 | 1.000 | EPA |
| 3100049000 | 31 | Beef, liver | 0.018000 | 1.000 | 1.000 | EPA |
| 3100049001 | 31 | Beef, liver-babyfood | 0.018000 | 1.000 | 1.000 | EPA |
| 3100044000 | 31 | Beef, meat | 0.003000 | 1.000 | 1.000 | EPA |
| 3100046000 | 31 | Beef, meat byproducts | 0.044000 | 1.000 | 1.000 | EPA |
| 3100046001 | 31 | Beef, meat byproducts-babyfood | 0.044000 | 1.000 | 1.000 | EPA |
| 3100045000 | 31 | Beef, meat, dried | 0.003000 | 1.920 | 1.000 | EPA |
| 3100044001 | 31 | Beef, meat-babyfood | 0.003000 | 1.000 | 1.000 | EPA |
| 4000096000 | 40 | Chicken, fat | 0.007000 | 1.000 | 1.000 | EPA |
| 4000096001 | 40 | Chicken, fat-babyfood | 0.007000 | 1.000 | 1.000 | EPA |
| 4000094000 | 40 | Chicken, liver | 0.031000 | 1.000 | 1.000 | EPA |
| 4000093000 | 40 | Chicken, meat | 0.010000 | 1.000 | 1.000 | EPA |
| 4000095000 | 40 | Chicken, meat byproducts | 0.031000 | 1.000 | 1.000 | EPA |
| 4000095001 | 40 | Chicken, meat byproducts-babyfoo | 0.031000 | 1.000 | 1.000 | EPA |
| 4000093001 | 40 | Chicken, meat-babyfood | 0.010000 | 1.000 | 1.000 | EPA |
| 4000097000 | 40 | Chicken, skin | 0.031000 | 1.000 | 1.000 | EPA |
| 4000097001 | 40 | Chicken, skin-babyfood | 0.031000 | 1.000 | 1.000 | EPA |
| 7000146000 | 70 | Egg, white | 0.028000 | 1.000 | 1.000 | EPA |
| 7000146001 | 70 | Egg, white (solids)-babyfood | 0.028000 | 1.000 | 1.000 | EPA |
| 7000145000 | 70 | Egg, whole | 0.028000 | 1.000 | 1.000 | EPA |
| 7000145001 | 70 | Egg, whole-babyfood | 0.028000 | 1.000 | 1.000 | EPA |
| 7000147000 | 70 | Egg, yolk | 0.028000 | 1.000 | 1.000 | EPA |
| 7000147001 | 70 | Egg, yolk-babyfood | 0.028000 | 1.000 | 1.000 | EPA |
| 8000161000 | 80 | Fish-shellfish, crustacean | 0.030000 | 1.000 | 1.000 | EPA |
| 3200171000 | 32 | Goat, fat | 0.081000 | 1.000 | 1.000 | EPA |
| 3200172000 | 32 | Goat, kidney | 0.044000 | 1.000 | 1.000 | EPA |
| 3200173000 | 32 | Goat, liver | 0.018000 | 1.000 | 1.000 | EPA |
| 3200169000 | 32 | Goat, meat | 0.003000 | 1.000 | 1.000 | EPA |
| 3200170000 | 32 | Goat, meat byproducts | 0.044000 | 1.000 | 1.000 | EPA |
| 3300189000 | 33 | Horse, meat | 0.003000 | 1.000 | 1.000 | EPA |
| 3600222000 | 36 | Milk, fat | 0.001300 | 1.000 | 1.000 | EPA |
| 3600222001 | 36 | Milk, fat-baby food/infant formu | 0.001300 | 1.000 | 1.000 | EPA |
| 3600223000 | 36 | Milk, nonfat solids | 0.001300 | 1.000 | 1.000 | EPA |
| 3600223001 | 36 | Milk, nonfat solids-baby food/in | 0.001300 | 1.000 | 1.000 | EPA |
| 3600225001 | 36 | Milk, sugar (lactose)-baby food/ | 0.001300 | 1.000 | 1.000 | EPA |
| 3600224000 | 36 | Milk, water | 0.001300 | 1.000 | 1.000 | EPA |
| 3600224001 | 36 | Milk, water-babyfood/infant form | 0.001300 | 1.000 | 1.000 | EPA |
| 3400293000 | 34 | Pork, fat | 0.300000 | 1.000 | 1.000 | EPA |
| 3400293001 | 34 | Pork, fat-babyfood | 0.300000 | 1.000 | 1.000 | EPA |
| 3400294000 | 34 | Pork, kidney | 0.160000 | 1.000 | 1.000 | EPA |
| 3400295000 | 34 | Pork, liver | 0.065000 | 1.000 | 1.000 | EPA |
| 3400290000 | 34 | Pork, meat | 0.010000 | 1.000 | 1.000 | EPA |
| 3400292000 | 34 | Pork, meat byproducts | 0.160000 | 1.000 | 1.000 | EPA |
| 3400292001 | 34 | Pork, meat byproducts-babyfood | 0.160000 | 1.000 | 1.000 | EPA |
| 3400290001 | 34 | Pork, meat-babyfood | 0.010000 | 1.000 | 1.000 | EPA |
| 3400291000 | 34 | Pork, skin | 0.160000 | 1.000 | 1.000 | EPA |
| 6000304000 | 60 | Poultry, other, fat | 0.007000 | 1.000 | 1.000 | EPA |
| 6000302000 | 60 | Poultry, other, liver | 0.031000 | 1.000 | 1.000 | EPA |
| 6000301000 | 60 | Poultry, other, meat | 0.010000 | 1.000 | 1.000 | EPA |
| 6000303000 | 60 | Poultry, other, meat byproducts | 0.031000 | 1.000 | 1.000 | EPA |
| 6000305000 | 60 | Poultry, other, skin | 0.031000 | 1.000 | 1.000 | EPA |
| 3900312000 | 39 | Rabbit, meat | 0.003000 | 1.000 | 1.000 | EPA |
| 1500326000 | 15 | Rice, bran | 0.420000 | 4.600 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500326001 | 15 | Rice, bran-babyfood | 0.420000 | 4.600 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500324000 | 15 | Rice, brown | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500324001 | 15 | Rice, brown-babyfood | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500325000 | 15 | Rice, flour | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500325001 | 15 | Rice, flour-babyfood | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500323000 | 15 | Rice, white | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 1500323001 | 15 | Rice, white-babyfood | 0.420000 | 1.000 | 0.750 | FT Avg |
| | | Full comment: FT Avg w 0.5LOD | | | | |
| 3500341000 | 35 | Sheep, fat | 0.081000 | 1.000 | 1.000 | EPA |
| 3500341001 | 35 | Sheep, fat-babyfood | 0.081000 | 1.000 | 1.000 | EPA |
| 3500342000 | 35 | Sheep, kidney | 0.044000 | 1.000 | 1.000 | EPA |
| 3500343000 | 35 | Sheep, liver | 0.018000 | 1.000 | 1.000 | EPA |
| 3500339000 | 35 | Sheep, meat | 0.003000 | 1.000 | 1.000 | EPA |
| 3500340000 | 35 | Sheep, meat byproducts | 0.044000 | 1.000 | 1.000 | EPA |
| 3500339001 | 35 | Sheep, meat-babyfood | 0.003000 | 1.000 | 1.000 | EPA |

```
5000385000 50   Turkey, fat                          0.007000   1.000  1.000       EPA
5000385001 50   Turkey, fat-babyfood                 0.007000   1.000  1.000       EPA
5000383000 50   Turkey, liver                        0.031000   1.000  1.000       EPA
5000383001 50   Turkey, liver-babyfood               0.031000   1.000  1.000       EPA
5000382000 50   Turkey, meat                         0.010000   1.000  1.000       EPA
5000384000 50   Turkey, meat byproducts              0.031000   1.000  1.000       EPA
5000384001 50   Turkey, meat byproducts-babyfood     0.031000   1.000  1.000       EPA
5000382001 50   Turkey, meat-babyfood                0.010000   1.000  1.000       EPA
5000386000 50   Turkey, skin                         0.031000   1.000  1.000       EPA
5000386001 50   Turkey, skin-babyfood                0.031000   1.000  1.000       EPA
8601000000 86A  Water, direct, all sources           0.047000   1.000  1.000   1   DPR SW
    Full comment: DPR SW RDF w 0.5LOD
8602000000 86B  Water, indirect, all sources         0.047000   1.000  1.000   1   DPR SW
    Full comment: DPR SW RDF w 0.5LOD
```

Summary of Residue Distribution Files (RDF) listed in H:\plohstroh\Documents\Propanil RCD\Dietary RA\DEEM Files\DEEM Residue\

| RDF # | File Name | N residues w freq's | N residues w/o freq's | N LODs | LOD Value | N Zeros |
|---|---|---|---|---|---|---|
| 1 | Water PRN.rdf | 0 | 1956 | 0 | 0 | 0 |

**2) Chronic (2 pages)**

US EPA Ver. 3.16, 03-08-d
DEEM-FCID Chronic analysis for PROPANIL NHANES 2003-2008 2-day
Residue file name: H:\plohstroh\Documents\Propanil RCD\Dietary RA\DEEM Files\DEEM Residue\PRN Chronic Tier 2 13 Nov 17.R08
Adjustment factor #2 used.
Analysis Date 11-13-2017/13:39:04 Residue file dated: 11-13-2017/12:22:08
NOEL (Chronic) = 1.5 mg/kg bw/day

Total exposure by population subgroup

| Population Subgroup | Total Exposure mg/kg body wt/day | Total Exposure Percent of NOEL | Total Exposure Margin of Exposure |
|---|---|---|---|
| Total US Population | 0.000157 | 0.01% | 9,527 |
| Hispanic | 0.000214 | 0.01% | 7,009 |
| Non-Hisp-White | 0.000131 | 0.01% | 11,420 |
| Non-Hisp-Black | 0.000162 | 0.01% | 9,243 |
| Non-Hisp-Other | 0.000349 | 0.02% | 4,302 |
| Nursing Infants | 0.000230 | 0.02% | 6,521 |
| Non-Nursing Infants | 0.000435 | 0.03% | 3,446 |
| Female 13+ PREG | 0.000130 | 0.01% | 11,513 |
| Children 1-6 | 0.000329 | 0.02% | 4,556 |
| Children 7-12 | 0.000194 | 0.01% | 7,729 |
| Male 13-19 | 0.000135 | 0.01% | 11,112 |
| Female 13-19/NP | 0.000111 | 0.01% | 13,482 |
| Male 20+ | 0.000164 | 0.01% | 9,145 |
| Female 20+/NP | 0.000107 | 0.01% | 14,033 |
| Seniors 55+ | 0.000099 | 0.01% | 15,106 |
| All Infants | 0.000372 | 0.02% | 4,034 |
| Female 13-50 | 0.000118 | 0.01% | 12,706 |
| Children 1-2 | 0.000386 | 0.03% | 3,889 |
| Children 3-5 | 0.000320 | 0.02% | 4,682 |
| Children 6-12 | 0.000200 | 0.01% | 7,492 |
| Youth 13-19 | 0.000123 | 0.01% | 12,219 |
| Adults 20-49 | 0.000153 | 0.01% | 9,777 |
| Adults 50-99 | 0.000108 | 0.01% | 13,945 |
| Female 13-49 | 0.000119 | 0.01% | 12,619 |

DEEM-FCID Chronic analysis for PROPANIL
Residue file: H:\plohstroh\Documents\Propanil RCD\Dietary RA\DEEM Files\DEEM Residue\PRN Chronic Tier 2 13 Nov 17.R08
Adjust. #2 used
Analysis Date 11-13-2017 Residue file dated: 11-13-2017/12:22:08
Q* = 0.035

| Food EPA Code | Crop Grp | Food Name | Residue (ppm) | Adj.Factors #1 | #2 |
|---|---|---|---|---|---|
| 3100044000 | 31 | Beef, meat | 0.003000 | 1.000 | 1.000 |
| 3100044001 | 31 | Beef, meat-babyfood | 0.003000 | 1.000 | 1.000 |
| 3100045000 | 31 | Beef, meat, dried | 0.003000 | 1.920 | 1.000 |
| 3100046000 | 31 | Beef, meat byproducts | 0.044000 | 1.000 | 1.000 |
| 3100046001 | 31 | Beef, meat byproducts-babyfood | 0.044000 | 1.000 | 1.000 |
| 3100047000 | 31 | Beef, fat | 0.081000 | 1.000 | 1.000 |
| 3100047001 | 31 | Beef, fat-babyfood | 0.081000 | 1.000 | 1.000 |
| 3100048000 | 31 | Beef, kidney | 0.044000 | 1.000 | 1.000 |
| 3100049000 | 31 | Beef, liver | 0.018000 | 1.000 | 1.000 |
| 3100049001 | 31 | Beef, liver-babyfood | 0.018000 | 1.000 | 1.000 |
| 4000093000 | 40 | Chicken, meat | 0.010000 | 1.000 | 1.000 |
| 4000093001 | 40 | Chicken, meat-babyfood | 0.010000 | 1.000 | 1.000 |
| 4000094000 | 40 | Chicken, liver | 0.031000 | 1.000 | 1.000 |
| 4000095000 | 40 | Chicken, meat byproducts | 0.031000 | 1.000 | 1.000 |
| 4000095001 | 40 | Chicken, meat byproducts-babyfoo | 0.031000 | 1.000 | 1.000 |
| 4000096000 | 40 | Chicken, fat | 0.007000 | 1.000 | 1.000 |
| 4000096001 | 40 | Chicken, fat-babyfood | 0.007000 | 1.000 | 1.000 |
| 4000097000 | 40 | Chicken, skin | 0.031000 | 1.000 | 1.000 |
| 4000097001 | 40 | Chicken, skin-babyfood | 0.031000 | 1.000 | 1.000 |
| 7000145000 | 70 | Egg, whole | 0.028000 | 1.000 | 1.000 |
| 7000145001 | 70 | Egg, whole-babyfood | 0.028000 | 1.000 | 1.000 |
| 7000146000 | 70 | Egg, white | 0.028000 | 1.000 | 1.000 |
| 7000146001 | 70 | Egg, white (solids)-babyfood | 0.028000 | 1.000 | 1.000 |
| 7000147000 | 70 | Egg, yolk | 0.028000 | 1.000 | 1.000 |
| 7000147001 | 70 | Egg, yolk-babyfood | 0.028000 | 1.000 | 1.000 |
| 8000161000 | 80 | Fish-shellfish, crustacean | 0.030000 | 1.000 | 1.000 |
| 3200169000 | 32 | Goat, meat | 0.003000 | 1.000 | 1.000 |
| 3200170000 | 32 | Goat, meat byproducts | 0.044000 | 1.000 | 1.000 |
| 3200171000 | 32 | Goat, fat | 0.081000 | 1.000 | 1.000 |
| 3200172000 | 32 | Goat, kidney | 0.044000 | 1.000 | 1.000 |
| 3200173000 | 32 | Goat, liver | 0.018000 | 1.000 | 1.000 |
| 3300189000 | 33 | Horse, meat | 0.003000 | 1.000 | 1.000 |
| 3600222000 | 36 | Milk, fat | 0.001300 | 1.000 | 1.000 |
| 3600222001 | 36 | Milk, fat-baby food/infant formu | 0.001300 | 1.000 | 1.000 |
| 3600223000 | 36 | Milk, nonfat solids | 0.001300 | 1.000 | 1.000 |
| 3600223001 | 36 | Milk, nonfat solids-baby food/in | 0.001300 | 1.000 | 1.000 |
| 3600224000 | 36 | Milk, water | 0.001300 | 1.000 | 1.000 |
| 3600224001 | 36 | Milk, water-babyfood/infant form | 0.001300 | 1.000 | 1.000 |
| 3600225001 | 36 | Milk, sugar (lactose)-baby food/ | 0.001300 | 1.000 | 1.000 |
| 3400290000 | 34 | Pork, meat | 0.010000 | 1.000 | 1.000 |
| 3400290001 | 34 | Pork, meat-babyfood | 0.010000 | 1.000 | 1.000 |
| 3400291000 | 34 | Pork, skin | 0.160000 | 1.000 | 1.000 |
| 3400292000 | 34 | Pork, meat byproducts | 0.160000 | 1.000 | 1.000 |
| 3400292001 | 34 | Pork, meat byproducts-babyfood | 0.160000 | 1.000 | 1.000 |
| 3400293000 | 34 | Pork, fat | 0.300000 | 1.000 | 1.000 |
| 3400293001 | 34 | Pork, fat-babyfood | 0.300000 | 1.000 | 1.000 |
| 3400294000 | 34 | Pork, kidney | 0.160000 | 1.000 | 1.000 |
| 3400295000 | 34 | Pork, liver | 0.065000 | 1.000 | 1.000 |
| 6000301000 | 60 | Poultry, other, meat | 0.010000 | 1.000 | 1.000 |
| 6000302000 | 60 | Poultry, other, liver | 0.031000 | 1.000 | 1.000 |
| 6000303000 | 60 | Poultry, other, meat byproducts | 0.031000 | 1.000 | 1.000 |
| 6000304000 | 60 | Poultry, other, fat | 0.007000 | 1.000 | 1.000 |
| 6000305000 | 60 | Poultry, other, skin | 0.031000 | 1.000 | 1.000 |
| 3900312000 | 39 | Rabbit, meat | 0.003000 | 1.000 | 1.000 |
| 1500323000 | 15 | Rice, white | 0.420000 | 1.000 | 0.750 |
| 1500323001 | 15 | Rice, white-babyfood | 0.420000 | 1.000 | 0.750 |
| 1500324000 | 15 | Rice, brown | 0.420000 | 1.000 | 0.750 |
| 1500324001 | 15 | Rice, brown-babyfood | 0.420000 | 1.000 | 0.750 |
| 1500325000 | 15 | Rice, flour | 0.420000 | 1.000 | 0.750 |
| 1500325001 | 15 | Rice, flour-babyfood | 0.420000 | 1.000 | 0.750 |
| 1500326000 | 15 | Rice, bran | 0.420000 | 4.600 | 0.750 |
| 1500326001 | 15 | Rice, bran-babyfood | 0.420000 | 4.600 | 0.750 |
| 3500339000 | 35 | Sheep, meat | 0.003000 | 1.000 | 1.000 |
| 3500339001 | 35 | Sheep, meat-babyfood | 0.003000 | 1.000 | 1.000 |
| 3500340000 | 35 | Sheep, meat byproducts | 0.044000 | 1.000 | 1.000 |
| 3500341000 | 35 | Sheep, fat | 0.081000 | 1.000 | 1.000 |
| 3500341001 | 35 | Sheep, fat-babyfood | 0.081000 | 1.000 | 1.000 |
| 3500342000 | 35 | Sheep, kidney | 0.044000 | 1.000 | 1.000 |
| 3500343000 | 35 | Sheep, liver | 0.018000 | 1.000 | 1.000 |
| 5000382000 | 50 | Turkey, meat | 0.010000 | 1.000 | 1.000 |
| 5000382001 | 50 | Turkey, meat-babyfood | 0.010000 | 1.000 | 1.000 |
| 5000383000 | 50 | Turkey, liver | 0.031000 | 1.000 | 1.000 |
| 5000383001 | 50 | Turkey, liver-babyfood | 0.031000 | 1.000 | 1.000 |
| 5000384000 | 50 | Turkey, meat byproducts | 0.031000 | 1.000 | 1.000 |
| 5000384001 | 50 | Turkey, meat byproducts-babyfood | 0.031000 | 1.000 | 1.000 |
| 5000385000 | 50 | Turkey, fat | 0.007000 | 1.000 | 1.000 |
| 5000385001 | 50 | Turkey, fat-babyfood | 0.007000 | 1.000 | 1.000 |
| 5000386000 | 50 | Turkey, skin | 0.031000 | 1.000 | 1.000 |
| 5000386001 | 50 | Turkey, skin-babyfood | 0.031000 | 1.000 | 1.000 |
| 8601000000 | 86A | Water, direct, all sources | 0.000160 | 1.000 | 1.000 |
| 8602000000 | 86B | Water, indirect, all sources | 0.000160 | 1.000 | 1.000 |

## C) Human Exposure Assessment For Propanil (52 pages)

# HUMAN EXPOSURE ASSESSMENT FOR PROPANIL

By

W. Wendy Zhao, Staff Toxicologist

January 8, 2018

California Environmental Protection Agency
Department of Pesticide Regulation
Human Health Assessment Branch
1001 I Street
P.O. Box 4015
Sacramento, CA 95812-4015
www.cdpr.ca.gov

**TABLE OF CONTENTS**

# I. ABSTRACT

Propanil (N-(3,4-dichlorophenyl) propanamide) is a synthetic acetanilide herbicide currently registered in California. Propanil is a selective post-emergent general use herbicide registered to control broadleaf and grass weeds on rice. There was no illness/injury case associated with exposure to propanil reported in California from 2010 through 2014. No dermal absorption study of propanil is available, so the default value of 50% was used in this exposure assessment.

The maximum and minimum average absorbed daily dosage (acute ADD), seasonal average daily dosage (SADD), annual average daily dosage (AADD), and lifetime average daily dosage (LADD) of seven scenarios are listed below:

- The acute ADD for agricultural workers handling propanil is estimated to range from 941 μg/kg/day for ground boom applicator spraying dry flowable, aqueous concentrate, flowable concentrate, or suspension formulations to 25,306 μg/kg/day for aerial mixer/loaders of aqueous concentrate, flowable concentrate, or suspension formulations.
- The acute ADD for field workers is estimated to range from 60.5 μg/kg/day for rice hand weeders to 951 μg/kg/day for rice scouters.
- The SADD for agricultural handlers is estimated to range from 67.9 μg/kg/day for ground boom applicator spraying dry flowable, aqueous concentrate, flowable concentrate, or suspension formulations to 4,581 μg/kg/day for aerial mixer/loaders of aqueous concentrate, flowable concentrate, or suspension formulations.
- SADD for field workers is estimated to range from 28.9 μg/kg/day for rice hand weeders to 455 μg/kg/day for rice scouters.
- The AADD for agricultural handlers is estimated to range from 11.3 μg/kg/day for ground boom applicator spraying dry flowable, aqueous concentrate, flowable concentrate, or suspension formulations to 763 μg/kg/day for aerial mixer/loaders of aqueous concentrate, flowable concentrate, or suspension formulations.
- AADD for field workers is estimated to range from 4.82 μg/kg/day for rice hand weeders to 75.8 μg/kg/day for rice scouters.
- The LADD for agricultural handlers is estimated to range from 6.03 μg/kg/day for ground boom applicator spraying dry flowable, aqueous concentrate, or flowable concentrate formulations to 407 μg/kg/day for aerial mixer/loader of aqueous concentrate, flowable concentrate, or suspension formulations.
- LADD for field workers is estimated to range from 2.57 μg/kg/day for rice hand weeders to 40.4 for rice scouters.

- Residential bystander spray drift Acute ADD for adult dermal exposure is estimated to range from 1.3 μg/kg/day to 196.88 μg/kg/day; for adult inhalation exposure (only aerial applications) ranges from 0.7 μg/kg/day to 13.56 μg/kg/day; for children1-2 yrs old dermal exposure range is 1.9 μg/kg/day to 288.59 μg/kg/day; for children 1-2 yrs old inhalation exposure (only aerial applications) ranges from 1.68 μg/kg/day to 41.53 μg/kg/day; for children 1-2 yrs old oral exposure range is 0 to 11.83 μg/kg/day.

## II. INTRODUCTION

Propanil [N-(3,4-dichlorophenyl) propanamide] is a selective post-emergent general use herbicide registered to control broadleaf and grass weeds in commercial settings. It is used alone or in combination with other herbicides. Propanil is primarily used on rice in California and the mid-southern states. It is also registered in states other than California for turf use at commercial sod farms. There are no existing or proposed residential uses of propanil.

Propanil was first registered as an herbicide in the U.S. in 1962 to control grasses and weeds in rice production, and was subject to both reregistration and tolerance assessment. In 2002, the United States Environmental Protection Agency (U.S. EPA) issued a tolerance reassessment decision for propanil and released the human health and ecological risk assessments for public comment. Comments were received from the Propanil Task Force II and the California Department of Pesticide Regulation (DPR). Subsequent to the tolerance reassessment, the use of propanil on small grains (spring wheat, oats, spring barley, and durum wheat) was voluntarily cancelled by the technical registrants (Dow AgroSciences, LLC and RiceCo, LLC) in 2003. The Reregistration Eligibility Decision (RED) by U.S. EPA (2003 and 2006) concluded the risk from occupational exposures was high even when personal protective equipment and contemporary methods of risk reduction were used.

In California, propanil products are restricted-use herbicides and may only be purchased and used by licensed applicators. No residential uses are allowed in the state. Drift-related crop damage may occur to foliage of non-target crops (fruit trees, grape vines, cotton and other crops), so propanil use was limited to defined use areas and to formulations with reduced volatility.

As of April 2017, 13 products containing propanil as the active ingredient (AI) are actively registered in California.

Propanil is classified as Category III based on the acute oral toxicity and Category IV based on acute dermal toxicity and inhalation toxicity, no dermal sensitization was observed. However, primary eye irritation was observed in rabbits (toxicity category II).

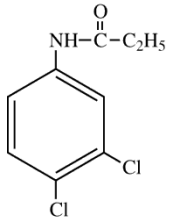
# III. FACTORS DEFINING EXPOSURE SCENARIOS

## 1. Physical and Chemical Properties

Physical and chemical properties of propanil shown below were obtained from U.S. EPA (2003 and 2006), GSI Environmental Inc. (2013; http://www.gsi-net.com/en/publications/gsi-chemical-database/single/459.html; accessed on September 9, 2014), and the Merck Index (Windholz *et al.,* 1983).

| | |
|---|---|
| Chemical Name: | N-(3,4-dichlorophenyl) propanamide |
| Common Name: | Propanil |
| Trade Name: | Duet, Riceshot, Stam, Wham, SuperWham, Propanil 4, Riceedge, and Willowood. |
| CAS-No: | 709-98-8 |

Structure:




| | |
|---|---|
| Empirical Formula: | $C_9H_9Cl_2NO$ |
| Molecular Weight: | 218.1 |
| Appearance: | White crystalline solid |
| Melting Range: | 91 - 93 ºC |
| Vapor Pressure: | 2.6 x $10^{-7}$ mm Hg at 30°C |
| Octanol/Water Partition Coefficient (log Kow): | 3.07 |
| Solubility: | 127 mg/L in water at 20 °C; and is completely soluble in ketones, alcohols, ethers and chlorinated hydrocarbons. |
| Density: | 1.054 g/$cm^3$ at 25°C |

## 2. Formulation and Label Uses:

As of December 2016, there are 14 propanil-containing products registered in California. They are all registered for use on rice. Propanil is a selective post-emergent herbicide applied using ground and aerial equipment.

Products containing propanil formulated as 8 dry flowable (60-81% AI), 3 aqueous concentrate (40-41.4% AI), 2 flowable concentrate liquid (41.2% AI), and 1 suspension (43.5% AI).

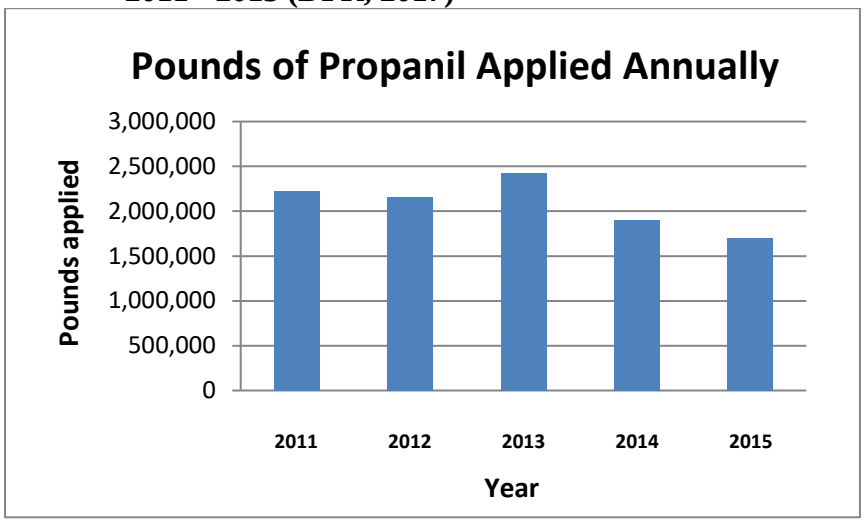
## 3. Target Weeds and Grasses:

Propanil is a selective post-emergent general use herbicide registered to control broadleaf and grass weeds in commercial settings. The target weeds and grasses include: barnyard grass (watergrass), brachiaris, coffeeweed, crabgrass, croton, curly indigo, ducksalad, foxtail, goose grass, gulf cockspur, Mexican weed, miller, morning glory, northern jointvetch, paragrass, pigweed, redstem, sesbania, small flower umbrella plant, smartweed, sourdock, spearhead, sprangletop and wiregrass.

## 4. Herbicide Use:

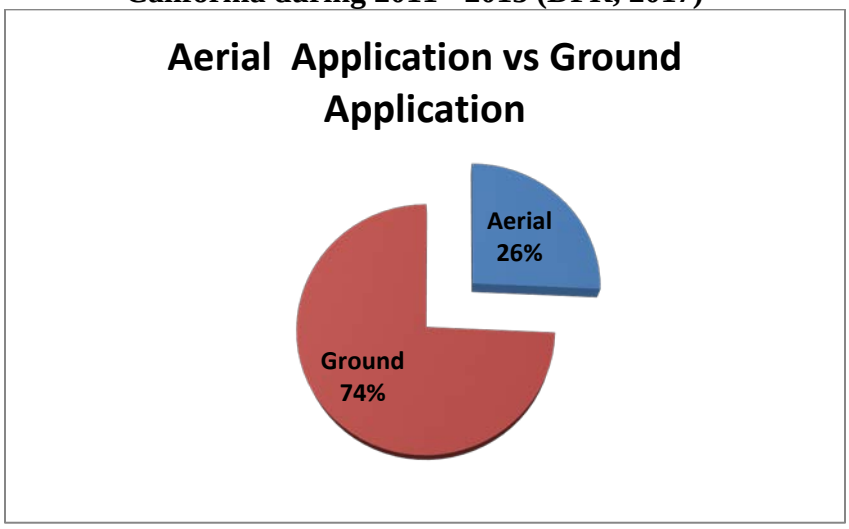
Based upon the data provided by Pesticide Use Report (PUR; DPR, 2017), the total annual usage of propanil in California was approximately 1,700,000 to 2,423,000 pounds AI per year during 2008 to 2012 (Figure 1).

**Figure 1. Total Pounds AI Used per year in California during 2011 - 2015 (DPR, 2017)**



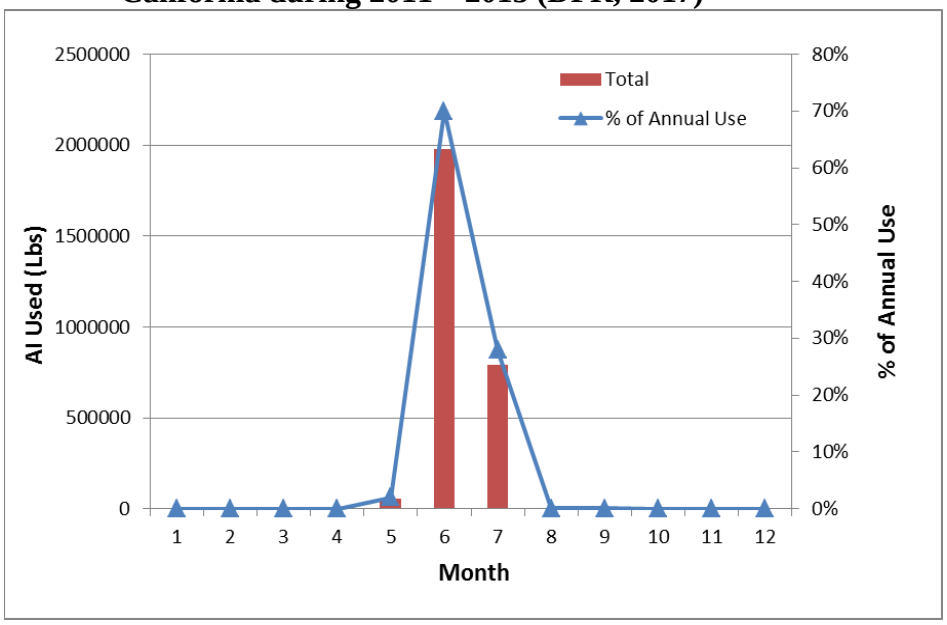

The products containing propanil in California are applied on rice using ground equipment such as tractor-mounted sprayers or aerially. Both rotary and fixed-wing aircraft are used in aerial applications. Based on 2011 to 2015 PUR (DPR, 2017), 26% of propanil application was applied by aerial method and 74% was applied by ground boom (see Figure 2, next page).

**Figure 2. Total Aerial Application versus Ground Application in California during 2011 - 2015 (DPR, 2017)**




The amount and relative percentage of season use are shown in Figure 3. The high usage months (above 5% of total annual usage) are 2 months, from June to July.

**Figure 3. Pounds and Relative Percentage of Season Uses of Propanil in California during 2011 – 2015 (DPR, 2017)**



## 5. Reported Illnesses

Between the years of 2010 and 2014, the most recent five years available information from California Pesticide Illness Query, there was no illness reported in California (DPR, 2016b). Further details of pesticide illnesses can be found in the risk characterization document.

## 6. Label Precaution:

As of April 2017, there are 13 products containing propanil registered in California. Among them, 10 products are classified as category III/IV toxicity (with the signal word CAUTION) and 3 products are classified as category II (with the signal word WARNING).

Base on the labels, propanil can be harmful if swallowed or absorbed through skin. The hazards of exposure and treatments of ingestion, inhalation, and dermal or eye contact are indicated on the product labels.

Pesticide/herbicide handlers are legally required to use personal protective equipment (PPE) and engineering controls listed on the label. Base on product labels of propanil:

- Mixers/loaders and handlers of concentrates must wear following PPE:
  - For body PPE, most products require coveralls, long-sleeved shirts, and pants. Chemical-resistant aprons are required when mixing/loading. There are two DF-Duet 60 products only require coveralls over short or long-sleeved shirts and short or long pants;
  - Chemical resistant footwear plus socks;
  - Chemical resistant gloves;
  - Protective eyewear;
  - Chemical-resistant headgear for overhead exposure.

- Applicators and other handlers of dilutes must wear:
  - Long-sleeved shirt and long pants, shoes plus socks, and chemical-resistant gloves, made of any waterproof material;
  - Enclosed cabs for aerial applicator;
  - Chemical-resistant headgear for overhead exposure.

The handler PPE requirements may be reduced or modified as specified in the Worker Protection Standard (WPS) when handlers use closed systems in a manner that meets the requirements listed in the WPS for agricultural pesticides [40 CFR 170.240 (d) (4-6)].

Human flagging is prohibited for most products. Based on the product labels, flagging to support aerial application is limited to use of the Global Positioning System or mechanical flaggers. However, there are three dry flowable formulation products (DF-

Duet 60, DF-Duet 60 CA, and RiceEdge 60DF) that do not include label language specifically prohibiting human flagging.

**7. Reentry Interval:**

Propanil product labels specify a restricted entry interval (REI) of 24 hours. The pre-harvest intervals (PHI) are at least 60 days.

**8. California Requirements**

The product labels contain many of the California regulation requirements. However, the California Code of Regulations [CCR 6738(b)(1)] requires that protective eyewear be worn during mixing, loading, and application activities. This requirement is not specified on some category III and IV propanil product labels.

**9. Significant Exposure Scenarios**

Handler

Based on current use patterns, workers may be exposed to propanil during and after applications to rice. In rice, the maximum recommended use rate per application is 6.0 lbs AI per application per acre and 8.0 lbs AI per acre per season.

The potential handler exposure scenarios are summarized in Table 1. These exposure scenarios will serve as the basis for the quantitative exposure assessments.

**Table 1. The Handler Exposure Scenarios for Propanil Agricultural Application[a].**

| Activity [b] | Formulation [c] | Application Method | Crop/Site | Maximum Use Rate (lb AI/acre)[d] | Typical Use Rate (lb AI/acre)[e] | Maximum Acres Treated per Day[f] | Typical Acres Treated per Day[f] |
|---|---|---|---|---|---|---|---|
| 1a. M/L | DF | Ground boom | Rice | 6.0 | 3.0 | 200 | 80 |
| 1b. M/L | DF | Aerial | Rice | 6.0 | 3.0 | 720 [g] | 720 [g] |
| 2a. M/L | L (AC, FC, Suspension) | Ground boom | Rice | 6.0 | 3.0 | 200 | 80 |
| 2b. M/L | L (AC, FC, Suspension) | Aerial | Rice | 6.0 | 3.0 | 720 [g] | 720 [g] |
| 3. A | DF, AC, FC, Suspension | Ground boom | Rice | 6.0 | 3.0 | 200 | 80 |
| 4. A | DF, AC, FC, Suspension | Aerial | Rice | 6.0 | 3.0 | 720 [g] | 720 [g] |
| 5. F [h] | DF | Aerial | Rice | 6.0 | 3.0 | 350[i] | 350 [i] |

a According to product label, the mixer/loaders wear coverall over long-sleeved shirt and long-pants (For DF formulation products, only short-sleeved shirt and short pants are required), chemical resistant apron, chemical resistant footwear, chemical resistant gloves made of any waterproof material; Chemical resistant footwear plus socks; protective eyewear. Applicators wear long-sleeved shirt and long pants, chemical-resistant headgear for overhead exposure, chemical-resistant gloves made of any waterproof material, shoes and socks.

b M/L: mixer/loader;
A: applicator;
F: flagger

c L: liquid;
AC: Aqueous concentrate;
FC: Flowable concentrate;
DF: Dry flowable.

d Maximum use rates are based on product labels.

e Typical use rates are based on the Reregistration Eligibility Decision (RED) (U.S. EPA, 2003 and 2006) and recent five years of pesticide use data (DPR, 2016a).

f Daily Maximum and Typical Treated values were based on the Reregistration Eligibility Decision (RED) (U.S. EPA, 2003 and 2006), and recent five years of pesticide use data (DPR, 2016a). Ground boom M/L/A was assumed to have exposures in the range of M/L and applicators in a day (M/L/A would mix/load part of the day, and apply for the remainder). For this reason, separate M/L/A scenarios were not prepared for these scenarios.

g Based on California regulation (Title 3, California Code of Regulations, Section 6462. Propanil), the maximum treated area by aircraft within each county per day is 720 acres. Therefore, the acres are different from 3200 acres for maximum and 1200 acres for typical assumptions in RED (U.S. EPA, 2003 and 2006).

h Most product labels state “Human flagging is prohibited.” However, three DUET 60 product labels do not specify that human flagging is prohibition. To protect all legal handlers, flagger exposures were evaluated in this exposure assessment.

i Acres of flagger handled per day from HED's Science Advisory Council for Exposure, Policy 009.1, "Standard Values for Daily Acres Treated in Agriculture." Health Effects Division, Office of Pesticide Programs (U.S. EPA, 2001).

## Post Application

Table 2 summarized major exposure scenarios for field workers who enter areas previously treated with propanil to perform specific work activities in these areas.

**Table 2. Representative and Represented Post-Application Agricultural Activities with Potential Exposure to Propanil**

| Representative Crop/Site [a] | Representative Reentry Activities [b] | Covered Crops | Covered Reentry Activities [c] |
|---|---|---|---|
| Rice | Scouting | - | Irrigating, Harvesting (Mech) |
| | Weeding (Hand) | - | Weeding (Mech) |

a Based on product labels, propanil is limited to use on rice in California.
b Representative reentry activities are considered to have most exposure.
c Covered reentry activities are considered to be covered by the representative activity and anticipated to have less exposure than that of the representative scenario(s).

Residential Exposure

Propanil does not have any residential uses. However, residential bystanders may be exposed to propanil via spray drift from nearby agricultural applications (see Appendix for details).

## IV. PHARMACOKINETICS

### 1. Dermal Absorption

There were no propanil-specific dermal studies available during the preparation of this Exposure Assessment Document (EAD). U.S. EPA estimated a dermal absorption factor of 20% by comparing the oral lowest observed adverse effect level (LOAEL) to dermal rabbit studies (U.S. EPA, 2003 and 2006). U.S. EPA used a dermal absorption factor for propanil derived from the ratio of the maternal LOAEL for a rabbit developmental toxicity study (oral gavage) (U.S. EPA RED, 2003 and 2006) to the LOAEL for rabbit 21-day dermal toxicity study (U.S. EPA RED, 2003 and 2006). However, DPR does not rely on toxicity ratios to determine dermal absorption. Determining dermal absorption by the ratio of oral to dermal toxicity studies is unreliable due to following reasons: 1) This approximation depends on the assumption that all of the difference between oral and dermal toxicity is due to dermal absorption, which may not be valid; 2) Toxicity studies use much higher doses than typical doses for dermal absorption studies, and the ratio may not generalize to lower doses; and 3) Dose determination in toxicity studies may not be sufficiently exact for determining dermal absorption.

Therefore, in the absence of acceptable data, this exposure assessment uses the Human Health Assessment (HHA) Branch default dermal absorption of 50% (Donahue, 1996). This default value is based on a review of data from forty pesticides, twenty-six of which were documented in Thongsinthusak *et al*. (1993).

### 2. Inhalation Absorption

In addition to dermal exposure, inhalation is the other major route of exposure considered in this exposure assessment. No inhalation absorption studies are available. Therefore, a

default inhalation absorption value of 100% was used for calculating doses absorbed via inhalation in accordance with HHA policy (Frank, 2008).

## V. ENVIRONMENTAL CONCENTRATIONS

### 1. Air

Ambient air concentrations of pesticides are limited by California law, including the Toxic Air Contaminants Act (California Health and Safety Code, Sections 39650-39761), which codifies the evaluation and control of toxic air contaminants (TAC). Propanil was included in the *Proposed Toxic Air Contaminant Monitoring for 2008* (Warmerdam, 2008). As part of the Air Resources Board (ARB) air monitoring program, propanil concentrations were monitored in the ambient air during peak application season and in the air surrounding application sites (Houston, 2008a and b; Aston, 2009; Houston, 2008b; Rider, 2009).

*Ambient Air*

Bystanders are defined as those individuals who are not directly involved with a pesticide application, but who may be exposed to airborne pesticide during or after the application, by spray drift or volatilized pesticide. Bystanders can be exposed from agricultural applications of propanil. The low vapor pressure of propanil ($2.6 \times 10^{-7}$ mm Hg at 30°C) indicates that there is a low potential for propanil to vaporize following application. Hence, spray drift of propanil during and immediately after an application during peak use periods is expected to be the primary pathway of exposure for bystanders.

At the request of DPR, ARB staff sampled ambient concentrations of propanil in Butte, Glenn, and Colusa County in 2008 (Houston, 2008a; Aston, 2009). Sampling was conducted for 8 weeks during June and July, which are the peak months for propanil applications. The 5 rural ambient sampling sites were Richvale Elementary School; Willows Middle School; Maxwell Elementary School; George Egling School; Public Works Office. A buffering algorithm within a Geographic Information System was used to calculate the amounts of propanil used within 1 mile and 5 miles from the edge or boundary of each community. Urban background concentrations were collected at the Chico Air Monitoring Station, approximately 24 miles away from propanil use. Each sampler inlet height was 1.5 meters above roofline or in an open secured area which meets siting criteria for the ambient monitoring.

Quality assurance consisted of blanks, collocated samples, and field spikes, and trip spikes samples. Concentrations of propanil in the system blanks and method blanks were less than the minimum detection limit (MDL), 0.02 $\mu g/m^3$. The laboratory quality control sample average recovery was 92% with a standard deviation of 10.3%. A total of 224 samples were collected, which included 4 field spikes and 4 trip spikes collected from 6 sampling sites. Additionally, 4 laboratory spikes were prepared and kept in the laboratory to correspond to the field/trip spikes. The measured ambient concentrations of propanil

spanned values of less than the Method Detection Limit (0.004 μg/m$^3$) to a maximum of 0.149 μg/m$^3$. The average concentration was 0.029 μg/m$^3$. Table 3 shows the results from all sites (μg/m$^3$).

**Table 3. Summary of Ambient Monitoring Results per Site in μg/m$^3$ [a]**

| Site [b] | Minimum | Maximum | Average | Standard Deviation |
|---|---|---|---|---|
| RICH | <0.02 | 0.149 | 0.045 | 0.036 |
| CHIC | <0.02 | 0.031 | 0.016 | 0.007 |
| WILL | <0.02 | 0.133 | 0.037 | 0.028 |
| MAXW | <0.02 | 0.088 | 0.039 | 0.023 |
| COLU | <0.02 | 0.066 | 0.023 | 0.015 |
| IAMS | <0.02 | 0.085 | 0.039 | 0.066 |
| Overall | <0.02 | 0.634 | 0.033 | 0.029 |

a This is Table 7 from the ARB document (Aston, 2009).

b Site location identification:
RICH: Richvale Elementary School
CHIC: Chico Air Monitoring Station
WILL: Willows Middle School
MAXW: Maxwell Elementary School
COLU: George English School
IAMS: Public Works Office

*Application Site Air*

As requested by DPR, ARB performed propanil application site air monitoring in Colusa County in 2008 (Houston, 2008b; Rider, 2009). DPR requested an estimated quantitation limit (EQL) of 1.0 μg/m$^3$. The actual EQL for this study was 0.02 μg/m$^3$. The air samples were collected using quartz filters. The used filters were extracted with 10 ml of dichloromethane. The MDL calculation followed U.S. EPA procedures [40 CFR 136, App. B]. All field samples were analyzed within 14 days of samples collection. All values of blanks for system and method were below the MDL.

Of the airborne samples collected, 14 had propanil concentrations higher than the EQL. With one exception, all measured concentrations were greater than the 0.019 μg/sample MDL. The concentrations ranged from 0.014 μg/m$^3$ to 55.9 μg/m$^3$. The highest concentrations of propanil were found in the east, southeast, south, and southwest areas during the time of the application. All of the pre-application background samples were below the EQL of 1.0 μg/m$^3$. Table 4 lists results of the samples exceeding the EQL.

There were irregularities in some of the airborne propanil data collected. Notably, Rider (2009) indicated that during the study, an aerial application of propanil (at 6 lb AI/acre) took place directly south of the study field. The plane involved in the off-site spraying application started and stopped in the vicinity of the east samplers. Therefore, the high concentrations noted (Table 4) are likely due to overspray at the east side. In addition, based on the previous report on the same monitoring study by Houston (2008b), fires occurred near the application site during the monitoring interval; those fires are the likely significant source of particulate matter measured in the 5$^{th}$ sampling cycle. For these reasons, these data were not used to calculate propanil residential bystander exposures.

**Table 4. Results Exceeding EQL among Propanil Samples during Application Air Monitoring at Colusa County, 2008 [a]**

| Location | Log # | Sample Name [b] | Average Flow (LPM) | Total Volume ($m^3$) | Date Analyzed | Results ($\mu g/m^3$) |
|---|---|---|---|---|---|---|
| North Side | 014 | NS-P-1 | 2.96 | 0.727 | 26-Jun | 12.51 |
| North Side | 040 | NS-P-2 | 3.17 | 1.692 | 27-Jun | 1.10 |
| Northwest Corner | 026 | NWC-P-1 | 3.07 | 0.728 | 26-Jun | 3.85 |
| East Side | 016 | ES-P-1 | 3.08 | 0.721 | 26-Jun | 30.4 |
| East Side | 039 | ES-P-2 | 3.16 | 1.743 | 27-Jun | 1.35 |
| South East Corner & Collocated | 017 | SEC-P-1 | 2.92 | 0.684 | 26-Jun | 27.6 |
| | 022 | SEC-P-1C | 3.05 | 0.712 | 26-Jun | 27.4 |
| | 032 | SEC-P-2C | 2.99 | 1.703 | 27-Jun | 1.20 |
| South Side | 023 | SS-P-1 | 2.93 | 0.719 | 26-Jun | 55.9 |
| South Side | 035 | SS-P-2 | 2.98 | 1.679 | 27-Jun | 1.62 |
| South Side | 067 | SS-P-4 | 2.97 | 2.143 | 1-Jul | 1.01 |
| South West Corner | 024 | SWC-P-1 | 2.79 | 0.687 | 26-Jun | 42.5 |
| South West Corner | 036 | SWC-P-2 | 3.01 | 1.695 | 27-Jun | 1.07 |
| West Side | 025 | WS-P-1 | 3.01 | 0.755 | 26-Jun | 11.38 |

a. These data are based on the study by ARB (Rider, 2009).
b. Site location identification for sample names:
NS=North Side
ES=East Side
SEC=Southeast Corner
SS=South Side
SWC=Southwest Corner
WS=West Side

## 2. Dislodgeable Foliar Residue (DFR)

Dislodgeable foliar residue (DFR) is defined as the amount of pesticide residue that can be removed from both sides of treated foliage surfaces using aqueous surfactant. DFR residues may be transferred to humans when they contact leaves that had been treated with pesticide. Together with an appropriate transfer coefficient, DFR can be used to estimate the pesticide amount transferred to a human who enters a previously treated field. Generally, to quantify DFR, the leaf disc samples are rinsed and dislodgeable residues are analyzed by gas-liquid chromatography. The DFR is reported as residue per leaf area ($\mu g/cm^2$). A general equation for calculating DFR and half-life (t ½) at a given time is:

$$DFR_t = DFR_0 \times exp(-kt)$$

in which $DFR_0$ represents initial DFR level, $t$ represents the time after treatment, and $k$ is the constant derived from regression. Usually, the data are analyzed by performing an exponential regression and the first-order rate kinetics (in which the rate is proportional to the amount of DFR removed from treated foliage) calculation of half-life.

Propanil-specific dissipation data for are not available. Based on U.S. EPA (2013), the initial HHA default DFR value is 25% of the maximum application rate applied for rice, and 10% per day as default residue dissipation (U.S. EPA, 2012).

# VI. EXPOSURE ASSESSMENT

## 1. Agricultural Use

### 1.1 Handler

As of July 2016, propanil-specific occupational exposure data were not available. Instead, exposure to handlers was estimated using generic surrogate data from the Pesticide Handlers Exposure Database (PHED) (Beauvais *et al*, 2007). PHED was used to estimate exposure of mixer/loader and applicator who handle products with propanil. The related values of body weight, amount treated per day, protection factors, etc., are all standard values based on HHA methodology DPR has used in previous EADs (Beauvais, 2007; Zhao, 2009).

PHED is a non-chemical specific exposure data base constructing using many studies on different AIs (PHED, 1995). There are two assumptions associated with the use of PHED exposure estimates (Versar, 1992): (1) exposure is primarily a function of the pesticide application method/equipment and formulation type, not the physical-chemical properties of a specific AI; and, (2) exposure is proportional to the amount of AI handled.

The limitations of the PHED data as a surrogate database were outlined by Beauvais *et. al.* (2007). In particular, dermal exposure estimates for different body parts are likely based on sets of observations from different individuals. Due to the nature of the PHED database uncertainty, the upper confidence limit on the generic exposures in the PHED database is used to derive the exposure estimates in this document. Short-term exposures are estimated using 90% upper confidence limit (UCL) on the 95$^{th}$ percentile of exposure estimate from PHED and long-term exposures are estimated using the 90% UCL on the arithmetic mean, based on HHA policy (Beauvais, *et. al.*, 2007). The method of calculating the confidence intervals is described in Powell (2007). Handler exposure scenarios and related exposure data are given in the PHED reports (Beauvais *et. al.*, 2007), and statements of assumptions used in the exposure calculations and results of PHED subsets are summarized in Table 5, next page.

**Table 5. Pesticide Handler Exposure Database (PHED) Exposure Estimates for Handlers of Propanil**

| Exposure Scenarios [a] | | | Application Rated (lb AI/acre) [d] | Acres/Day (A/day) [e] | Mean Exposure [f] (µg/lb AI) | | N [g] | Scen# [h] |
|---|---|---|---|---|---|---|---|---|
| Task [b] | FM [c] | Method | | | Dermal | Inhalation | | |
| 1a. M/L | DF | Ground boom | Rice = 6 (max) | 200 (max) | 94.2 | 0.66 | 16-26 | 2 |
| | | | Rice = 3 (typical) | 80 (typical) | 94.2 | 0.66 | 16-26 | 2 |
| 1b. M/L | DF | Aerial | Rice = 6 (max) | 720 | 94.2 | 0.66 | 16-26 | 2 |
| | | | Rice = 3 (typical) | 720 | 94.2 | 0.66 | 16-26 | 2 |
| 2a. M/L | L (AC, FC, suspension) | Ground boom | Rice = 6 (max) | 200 (max) | 229 | 2.35 | 72-122 | 5 |
| | | | Rice = 3 (typical) | 80 (typical) | 229 | 2.35 | 72-122 | 5 |
| 2b. M/L | L (AC, FC, suspension) | Aerial | Rice = 6 (max) | 720 | 229 | 2.35 | 72-122 | 5 |
| | | | Rice = 3 (typical) | 720 | 229 | 2.35 | 72-122 | 5 |
| 3. A | DF, AC, FC, suspension | Ground boom | Rice = 6 (max) | 200 (max) | 25.5 | 1.18 | 22-42 | 11 |
| | | (Open Cab) | Rice = 3 (typical) | 80 (typical) | 25.5 | 1.18 | 22-42 | 11 |
| 4. A | DF, AC, FC, suspension | Aerial | Rice = 6 (max) | 720 | 12.1 | 0.025 | 14-28 | 18 |
| | | (Closed Cockpit) | Rice = 3 (typical) | 720 | 12.1 | 0.025 | 14-28 | 18 |
| 5. F [i] | DF | Aerial | Rice = 6 (max) | 350 | 32.6 | 0.200 | 18-28 | 7 |
| | | | Rice = 3 (typical) | 350 | 32.6 | 0.200 | 18-28 | 7 |

a The exposure scenarios are based on the product labels.

b M/L = mixer/loader; A = applicator; F = flagger.
Protective clothing and equipment for various scenarios are based on product label and California regulations (see "Label precaution" section).

c FM = Formulation; AC = Aqueous Concentrate; FC = Flowable Concentrate; DF = Dry Flowable.

d Maximum application rates are values found on currently registered labels and are used to estimate short-term exposure; typical (average) application rate to rice is based on the RED (U.S. EPA, 2003 and 2006) and recent five years California use data (DPR. 2016) are used to estimate long-term exposure. AI = active ingredient; A = Acre.

e Maximum and typical daily acres to be treated in each scenario are based on the RED (U.S. EPA, 2003 and 2006), except for aerial application where the maximum daily acres is 720 acres/day per county and is based on California propanil regulation (Title 3, California Code of Regulation, Section 6462. Propanil).

f The exposure data are from PHED (PHED, 1995). Dermal values are the sum of dermal (non-hand) and hand (Beauvais, *et. al.*, 2007). Appropriate protection factors were applied depending on label precaution and listed in the guideline document (Beauvais, *et. al.*, 2007). Based on the product labels, mixer/loader must wear:

- Coveralls over short-sleeved shirt and pants for two of eight DF products, the remaining six of eight DF products require the mixer/loader to wear coveralls over long-sleeved shirt and pants and chemical-resistant apron.
  - To protect all mixer/loaders handling DF products, dermal exposure values of M/L DF formulation from the PHED database were adjusted using the 90% protection factor only on chest, back, upper arm, and thigh (covered by short-sleeved shirt and pants) exposure based on HHAB practice (Thongsinthusak, *et al.*, 1991).
  - The remaining product labels require mixer/loaders to wear coveralls over long-sleeved shirt and pants, and chemical-resistant apron. Therefore, dermal exposure values of M/L for these formulations from the PHED database were adjusted by the 90% protection factor on

body dermal exposure, further deducting chemical-resistant apron protected area (chest and ½ of thighs) by the 95% protection factor based on HHAB practice (Thongsinthusak, *et al.*, 1991).

- Based on product labels, all handlers wear chemical-resistant gloves (90% protection factor),
- All mixer/loader dermal exposure was further reduced by deducting 1/4 of the head exposure. This is based on product labels requiring the mixer/loader to wear protective eyewear covering ½ of face or ¼ of head and 75% protection factor (Thongsinthusak, *et al.*, 1991).
- Based on Worker Protection Standard (WPS) [40 CFR 170.240 (d) (4-6)], "Persons occupying a closed cab may substitute a long-sleeved shirt, long pants, shoes, and socks for labeling-specified personal protective equipment." Therefore, the pilot is not required to wear gloves in a closed cockpit.
- Chemical-resistant headgear is required by the label for protection from overhead exposure. Therefore, the flagger head exposure was reduced using the 95% protection factor based on HHAB practice (Thongsinthusak, 1991).

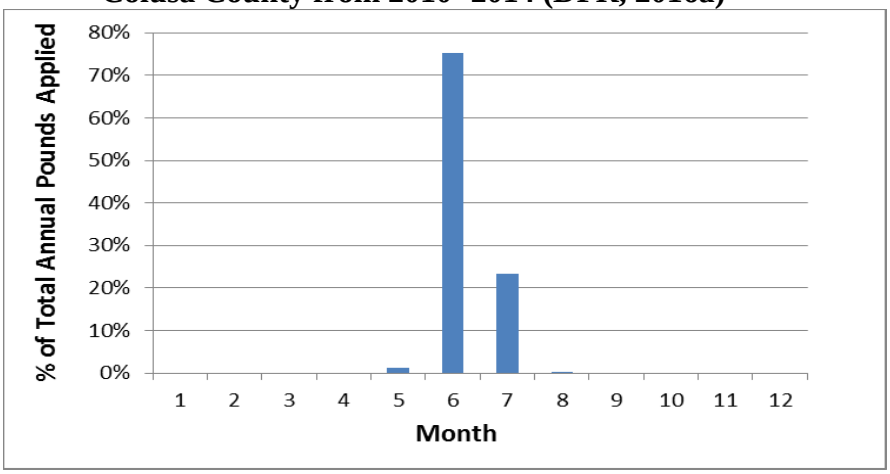
g N = Number of observations for dermal (non-hand), hand, and inhalation in PHED data set.

h Scen # = Scenario number corresponding to the scenarios as numbered in the HHAB guidance document (Beauvais *et. al*., 2007).

i Most product labels indicate “Human flagging is prohibited.” However, three DUET 60 product labels do not include flagger prohibition language. To protect all legal handlers, flagger exposure was evaluated in this exposure assessment. Based on product labels requiring chemical-resistant headgear for overhead exposure, flagger head exposure was reduced by the 95% protection factor.

Temporal patterns were investigated by plotting percent of annual use based on total pounds applied per month for 2010–2014 (DPR, 2016a). This seasonal pattern information was used to estimate intermediate and long-term exposure of workers involved in propanil applications. For the exposure assessment, data from the highest use county (Colusa) over the given-year period were used as surrogates. To estimate annual exposure, only the months showing use greater than or equal to 5% of the annual pounds applied over the five-year period were considered as crucial and counted. These county-based data were further grouped by application method to screen for the highest use counties in various categories. Data showing applications in Colusa County are summarized in Figure 4.

**Figure 4. Percent of Annual Pounds Applied of Propanil to Rice in Colusa County from 2010 -2014 (DPR, 2016a)**




The highest ground application use of propanil occurs in 2 months, June to July. Table 6 summarizes the estimates of acute, seasonal, annual, and lifetime exposures for propanil handlers. Based on methodology DPR has used in previous EADs (Beauvais, 2007; Zhao, 2009), short-term exposure estimates assume the maximum application rate allowed by product labels, and a reasonable maximum application size. For seasonal, annual, and lifetime exposures, the typical application rate and typical application size was used to represent general exposure scenarios that handlers encounter over longer intervals.

**Table 6. Estimates of Short-, Intermediate-, and Long-Term Exposure to Propanil Handlers**

| Job Category [a] | Formulation [b] | Use Rate [c] (lb AI/A or gal) | Acres/Day [d] (A/day) | Acute ADD [e] (µg/kg/day) | SADD [f] (µg/kg/day) | AADD [g] (µg/kg/day) | LADD [h] (µg/kg/day) |
|---|---|---|---|---|---|---|---|
| Ground boom, M/L | DF | Rice=6.0 (max) | 200 (max) | 2,960 | | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 210 | 35.0 | 18.7 |
| Aerial, M/L | DF | Rice=6.0 (max) | 720 | 10,656 | | | 173 |
| | | Rice=3.0 (typical) | 720 | | 1,949 | 325 | |
| Ground boom, M/L | L (AC, FC, suspension) | Rice=6.0 (max) | 200 (max) | 7029 | | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 506 | 84.3 | 44.9 |
| Aerial, M/L | L (AC, FC, suspension) | Rice=6.0 (max) | 720 | 25,306 | | | |
| | | Rice=3.0 (typical) | 720 | | 4,581 | 763 | 407 |
| Ground boom, A | DF, AC, FC, suspension | Rice=6.0 (max) | 200 (max) | 941 | | | |
| | | Rice=3.0 (typical) | 80 (typical) | | 67.9 | 11.3 | 6.03 |
| Aerial, A [i] | DF, AC, FC, suspension | Rice=6.0 (max) | 720 | 1271 | | | |
| | | Rice=3.0 (typical) | 720 | | 228 | 38.0 | 20.3 |
| Flagger [j] | DF | Rice=6.0 (max) | 350 | 1761 | | | |
| | | Rice=3.0 (typical) | 350 | | 317 | 52.9 | 28.2 |

a The exposure scenarios are based on the product labels. M/L = mixer/loader; A = applicator.

b FM = Formulation; DF = Dry Flowable; AC = Aqueous Concentrate; FC = Flowable concentrate.

c The maximum use rates based on the currently registered product labels are used to estimate short-term exposure; typical application rate based on RED (U.S. EPA, 2003 and 2006) and the most recent five years California use data (DPR. 2016) are used to estimate long-term exposure. AI = Active ingredient; A = Acre.

d Maximum and typical (average) daily acres to be treated in each scenario based on the RED (U.S. EPA, 2003 and 2006). Based on California regulation (Title 3, California Code of Regulations, Section 6462. Propanil), the maximum treated area by aircraft within each county per day is 720 acres.

e Acute Absorbed Daily Dosage (Acute ADD). Acute ADD = (short-term dermal exposure rate [µg/lb AI handled] x dermal absorption rate + short-term inhalation exposure rate [µg/lb AI handled] x inhalation absorption rate) x max use rate x max daily treated acres ÷ body weight. Calculation assumptions include:

- The 90% upper confidence limit of the 95$^{th}$ percentile short-term exposure estimate based on HHAB guidance document (Beauvais *et. al*., 2007), the multipliers from Powell (2007).
- Dermal absorption rate = 50 % (default dermal absorption rate based on HHAB practice);
- Inhalation absorption is assumed to be 100% (default inhalation absorption rate based on HHAB practice (Frank, 2008);
- Body weight = 70 kg for both male and female (U.S. EPA, 1997).
- Maximum application rate based on product labels, 6 lb AI/acre

- Maximum daily treated acres based on the RED (U.S. EPA, 2003 and 2006), 200 acres for ground application. For aerial application, U.S. EPA used 3200 acres for maximum estimate, however, based on California propanil regulation (Title 3, California Code of Regulations, Section 6462. Propanil), the maximum aerial daily acre is 720 acres/day per county in California.

f Seasonal Average Daily Dosage (SADD). Seasonal ADD = (long-term dermal exposure rate [µg/lb AI handled] x dermal absorption rate + long-term inhalation exposure rate [µg/lb AI handled] x inhalation absorption rate) x typical use rate x typical daily treated acres ÷ body weight. Calculation assumptions include:

- The 90% upper confidence limit of the arithmetic mean long-term exposure estimate based on HHAB guidance document (Beauvais *et. al*. (2007); multipliers from Powell (2007).
- Dermal absorption rate = 50 % (default dermal absorption rate based on HHAB practice) (Donahue, 1996);
- Inhalation absorption is assumed to be 100% (default inhalation absorption rate based on HHAB practice) (Frank, 2008);
- Body weight = 70 kg for both male and female (U.S. EPA, 1997).
- Typical (average) application rate based on RED (U.S. EPA, 2003 and 2006) and recent five years PUR data (DPR, 2016a), 3 lb AI/acre
- Typical (average) daily treated acres based on RED (U.S. EPA, 2003 and 2006), 80 acres for ground application. Based on California regulation (Title 3, California Code of Regulations, Section 6462. Propanil), propanil aerial application is allowed up to 720 acres/day per county.

g Annual Average Daily Dosage (AADD) = SADD x annual use months per year/12 months in a year. The estimated high-use season for handler was based on the California Pesticide Use Summaries Database (DPR, 2016a, see text and Figure 4).

h Lifetime Annual Daily Dosage = AADD x 40 years of work in a lifetime/75 years in a lifetime.

i Based on Worker Protection Standard (WPS) [40 CFR 170.240 (d) (4-6)],"Persons occupying an enclosed cockpit may substitute a long-sleeved shirt, long pants, shoes, and socks for labeling-specified personal protective equipment." The pilot is not required to wear gloves and eyewear.

j Most product labels include the language: “Human flagging is prohibited.” However, three DUET 60 product labels do not prohibit the use of a flagger. To protect all legal handlers, flagger exposure was evaluated in this exposure assessment.

### 1.2 Field Workers

Field workers can be exposed to propanil residues by entering previously treated fields to perform certain agricultural activities, including scouts, weeding, harvesting, etc. All current propanil labels registered in California require a REI of 24 hours and a PHI of at least 60 days.

The major route of pesticide exposure for reentry workers is dermal exposure, most likely by contact with treated foliage and transfer of residues to the skin. There is no propanil-specific monitoring study available for post-application exposure. Therefore, a reentry dermal exposure assessment has been extrapolated using a default dermal transfer coefficient (TC). The TC is a parameter that estimates the rate of transfer from the treated surface (e.g., foliage during reentry) to the worker. The TC is estimated based on empirical data from studies in which both DFR and dermal exposure have been measured. TC is defined as a function of hourly dermal exposure in μg/hr, foliar residue (DFR) in μg/cm$^2$, and the DFR expected at the time of reentry. The extent of worker contact with treated foliage depends on the crop height and fullness of the foliage. Therefore, the same activity, such as scouting, can have different TCs for different crops. Hourly dermal exposure of workers entering a treated field is estimated by multiplying the dermal TC for a crop with the DFR at the time of entry.

No propanil-specific DFR data were available up to date of this EAD was prepared. Therefore, the DFR value was based on a default of 25% of the maximum rate applied for the initial rice DFR (U.S. EPA. 2013). Reentry workers are not required to wear protective clothing unless entering before expiration of the REI. Therefore, field worker exposure calculations were not corrected for any protection factors.

The absorbed daily dosage (ADD) was calculated as shown in the equation below (Zweig *et al.*, 1984; Zweig *et al.*, 1985), using the dermal absorption factor (DAF) of 50% (default dermal absorption according to DPR policy (Donahue, 1996); default exposure duration (ED) of 8 hours; and default body weight (BW) of 70 kg (U.S. EPA, 1997).

$$ADD\ (\mu g / kg / day) = \frac{DAF \times DFR\ (\mu g / cm^2) \times TC\ (cm^2 / hour) \times ED\ (hours / day)}{BW\ (kg)}$$

Acute exposures were estimated using DFR at the expiration of REI and PHI since it is the earliest time workers could enter and because these values result in the highest amount of DFR that workers would typically contact. Table 7 summarizes the default DFR and dermal TCs used to estimate daily and acute propanil exposures of field workers.

For long-term exposure estimates, it was assumed that workers would not always enter fields at the expiration of the REI and PHI. Seasonal, annual, and lifetime exposures were estimated for all activities other than harvesting at an assumed average reentry of the REI expiration plus 7 days and PHI plus 10 days for harvesting. These assumed reentry times were based on the reasonable assumption that workers generally enter fields

an average of 7 – 10 days after expiration of REI and PHI (Beauvais, 2008). The laboratory half-life of propanil is 2-3 days in water/soil, and 0.5 day in aerobic soil. However, half-life of propanil in plant residues is not available. Therefore, the default half-life of 35 days (U.S. EPA, 2003 and 2006) was used to calculate the average DFR.

The annual exposure period is estimated based on the application data (DPR, 2016a) showed in Figure 5. The percent of annual use was calculated based on monthly acres treated, not number of applications. The focus was on acres treated because reentry frequency is dependent on the size of the field treated. Likewise, by using treated acres, this exposure assessment recognizes that the same acres may be treated with multiple applications of propanil.

Because propanil use peak occurs in June and July, protective clothing is often not worn by fieldworkers unless required for early reentry. Therefore, fieldworker exposure estimates were based on the assumption that no protective clothing or equipment would be used.

**Table 7. Estimated Acute Dermal Exposure of Rice Field Workers to Propanil**

| Crops | Representative Reentry Activities [a] | REI/PHI [b] (day) | TC [c] ($cm^2$/hr) | DFR(day 0) [d] (μg/$cm^2$) | DFR(day 1) [e] (μg/$cm^2$) | Daily Exposure [f] (μg/person/day) | Acute ADD [g] (μg/kg/day) |
|---|---|---|---|---|---|---|---|
| Rice | Scouting | REI = 1 | 1100 | 16.81 | 15.13 | 133159 | 951 |
| Rice | Weeding | REI = 1 | 70 | 16.81 | 15.13 | 8474 | 60.5 |

a Workers were assumed to wear a long pants, long-sleeved shirt, without gloves.
b REI (restricted entry interval) and PHI (pre-harvest interval) were taken from the product label.
c TC (transfer coefficient) values are taken from Agricultural Default Transfer Coefficients (U.S. EPA, 2013).
d DFR (dislodgeable foliar residues) values at the expiration of the REI or PHI, see Dislodgeable Foliar Residues section. Since no DFR data are available for rice, the default DFR (25% of the maximum use rate (6 lb AI/acre), expressed as 16.81 μg/$cm^2$) was used as initial DFR (U.S. EPA, 2013).
e Based on product label, the restricted entry interval is 24 hours, and U.S. EPA recommends when chemical-specific DFR unavailable, 10% per day is used as default residue dissipation to calculate the DFR on a specific day. Therefore, the DFR on REI was adjusted to 15.13 μg/$cm^2$.
f Daily exposure (μg/person/day) = DFR * dermal transfer coefficient * work hours/day (8 hr/day).
g Acute ADD (Absorbed Daily Dosage) = daily exposure * 50% dermal absorption (default) ÷ 70 kg body weight (U.S. EPA, 1997).

Figure 5 summarizes the applications of propanil to rice in the Colusa County from 2010 through 2014 (DPR, 2016a). Colusa County was selected because it has the largest number of rice acres treated with propanil during last five years in California (DPR, 2016a). High-use periods (>5% of annual use) occurred in June and July. Therefore, the annual exposure to propanil by workers involved in rice field work activities is estimated to occur for 2 months from June to July. There is no available task-specific data on rice field activities.

**Figure 5. Percent of Annual Acres Treated of Propanil to Rice in Colusa County from 2010 -2014 (DPR, 2016a)**

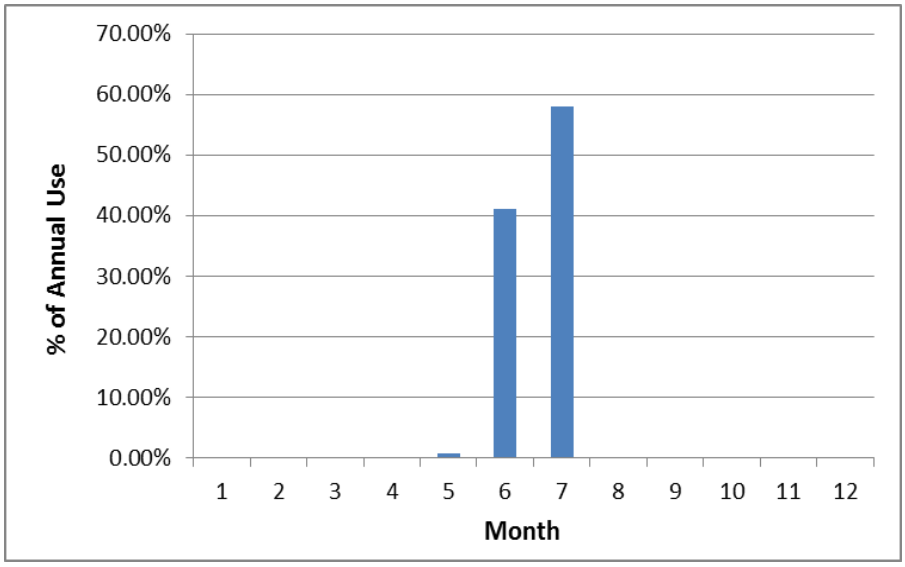



Table 8 summarizes the estimates of intermediate and long-term exposure to propanil for field workers.

**Table 8. Estimates of Rice Field Worker Exposure to Propanil**

| Task [a] | Acute ADD [b] (µg/kg/day) | Ave DFR [c] (µg/cm$^2$) | TC [d] (cm$^2$/hr) | SADD [e] (µg/kg/day) | Exposure Months [f] | AADD [g] (µg/kg/day) | LADD [h] (µg/kg/day) |
|---|---|---|---|---|---|---|---|
| Scouting | 951 | 7.24 | 1100 | 455 | 2 | 75.8 | 40.4 |
| Weeding | 60.5 | 7.24 | 70 | 28.9 | 2 | 4.82 | 2.57 |

a Based on product labels, propanil can only be used on rice in California. Scouting is assumed to be the scenario with the highest exposure. Therefore, scouting exposure will cover other activities such as harvesting (Mech). Weeding (hand) is to be the assumed the scenario with the highest exposure covering all weeding methods (Mech).

b Acute Absorbed Daily Dosage (ADD) is from Table 7.

c Average DFR. According to HHAB practice, the DFR value at the assumed average reentry interval of expiration of REI plus 7 days. Based on U.S. EPA (2012), if chemical-specific DFR unavailable, 10% per day is used as default residue dissipation to calculate the average DFR of propanil. The DFR on the average REI was estimated based on a log-linear regression model (Edmiston et al., 2002).

d TC (transfer coefficient) values are from the Agricultural Default Transfer Coefficients (U.S. EPA, 2013).

e Seasonal Average Daily Dosage (SADD) = average DFR * TC * work hours/day (the work hours were assumed 8 hr/day) * 50% dermal absorption (default dermal absorption based on HHAB practice) ÷ 70 kg body weight (U.S. EPA, 1997).

f The annual exposure months for field workers are determined by application periods based on the PUR database (Figure 5 and text).

g Annual Average Daily Dosage (AADD) = SADD * annual exposure months /12 months in a year.

h Lifetime Average Daily Dosage (LADD) = AADD * (40 years of work in a lifetime) / (75 years in a lifetime).

## 2. Residential and Institutional Use

Propanil is not registered for residential (home) or other non-agricultural use, nor is it used in or around public buildings, schools or recreational areas where children might be exposed. Therefore, there are no residential or other non-occupational risk concerns.

## 3. Residential Bystander Exposure to Spray Drift

The residential bystander exposure to propanil spray drift through dermal contact with turf or inhalation was estimated using horizontal deposition and air concentrations derived using computer modeling (see Appendix A-1 for details). Table 9 shows the residential bystander short-term exposure estimates for ground boom, fixed-wing aerial, and rotary aerial application methods.

**Table 9. Residential Bystander Acute Absorbed Daily Dosage (ADD) Exposure to Propanil Due to Spray Drift**

**a. 40 Swath Ground Boom Application Method [a]**

| Downwind Distance (feet) | Adult (μg/kg/day) | | Child 1-2 yrs old (μg/kg/day) | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | Oral | | |
| | Dermal | Inhalation [b] | Dermal | Inhalation | Hand-to-mouth | Object-to-mouth | Soil Ingestion |
| 25 | 24.64 | 6.89 | 36.12 | 16.33 | 0.74 | 0.02 | 0.00 |
| 50 | 16.34 | 5.73 | 23.95 | 13.63 | 0.49 | 0.01 | 0.00 |
| 75 | 12.19 | 5.07 | 17.87 | 11.95 | 0.37 | 0.01 | 0.00 |
| 100 | 9.60 | 4.40 | 14.07 | 10.27 | 0.29 | 0.01 | 0.00 |
| 150 | 7.00 | 4.34 | 10.27 | 10.06 | 0.21 | 0.01 | 0.00 |
| 200 | 5.45 | 4.28 | 7.98 | 9.86 | 0.16 | 0.01 | 0.00 |
| 250 | 4.41 | 4.22 | 6.46 | 9.65 | 0.13 | 0.00 | 0.00 |
| 300 | 3.63 | 3.98 | 5.32 | 9.13 | 0.11 | 0.00 | 0.00 |

a The exposures shown in the table were estimated using the AgDRIFT computer model. See Appendix A-1 for details.

b AgDRIFT does not estimate air concentrations for ground boom so the fixed-wing aerial air concentrations shown in Table 9b were used as surrogate inhalation estimates of exposure.

**b. 50 Swath Fixed-Wing Aerial Application Method [a]**

| Downwind Distance (feet) | Adult (μg/kg/day) | | Child 1-2 yrs old (μg/kg/day) | | | | |
|---|---|---|---|---|---|---|---|
| | Dermal | Inhalation | Dermal | Inhalation | Oral | | |
| | | | | | Hand-to-mouth | Object-to-mouth | Soil Ingestion |
| 0 | 117.89 | 9.65 | 172.81 | 28.09 | 7.09 | 0.22 | 0.00 |
| 25 | 64.59 | 6.89 | 94.68 | 16.33 | 3.88 | 0.12 | 0.00 |
| 50 | 47.47 | 5.73 | 69.58 | 13.63 | 2.85 | 0.09 | 0.00 |
| 100 | 27.50 | 4.40 | 40.30 | 10.27 | 1.65 | 0.05 | 0.00 |
| 250 | 14.92 | 4.22 | 21.86 | 9.65 | 0.90 | 0.03 | 0.00 |
| 500 | 9.86 | 3.00 | 14.45 | 7.04 | 0.59 | 0.02 | 0.00 |
| 1000 | 5.45 | 1.46 | 7.98 | 3.49 | 0.33 | 0.01 | 0.00 |

a The exposures shown in the table were estimated using the AGDISP computer model. See Appendix A for details.

**c. 50 Swath Rotary Aerial Application Method [a]**

| Downwind Distance (feet) | Adult (μg/kg/day) | | Child 1-2 yrs old (μg/kg/day) | | | | |
|---|---|---|---|---|---|---|---|
| | Dermal | Inhalation | Dermal | Inhalation | Oral | | |
| | | | | | Hand-to-mouth | Object-to-mouth | Soil Ingestion |
| 0 | 196.88 | 13.56 | 288.59 | 41.53 | 11.83 | 0.36 | 0.00 |
| 25 | 59.14 | 6.76 | 86.69 | 17.85 | 3.55 | 0.11 | 0.00 |
| 50 | 34.24 | 5.06 | 50.19 | 12.76 | 2.06 | 0.06 | 0.00 |
| 100 | 17.77 | 3.69 | 26.05 | 8.93 | 1.07 | 0.03 | 0.00 |
| 250 | 7.52 | 2.43 | 11.03 | 5.84 | 0.45 | 0.01 | 0.00 |
| 500 | 4.67 | 1.50 | 6.84 | 3.60 | 0.28 | 0.01 | 0.00 |
| 1000 | 2.33 | 0.70 | 3.42 | 1.68 | 0.14 | 0.00 | 0.00 |

a The exposures shown in the table were estimated using the AGDISP computer model. See Appendix A for details.

## VII. EXPOSURE APPRAISAL

### 1. Use of the PHED Database as Source of Surrogate Data to Estimate Handler Dermal and Inhalation Exposure.

For agricultural uses, there is no propanil specific monitoring study available. All handler exposure scenarios lack chemical-specific handler exposure data for propanil, and therefore, PHED (1995) was used as surrogate.

PHED combines measurements from multiple studies conducted using different protocols, analytical methods, and residue detection limits. Most dermal exposure studies in the PHED use the patch dosimetry method of Durham and Wolfe (1962) whereby residues on small patches placed on different regions of the body are extrapolated to estimate exposure to that region. In some of these studies, patches are placed on only a few body regions, such as the hands, arms or face. PHED dermal exposure estimates for each body region are based on different sets of individuals. For some handler scenarios, the number of matching observations in the PHED is so small that it is likely the exposure estimates do not adequately represent the target scenario. This exposure

assessment calculates upper confidence limits on the exposure statistics to adjust for the uncertainty introduced by using surrogate data. In the absence of chemical-specific exposure monitoring data, the application of PHED surrogate exposure data provides the reasonable exposure estimates.

Data quality grades in PHED are assigned based on Quality Assurance/Quality Control data provided in exposure study reports. Grades A and B are high-quality grades, with lab recoveries of 90-110% and 80-100%, respectively. Field recoveries range 70-120% and 50-120%, respectively. Grade C represents moderate quality, with lab and field recoveries of 70-120% and 30-120%, respectively. Grade D and E are the lowest quality grades, and are assigned to PHED data that do not meet basic quality assurance (U.S. EPA, 1998).

In this exposure assessment, PHED was used to estimate 6 agricultural dermal and inhalation handler exposure scenarios. The exposure values for each scenario were then used to calculate ADDs. Table 10 summarizes data quality grades and the number of observations for each PHED data set used in the exposure estimates.

**Table 10. Data Quality in the Pesticide Handler Exposure Database Used to Estimate Handler Exposure [a]**

| Exposure Subsets [b] | Dermal Exposure | | Hand Exposure | | Inhalation Exposure | | Scenario# [d] |
|---|---|---|---|---|---|---|---|
| | Obs [c] | Grade | Obs [c] | Grade | Obs [c] | Grade | |
| 1. M/L, DF | 16-26 | AB | 21 | AB | 23 | AB | 2 |
| 2. M/L, L (AC, FC, suspension) | 72-122 | AB | 59 | AB | 85 | AB | 5 |
| 3. A, DF, AC, FC, Suspension, Ground boom (Open Cab) | 23-42 | AB | 29 | AB | 22 | AB | 11 |
| 4. A, DF, AC, FC, Suspension, Aerial (Closed Cockpit) | 10-28 | AB | 36 | AB | 15 | AB | 18 |
| 5. Flagger [e] | 18-28 | AB | 30 | AB | 28 | AB | 7 |

a Data are from Pesticide Handlers Exposure Database (PHED, 1995). Data quality grades are described in Versar (1992).

b M/L = Mixer/loader; A = Applicator.
DF = Dry flowable; AC = Aqueous concentrate, FC = Flowable concentrate.

c Obs. = Number of observations.

d The scenario number of the scenario in the HHAB guidance document (Beauvais *et. al.*, 2007).

The PHED grades of (AB) coupled with the samples sizes shown in Table 10 for all surrogates used indicate that the dermal exposure assessments for both subsets can be interpreted to be based on high quality data. In these subsets the quality grades for dermal covered and hand are high (AB), and the number of observations are generally greater than 15. Inhalation exposure assessments also used high quality grade (A or B) and the number of observations greater than 15.

U.S. EPA also used PHED to estimate handler exposure; however, U.S. EPA approaches PHED data differently than HHA. First, as explained in U.S. EPA's policy for use of PHED data (U.S. EPA, 1998): "Once the data for a given exposure scenario have been selected, the data are normalized (i.e., divided by) by the amount of pesticide handled resulting in standard unit exposures (milligrams of exposure per pound of active ingredient handled). Following normalization, the data are statistically summarized. The distribution of exposure values for each body part (i.e., chest upper arm) is categorized as normal, lognormal, or "other" (i.e., neither normal nor lognormal). A central tendency value is then selected from the distribution of the exposure values for each body part. These values are the arithmetic mean for normal distributions, the geometric mean for lognormal distributions, and the median for all "other" distributions. Once selected, the central tendency values for each body part are composited into a "best fit" exposure value representing the entire body." The U.S. EPA method differs from HHA in 3 main ways: 1) U.S. EPA uses various central tendency estimates (often the geometric mean or median, as PHED data rarely follow a normal distribution), while HHA uses the arithmetic mean as the appropriate statistic regardless of the sample distribution (Powell, 2003); 2) HHA bases acute exposures on the 95$^{th}$ percentile estimate, while U.S. EPA uses a central tendency estimate for all exposure durations; and, 3) As explained in the Exposure Assessment section, for calculation of the actual exposure estimate HHA uses upper 90% confidence limits for both 95$^{th}$ percentile and mean exposures, while U.S. EPA does not**.** U.S. EPA released a table summarizing data used to estimate handler exposures (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data) (U.S. EPA, 2016). For many handler scenarios, U.S. EPA no longer relies on PHED and instead uses newer data supplied by the Agricultural Handlers Exposure Task Force (AHETF). DPR is reviewing newer studies included in U.S. EPA's Occupational Pesticide Handler Unit Exposure Surrogate Reference Table. Data from those studies will be used by DPR as appropriate when the review is complete. The additional uncertainties from relying on older PHED data for the handler exposure estimates will be considered during the mitigation phase.

**2. Estimating the Dermal Absorption Based on the Default Dermal Absorption Value**

A specific propanil dermal absorption study is unavailable and U.S. EPA estimated propanil dermal absorption by comparing the LOAEL of oral and dermal rabbit studies (U.S. EPA, 2003 and 2006). This exposure assessment reviewed and concludes that dermal absorption cannot be determined by the toxicity ratio method (See Section IV-1). Based on HHAB practice, the default dermal absorption of 50% (Donahue, 1996) was used as a dermal absorption rate for exposure/risk assessment. The Donahue default is based on a review of 40 compounds that showed the mean rat dermal absorption was 19 ±14% (Thongsinthusak *et al*., 1993). At the 95$^{th}$ percentile, dermal absorption for pesticides is approximately 42%. Therefore, it is likely 50% is an overestimation of the dermal absorption rate.

**3. Estimating the Field Worker Exposure Based on Default DFR Data.**

When DFR data is unavailable, the default DFR (25% of the maximum use rate) is used as a surrogate and a reasonable upper-bound estimate based on U.S. EPA (2013). However, use of the default DFR may overestimate the acute ADD for some workers for two reasons: 1) workers may enter the treated field on the expiration of REI, and 2) the default DFR of 25% of the maximum use rate is may be higher than the actual (but unknown) initial DFR value.

**4. Estimating Long-term Exposure of Field Workers by Using the Average DFR on an Assumed Average Reentry Day**

The field workers do not always enter fields on the exact day of REI or PHI expiration. Seasonal, annual, and lifetime exposures were estimated for an assumed average reentry of the expiration of the REI plus 7 days for all activities other than harvesting, and PHI plus 10 days for harvesting. These assumed reentry times were not based on data; rather, they were based on the reasonable assumption that workers are likely to enter fields an average of 7 and 10 days after expiration of REI and PHI, respectively (Beauvais, 2008). The assumed average DFR on these days may need additional refinement.

**5. Estimating Residential Bystander Exposure to Spray Drift Using Computer Modeling**

Using computer modeling to estimate residential bystander exposure from spray drift is preferable to using measured horizontal deposition or air concentrations because measured concentrations cannot be assumed to have captured the highest concentrations possible under a given use scenario. In addition, the measured values are only one set of samples from that one set of environmental conditions under which those samples were measured. It is not possible to develop air concentration estimates for other scenarios using measured data. However, there is uncertainty introduced in using computer models to estimate environmental concentrations. The models are built upon assumptions which can lead to an over or under estimation of the environmental concentrations. For example, the AgDRIFT ground boom model has only two ASAE spray quality categories: 1) very fine to fine and 2) fine to medium/coarse. This is because the AgDRIFT ground boom model is an empirical model that was fit to field studies. Analysis of the field studies on which the AgDRIFT model is based only supports those two spray quality categories (Hewitt *et al*., 2001). The propanil ground boom regulations (CCR Section 6462. Propanil) requires very coarse to extra coarse ASAE spray quality. The AgDRIFT modeled horizontal deposition may be an over estimate with respect to propanil ground boom applications because spray drift is affected most significantly by spray quality (droplet spectrum). Coarser spray tends to show less spray drift, all other factors held constant.

The AGDISP is a well vetted Lagrangian first principles model that uses physics equations to follow the behavior of droplets after they are release from aircraft nozzles. Comparisons of AGDISP output with measured field data have shown that the model tends to overestimate the field measurement (Bird *et al*., 1992; Hoffman, 2006).

Therefore, AGDISP results will most likely overestimate residential bystander exposure estimates.

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# Appendix A

## Estimates of Residential Bystander Exposure to Propanil Due to Spray Drift

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## I. Background

This document describes methods employed to estimate residential bystander short-term daily exposure to propanil residues associated with ground boom and aerial applications made to rice in California.

## II. Modeling methods

The Human Health Assessment Branch procedures for modeling spray drift to provide inputs for residential bystander exposure estimation are described in Barry (2015). Following those methods, horizontal deposition was estimated using the AgDRIFT 2.1.1 model (Teske *et al.*, 2003) for the ground boom applications. Horizontal deposition and 1-hr air concentrations for aerial applications were estimated using the AGDISP version 8.28 model (Teske and Curbishley, 2013). The horizontal deposition estimates used in the exposure assessment are for the 50 ft wide turf deposition scenario as outlined in the US EPA residential SOP for turf (U.S. EPA, 2012). This is the same turf deposition scenario used in the addendum to the residential SOP for spray drift (U.S. EPA, 2013). The AgDRIFT model does not provide air concentrations so inhalation exposure for ground boom applications was not calculated. For aerial applications the air concentration estimates used in the exposure assessment are 1-hour time-weighted averages as output by the AGDISP model.

### A. Exposure Scenario Development

Propanil is an herbicide labeled only for application to rice and is applied primarily in the Sacramento Valley (SV) during the months of May through July (Table 1). Therefore, only short term exposure estimates are provided in this analysis.

**Table 1. Number of propanil applications tally statewide from 2010-2014 [1]**

| Region | Months | | Total |
|---|---|---|---|
| | May through July | Other | |
| Sacramento Valley [2] | 27555 | 153 | 27708 (98.2%) |
| Other [3] | 484 | 24 | 508 (1.8%) |
| Total | 28039 (99.4%) | 177 (0.6%) | 28218 (100.0%) |

[1] Data from CDPR PUR 2010-2014 (DPR, 2016)
[2] Sacramento Valley counties = Butte, Colusa, Glen, Placer, Sacramento, Sutter, Tehama, Yolo, and Yuba.
[3] Other counties = El Dorado, Fresno, Merced, San Joaquin, Solano, Stanislaus, and Ventura.

## 1. Ground Boom Application

The AgDRIFT model has a ground boom application default swath width of 45 ft and a maximum of 20 swaths per model run. Assuming a square field, the largest block AgDRIFT will simulate in a single model run for ground boom applications is 18.6 acres. Larger applications can be simulated by overlaying multiple sets of 20 swaths. The overlay method is described in Barry (2015) and shows that for ground boom applications it is only necessary to 2 sets of 20 swaths for a total of 40 swaths. If it is assumed that the application produced by overlaying 2 sets of 20 swaths is square then the resulting spray application area is 74.4 acres (Table 2). Any additional 20 swath sets will deposit spray drift on the first 2 downwind swath sets. The 95$^{th}$ percentile ground boom spray application area of propanil to rice between 2010 and 2014 was 170 acres (DPR, 2016). However, as discussed above, the 74.4 acre estimates produced by overlaying two 20 swath blocks will be sufficient to estimate horizontal deposition for all larger ground boom application sizes.

**Table 2. AgDRIFT ground boom simulations of 20 swath sets[a]**

| Set | Swath Width (ft) | Number of Swaths | Total Application Area Width (Sum of Set Widths) | Upwind Offset (ft) | Total Number of Swaths | Resulting Application Size (acres) | Deposition Curve Distance at Set 1 Downwind Edge (ft) | Section of Deposition Curve added to Set 1 Deposition Curve (ft) |
|---|---|---|---|---|---|---|---|---|
| 1 | 45 ft | 20 | 900 ft | 0 ft | 20 | 18.6 ac | 0 ft | 0 ft to 997.4 ft |
| 2 | 45 ft | 20 | 1800 ft | 900 ft | 40 | 74.4 ac[b] | 900 ft | 900 ft to 997.4 ft |

[a] Each set of 20 swaths is 900 ft wide. Downwind deposition curves are offset by the appropriate number of feet and then overlaid. When overlaying, upwind deposition curves are allowed to drop to zero at the model domain limit of 997.4 ft. (Table source is Barry, 2015)

[b] This assumes that the application is square and measures 1800ft x 1800 ft.

Propanil labels state for ground boom applications a boom height of up to 4 ft (48 inches) is allowed. The low boom height in the AgDRIFT ground boom model is 20 inches. The high boom height is 50 inches. Therefore, the high boom was selected for these simulations. Propanil labels state that a spray quality of ASAE medium or coarser is required. In addition, California Code of Regulations (CCR) 6462. Propanil requires for ground boom applications a spray with "… not less than 500 microns volume median diameter (Dv0.5) with not more than ten percent of the diameter by volume (Dv0.1) less than 200 microns." This places the propanil regulation required spray quality in the ASAE very coarse to extremely coarse classification. The AgDRIFT ground boom model has two spray quality categories: ASAE very fine to fine and ASAE fine to medium/coarse. The ASAE fine to medium/coarse was selected for these simulations.

## 2. Aerial Application

The Department of Pesticide Regulation (DPR) Enforcement Branch staff obtained a list of aircraft used in the Sacramento Valley rice counties (K. Everett, personal communication September 7, 2016 and September 8, 2016). The aircraft on list that were also found in the AGDISP aircraft library were included in this analysis and are shown in Table 3.

**Table 3. Sacramento Valley rice counties[1] aircraft screened for estimating bystander exposure due to propanil spray drift.**

| Aircraft | Speed (mph) | Aircraft Weight (lbs) | Semispan or rotor radius (ft) | Swath Width (ft) | No. of nozzles |
|---|---|---|---|---|---|
| Ag-Cat B (Bi-plane) | 115 | 5022 | 21 | 51 | 60 |
| AT-301 | 120 | 5600 | 23 | 54 | 60 |
| AT-402A | 130 | 6351 | 26 | 61 | 60 |
| AT-502A | 135 | 7525 | 26 | 62 | 60 |
| AT-502B | 135 | 7000 | 26 | 62 | 60 |
| AT-602 | 145 | 9052 | 28 | 67 | 60 |
| AT-802A | 145 | 11160 | 29 | 70 | 60 |
| Ayers Thrush S2R-G6 | 140 | 7665 | 24 | 58 | 60 |
| Ayers Thrush S2R-G10 | 145 | 7765 | 24 | 58 | 60 |
| 188 Ag Husky | 106 | 3353 | 21 | 50 | 60 |
| Piper PA-25 Pawnee | 100 | 2150 | 18 | 43 | 60 |
| Bell 204B | 92 | 6650 | 24 | 58 | 60 |
| Bell 205 | 92 | 7697 | 24 | 58 | 60 |
| Bell 206B Jet Ranger III | 69 | 2398 | 17 | 41 | 60 |

[1] Sacramento Valley counties = Butte, Colusa, Glen, Placer, Sacramento, Sutter, Tehama, Yolo, and Yuba.

The aircraft shown in Table 3 were screened to find the largest horizontal deposition at selected distances between the application edge (0 ft from the treated field) and 1000 ft downwind. All screening simulations were conducted with aircraft and application parameters shown below:

1) Boom length of 75% of wingspan fixed wing or 90% rotor diameter – propanil label maximum boom lengths.
2) Swath width of 1.2xwingspan or 1.2xrotor diameter – AGDISP default (Teske and Curbishley, 2013).

3) Swath-displacement of 50% swath width – typical for ASAE very coarse to extra coarse spray quality (Teske *et al.*, 1998).
4) Number of swaths - 50 swaths. This is the maximum the AGDISP model will simulate in one run. Maximum field size varies with the swath width of the individual aircraft and is between 96 acres (Bell 206B) and 281 acres (AT-802A).
5) Spray quality ASABE very coarse to extremely coarse – required by California Code of Regulations (CCR) 6462. Propanil.
6) Finished spray volume of 10 gal/ac – propanil label requirement.
7) Number of nozzles – 60 nozzles required to deliver the propanil label specification of 10 gal/ac finished spray volume.
8) Non-volatile active ingredient application rate of 6 lb/ac – propanil label maximum rate.
9) Release Height – 10 ft above crop canopy as required by CCR 6460. Drift Control.

The meteorological conditions used for all AGDISP simulations were based on:
1) CCR 6460. Drift Control requirements for wind speed no higher than 10 mph at the time of propanil aerial application
2) Analysis of 5 years of meteorological data from California Irrigation Management System (CIMIS) located in Durham, California in Butte County for air temperature and humidity.

The Durham CIMIS station is located Butte County in a representative rice area of the SV. Table 1 showed that most applications occur in June and July. The propanil labels state that propanil needs to be activated by exposure to 8 hours of sunlight following application. Sunset in the Sacramento Valley during June and July is between 2015 and 2035 hrs Pacific Daylight Time (PST). Therefore, an application of propanil is likely to be completed no later than about 0900 hrs (PST). The highest air temperature and the lowest humidity was at 0900 hrs were selected for this analysis. These assumptions and analysis result in the following meteorological inputs:

1) Wind speed of 10 mph – label maximum allowed wind speed
2) Air temperature 85°F – Maximum over 5 years from the Durham CIMIS station
3) Humidity 35%. – Maximum over of 5 years from the Durham CIMIS station

Results for each aircraft were compared within fixed wing and rotary categories to select aircraft that produced the highest 50 ft width horizontal deposition at selected distances between application edge (0 ft) and 1000 ft downwind. The 50 ft width horizontal deposition was obtained directly from the AGDISP model using the Deposition Assessment feature in the Toolbox section of the model. The swath set overlay technique used for ground boom was not necessary for aerial applications for two reasons: 1) for larger swath widths the 50 swath set is large enough that all the horizontal deposition from a second set of 50 swaths would land on the first set of 50 swaths and 2) for the smallest swath widths the extreme far field part of the downwind deposition curve from the second set of swaths does not contributes insignificant deposition to the results (0.0005 fraction of the amount applied or less).

AGDISP provides an estimate of the 1-hr time weighted average (TWA) air concentration at user selected downwind distances. Air concentrations were only produced for the aircraft ultimately chosen as input for the exposure estimation.

# III. Deposition and Air Concentration Estimates

## A. Ground Boom Application Deposition

Table 4 presents the horizontal deposition estimates for the ground boom medium/coarse spray quality and high boom. These estimates are the 50$^{th}$ percentile horizontal deposition of 2 sets of 20 swaths for a total of 40 swaths as described in Barry (2015).

**Table 4. Ground boom horizontal deposition. High boom, medium/coarse spray quality, and 40 swath 50$^{th}$ percentile[a]**

| Point Estimates | | | 50 ft Wide Lawn Estimates | | | |
|---|---|---|---|---|---|---|
| | | | Location of 50 ft wide Lawn | | 50 ft Width Average Deposition | |
| Dist (ft) | Fraction of Rate | 6 lb/ac µg/cm$^2$ | Start | End | Fraction of Rate | 6 lb/ac µg/cm$^2$ |
| 25 | 0.0166 | 1.11 | 25 | 75 | 0.0095 | 0.64 |
| 50 | 0.0086 | 0.58 | 50 | 100 | 0.0063 | 0.42 |
| 75 | 0.0061 | 0.41 | 75 | 125 | 0.0047 | 0.32 |
| 100 | 0.0046 | 0.31 | 100 | 150 | 0.0037 | 0.25 |
| 150 | 0.0030 | 0.20 | 150 | 200 | 0.0027 | 0.18 |
| 200 | 0.0023 | 0.16 | 200 | 250 | 0.0021 | 0.14 |
| 250 | 0.0019 | 0.12 | 250 | 300 | 0.0017 | 0.11 |
| 300 | 0.0016 | 0.1044 | 300 | 350 | 0.0014 | 0.10 |

[a] The development procedure for these deposition estimates is described in Barry (2015).

## B. Aerial Application Deposition

The aerial application horizontal deposition results indicate that no one aircraft produces the maximum deposition at all downwind distances (Appendix A-1). The aircraft were evaluated based on the 50 ft width deposition. Tables 5 and 6 show for selected distances the 50 ft width deposition and the aircraft that produced the highest 50 ft width deposition at each distance for fixed-wing and rotary aircraft, respectively (see the footnotes).

**Table 5. Fixed-wing aerial application maximum horizontal deposition at selected distances[a]**

| 50 ft wide Turf Distance Downwind | | 50 ft width Average Deposition | |
|---|---|---|---|
| Start (ft) | End (ft) | Fraction of Application Rate | 6 lbs/ac ($\mu g/m^2$) |
| 0 [b] | 50 | 0.0909 | 6.11 |
| 25 [c] | 75 | 0.0498 | 3.35 |
| 50 [c] | 100 | 0.0366 | 2.46 |
| 100 [c] | 150 | 0.0212 | 1.43 |
| 250 [d] | 300 | 0.0115 | 0.77 |
| 500 [d] | 550 | 0.0076 | 0.51 |
| 1000 [d] | 1050 | 0.0042 | 0.28 |

[a] Spray quality is very coarse to extremely coarse spray quality and 50 swaths. A full list of AGDISP model inputs are outlined above. The aircraft producing the maximum deposition at each distance is indicated by the footnotes in the "start" distance column. The development procedure for these deposition estimates is described in Barry (2015).
[b] Piper PA-25 Pawnee.
[c] Ayers Thrush S2R-G6.
[d] Ag-Cat B (Bi-plane).

**Table 6. Rotary aerial application maximum horizontal deposition at selected distances [a]**

| 50 ft wide Turf Distance Downwind | | 50 ft width Average Deposition | |
|---|---|---|---|
| Start (ft) | End (ft) | Fraction of Application Rate | 6 lbs/ac ($\mu g/m^2$) |
| 0 [b] | 50 | 0.1518 | 10.21 |
| 25 [b] | 75 | 0.0456 | 3.07 |
| 50 [b] | 100 | 0.0264 | 1.78 |
| 100 [b] | 150 | 0.0137 | 0.92 |
| 250 [b] | 300 | 0.0058 | 0.39 |
| 500 [c] | 550 | 0.0036 | 0.24 |
| 1000 [c] | 1050 | 0.0018 | 0.12 |

[a] Spray quality is very coarse to extremely coarse spray quality and 50 swaths. A full list of AGDISP model inputs are outlined above. The aircraft producing the maximum deposition at each distance is indicated by the footnotes in the "start" distance column. The development procedure for these deposition estimates is described in Barry (2015).
[b] Bell 206B Jet Ranger III
[c] Bell 204B

## C. Aerial Application Air Concentrations

Tables 7 and 8 shows the AGDISP estimated 1-hr TWA air concentrations at each of the 50 ft width deposition distances shown in Tables 5 and 6 for fixed-wing and rotary aircraft, respectively. The same aircraft used for the horizontal deposition at each distance is used for the air concentrations.

**Table 7. Fixed-wing aerial application 1-hr time weighted average air concentrations at selected distances [a]**

| Distance (ft) | Air Concentration ($\mu g/m^3$) | |
|---|---|---|
| | 1.7 ft above ground (Child 1-2 yrs) | 5 ft above ground (Adult) |
| 0 [b] | 54.0 | 34.4 |
| 25 [c] | 31.4 | 24.6 |
| 50 [c] | 26.2 | 20.5 |
| 100 [c] | 19.7 | 15.7 |
| 250 [d] | 18.6 | 15.1 |
| 500 [d] | 13.5 | 10.7 |
| 1000 [d] | 6.7 | 5.2 |

[a] Very coarse to extremely coarse spray quality and 50 swaths. AGDISP model inputs are outlined above. The aircraft used at each distance is indicated by the footnotes in the distance column. The development procedure for these deposition estimates is described in Barry (2015).
[b] Piper PA-25 Pawnee
[c] Ayers Thrush S2R-G6
[d] Ag-Cat B (Bi-plane)

**Table 8. Rotary aerial application 1-hr time weighted average air concentrations at selected distances [a]**

| Distance (ft) | Air Concentration ($\mu g/m^3$) | |
|---|---|---|
| | 1.7 ft above ground (Child 1-2 yrs) | 5 ft above ground (Adult) |
| 0 [b] | 77.83 | 47.79 |
| 25 [b] | 34.09 | 23.98 |
| 50 [b] | 24.44 | 17.98 |
| 100 [b] | 17.16 | 13.17 |
| 250 [b] | 11.23 | 8.66 |
| 500 [c] | 6.89 | 5.33 |
| 1000 [c] | 3.22 | 2.49 |

[a] Very coarse to extremely coarse spray quality and 50 swaths. AGDISP model inputs are outlined above. The aircraft used at each distance is indicated by the footnotes in the distance column. The development procedure for these deposition estimates is described in Barry (2015).
[b] Bell 206B Jet Ranger III
[c] Bell 204B

# IV. Exposures Estimates

The horizontal deposition and air concentrations estimated using AgDRIFT and AGDISP earlier in this document are used here to estimate bystander exposure to propanil as a result of spray drift. These estimates are developed according to the U.S. EPA Standard Operation Procedures (SOP) for residential pesticide exposure assessment (U.S. EPA, 2012). Adults are exposed through dermal contact with turf and inhalation. Children 1-2 years old are exposed through dermal contact with turf, hand-to-mouth ingestion, object-to-mouth ingestion, incidental soil ingestion, and inhalation.

Tables 9a and 9b show the adult and child acute average daily dose (Acute ADD), respectively, associated with propanil spray drift due to ground boom.

**Table 9a. Propanil acute average daily dose (Acute ADD) for residential bystander adult exposure to ground boom application spray drift**

| Distance (ft) | Acute Average Daily Dose (Acute ADD) (µg/kg/day) | |
|---|---|---|
| | Dermal[1] | Inhalation[2] |
| 25 | 24.64 | 6.89 |
| 50 | 16.34 | 5.73 |
| 75 | 12.19 | 5.07 |
| 100 | 9.60 | 4.40 |
| 150 | 7.00 | 4.34 |
| 200 | 5.45 | 4.28 |
| 250 | 4.41 | 4.22 |
| 300 | 3.63 | 3.98 |

**Table 9b. Propanil acute average daily dose (Acute ADD) for residential bystander child 1-2 yrs old exposure to ground boom application spray drift**

| Distance (ft) | Acute Average Daily Dose (Acute ADD) (µg/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal [1] | Inhalation [2] | Hand-to-mouth [3] | Object-to-mouth [3] | Soil ingestion [3] |
| 25 | 36.12 | 16.33 | 0.74 | 0.02 | 0.00 |
| 50 | 23.95 | 13.63 | 0.49 | 0.01 | 0.00 |
| 75 | 17.87 | 11.95 | 0.37 | 0.01 | 0.00 |
| 100 | 14.07 | 10.27 | 0.29 | 0.01 | 0.00 |
| 150 | 10.27 | 10.06 | 0.21 | 0.01 | 0.00 |
| 200 | 7.98 | 9.86 | 0.16 | 0.01 | 0.00 |
| 250 | 6.46 | 9.65 | 0.13 | 0.00 | 0.00 |
| 300 | 5.32 | 9.13 | 0.11 | 0.00 | 0.00 |

[1] Dermal Acute ADD calculated using the U.S. EPA Residential SOP equation (U.S. EPA, 2012) and default parameter values except:

Dermal absorption factor = 0.50 (Donahue, 1996)

Body weight for adult = 70 kg for both male and female (Thongsinthusak et al., 1993); body weight for child = 13 kg for both male and female (Andrews and Patterson, 2000)

[2] AgDRIFT does not estimate air concentrations for ground boom, so inhalation exposure was estimated using the fixed-wing aircraft inhalation exposure estimates

[3] Hand-to-Mouth, Object-to-Mouth, and Soil Ingestion Acute ADDs were calculated using the U.S. EPA Residential SOP equation (USEPA, 2012) and default parameter values except body weight (13 kg for both male and female child 1-2 yrs old; Andrews and Patterson, 2000).

Tables 10a and 10b show the adult Acute ADD for fixed-wing and rotary aircraft, respectively. Tables 11a and 11b show the child 1-2 yrs old Acute ADD for fixed-wing and rotary aircraft, respectively. Full exposure results for all aircraft can be found in Appendix A-2.

**Table 10a. Propanil acute average daily dose (Acute ADD) for residential bystander adult exposure to fixed-wing aerial application spray drift [a]**

| Distance (ft) | Acute Average Daily Dose (Acute ADD) (ug/kg/day) | |
|---|---|---|
| | Dermal [b] | Inhalation [c] |
| 0 [d] | 117.89 | 9.65 |
| 25 [e] | 64.59 | 6.89 |
| 50 [e] | 47.47 | 5.73 |
| 100 [e] | 27.50 | 4.40 |
| 250 [f] | 14.92 | 4.22 |
| 500 [f] | 9.86 | 3.00 |
| 1000 [f] | 5.45 | 1.46 |

**Table 10b. Propanil acute average daily dose (Acute ADD) for residential bystander adult exposure to rotary aerial application spray drift**

| Distance (ft) | Acute Average Daily Dose (Acute ADD) (ug/kg/day) | |
|---|---|---|
| | Dermal [3] | Inhalation [4] |
| 0 [g] | 196.88 | 13.56 |
| 25 [g] | 59.14 | 6.76 |
| 50 g | 34.24 | 5.06 |
| 100 [g] | 17.77 | 3.69 |
| 250 [g] | 7.52 | 2.43 |
| 500 [h] | 4.67 | 1.50 |
| 1000 [h] | 2.33 | 0.70 |

[a] The aircraft used at each distance is indicated by the footnotes in the distance column

[b] Dermal Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:

- Dermal absorption factor = 0.50 (Donahue, 1996)
- Body weight = 70 kg for both male and female (Thongsinthusak et al., 1993)

[c] Inhalation Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:

- Inhalation rate = 0.28 m3/kg/day (Andrews and Patterson, 2000)
- Inhalation absorption is assumed to be 100% (Cochran, 2008)

[d] Piper PA-25 Pawnee

[e] Ayers Thrush S2R-G6

[f] Ag-Cat B (Bi-plane)

[g] Bell 206B Jet Ranger III

[h] Bell 204B

**Table 11a. Propanil acute average daily dose (Acute ADD) for residential bystander child 1-2 years old exposure to fixed-wing aerial application spray drift [a]**

| Distance (ft) | Acute Average Daily Dose (ADD) (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal [b] | Inhalation [c] | Hand-to-mouth [d] | Object-to-mouth [e] | Soil ingestion [f] |
| 0 [g] | 172.81 | 28.09 | 7.09 | 0.22 | 0.00 |
| 25 [h] | 94.68 | 16.33 | 3.88 | 0.12 | 0.00 |
| 50 [h] | 69.58 | 13.63 | 2.85 | 0.09 | 0.00 |
| 100 [h] | 40.30 | 10.27 | 1.65 | 0.05 | 0.00 |
| 250 [i] | 21.86 | 9.65 | 0.90 | 0.03 | 0.00 |
| 500 [i] | 14.45 | 7.04 | 0.59 | 0.02 | 0.00 |
| 1000 [i] | 7.98 | 3.49 | 0.33 | 0.01 | 0.00 |

**Table 11b. Propanil acute average daily dose (Acute ADD) for residential bystander children 1-2 years old exposure to rotary aerial application spray drift [a]**

| Distance (ft) | Acute Average Daily Dose (Acute ADD) (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal [b] | Inhalation [c] | Hand-to-mouth [d] | Object-to-mouth [e] | Soil ingestion [f] |
| 0 [j] | 288.59 | 41.53 | 11.83 | 0.36 | 0.00 |
| 25 [j] | 86.69 | 17.85 | 3.55 | 0.11 | 0.00 |
| 50 [j] | 50.19 | 12.76 | 2.06 | 0.06 | 0.00 |
| 100 [j] | 26.05 | 8.93 | 1.07 | 0.03 | 0.00 |
| 250 [j] | 11.03 | 5.84 | 0.45 | 0.01 | 0.00 |
| 500 [k] | 6.84 | 3.60 | 0.28 | 0.01 | 0.00 |
| 1000 [k] | 3.42 | 1.68 | 0.14 | 0.00 | 0.00 |

[a] The aircraft used at each distance is indicated by the footnotes in the distance column

[b] Dermal Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:
- Dermal absorption factor = 0.50 (Donahue, 1996)
- Body weight = 13 kg for both male and female (Andrews and Patterson, 2000)

[c] Inhalation Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:
- Inhalation rate = 0.52 $m^3$/kg/day (Andrews and Patterson, 2000)
- Inhalation absorption is assumed to be 100% (Cochran, 2008)

[d] Hand-to-Mouth, Object-to-Mouth, and Soil Ingestion AcuteDDs were calculated using the U.S. EPA Residential SOP equation (U.S. EPA, 2012) and default parameter values except:
- Body weight = 13 kg for both male and female child 1-2 yrs old (Andrews and Patterson, 2000)

[e] Object-to-Mouth Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:
- Body weight = 13 kg for both male and female child 1-2 yrs old (Thongsinthusak *et al.*, 1993)

[f] Soil Ingestion Acute ADD calculated using the US EPA Residential SOP equation (USEPA, 2012) and default parameter values except:
- Body weight = 13 kg for both male and female child 1-2 yrs old (Thongsinthusak *et al.*, 1993)

[g] Piper PA-25 Pawnee

[h] Ayers Thrush S2R-G6

[i] Ag-Cat B (Bi-plane)

[j] Bell 206B Jet Ranger III

[k] Bell 204B

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## Appendix A-1. Complete AGDISP Results for Aerial Applications.

| 50 ft Width Turf Average Deposition (Fraction of Application Rate) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Start** | **End** | **Ag-Cat (BiPlane)** | **AT-301** | **AT-402A** | **AT-502A** | **AT-502B** | **AT-602** | **AT-802A** | **Ayers Thrush S2R-G6** | **Ayers Thrush S2R-G10** | **188 Ag Husky** | **Piper PA-25 Pawnee** | **Bell 204B** | **Bell 205** | **Bell 206B Jet Ranger III** |
| 0 | 50 | 0.0721 | 0.0819 | 0.0670 | 0.0684 | 0.0665 | 0.0613 | 0.0641 | 0.0822 | 0.0824 | 0.0794 | 0.0909 | 0.0824 | 0.0815 | 0.1518 |
| 25 | 75 | 0.0385 | 0.0473 | 0.0415 | 0.0433 | 0.0420 | 0.0415 | 0.0442 | 0.0498 | 0.0493 | 0.0397 | 0.0422 | 0.0341 | 0.0335 | 0.0456 |
| 50 | 100 | 0.0317 | 0.0341 | 0.0322 | 0.0327 | 0.0322 | 0.0314 | 0.0331 | 0.0366 | 0.0360 | 0.0320 | 0.0322 | 0.0219 | 0.0213 | 0.0264 |
| 100 | 150 | 0.0211 | 0.0198 | 0.0189 | 0.0193 | 0.0189 | 0.0189 | 0.0197 | 0.0212 | 0.0210 | 0.0203 | 0.0180 | 0.0124 | 0.0121 | 0.0137 |
| 250 | 300 | 0.0115 | 0.0080 | 0.0081 | 0.0082 | 0.0080 | 0.0082 | 0.0084 | 0.0085 | 0.0085 | 0.0091 | 0.0075 | 0.0058 | 0.0057 | 0.0058 |
| 500 | 550 | 0.0076 | 0.0043 | 0.0045 | 0.0046 | 0.0043 | 0.0044 | 0.0048 | 0.0047 | 0.0049 | 0.0055 | 0.0047 | 0.0036 | 0.0036 | 0.0035 |
| 1000 | 1050 | 0.0042 | 0.0023 | 0.0027 | 0.0028 | 0.0025 | 0.0027 | 0.0030 | 0.0027 | 0.0028 | 0.0031 | 0.0025 | 0.0018 | 0.0018 | 0.0017 |

## Appendix A-2. Complete Set of Aerial Application Acute Average Daily Dose (Acute ADD) Exposure Estimates

## Ag-Cat (Bi-Plane) – Fixed-Wing

| Downwind Distance (ft) | Acute ADD Adult (ug/kg/day) | |
|---|---|---|
| | Dermal | Inhalation |
| 0 | 93.51 | 9.59 |
| 25 | 49.93 | 7.19 |
| 50 | 41.11 | 6.41 |
| 100 | 27.37 | 5.57 |
| 250 | 14.92 | 4.22 |
| 500 | 9.86 | 3.00 |
| 1000 | 5.45 | 1.46 |

| Downwind Distance (ft) | Acute ADD Child (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal | Inhalation | Oral | | |
| | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 137.07 | 27.01 | 5.62 | 0.17 | 0.00 |
| 25 | 73.19 | 16.50 | 3.00 | 0.09 | 0.00 |
| 50 | 60.27 | 14.26 | 2.47 | 0.08 | 0.00 |
| 100 | 40.11 | 12.39 | 1.64 | 0.05 | 0.00 |
| 250 | 21.86 | 9.65 | 0.90 | 0.03 | 0.00 |
| 500 | 14.45 | 7.04 | 0.59 | 0.02 | 0.00 |
| 1000 | 7.98 | 3.49 | 0.33 | 0.01 | 0.00 |

## Ayers Thrush S2R-G6 – Fixed-Wing

| Downwind Distance (ft) | Acute ADD Adult (ug/kg/day) | |
|---|---|---|
| | Dermal | Inhalation |
| 0 | 106.61 | 9.13 |
| 25 | 64.59 | 6.89 |
| 50 | 47.47 | 5.73 |
| 100 | 27.50 | 4.40 |
| 250 | 11.02 | 3.03 |
| 500 | 6.10 | 2.08 |
| 1000 | 3.50 | 1.02 |

| Downwind Distance (ft) | Acute ADD Child (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal | Inhalation | Oral | | |
| | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 156.27 | 23.32 | 6.41 | 0.19 | 0.00 |
| 25 | 94.68 | 16.33 | 3.88 | 0.12 | 0.00 |
| 50 | 69.58 | 13.63 | 2.85 | 0.09 | 0.00 |
| 100 | 40.30 | 10.27 | 1.65 | 0.05 | 0.00 |
| 250 | 16.16 | 7.10 | 0.66 | 0.02 | 0.00 |
| 500 | 8.94 | 4.91 | 0.37 | 0.01 | 0.00 |
| 1000 | 5.13 | 2.45 | 0.21 | 0.01 | 0.00 |

## Piper Pawnee PA-25 – Fixed-Wing

| Downwind Distance (ft) | Acute ADD Adult (ug/kg/day) | |
|---|---|---|
| | Dermal | Inhalation |
| 0 | 117.89 | 9.65 |
| 25 | 54.73 | 6.53 |
| 50 | 41.76 | 5.53 |
| 100 | 23.35 | 4.33 |
| 250 | 9.73 | 2.94 |
| 500 | 6.10 | 1.93 |
| 1000 | 3.24 | 0.91 |

| Downwind Distance (ft) | Acute ADD Child (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal | Inhalation | Oral | | |
| | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 172.81 | 28.09 | 7.09 | 0.22 | 0.00 |
| 25 | 80.23 | 15.32 | 3.29 | 0.10 | 0.00 |
| 50 | 61.22 | 12.65 | 2.51 | 0.08 | 0.00 |
| 100 | 34.22 | 10.03 | 1.40 | 0.04 | 0.00 |
| 250 | 14.26 | 6.84 | 0.58 | 0.02 | 0.00 |
| 500 | 8.94 | 4.57 | 0.37 | 0.01 | 0.00 |
| 1000 | 4.75 | 2.18 | 0.19 | 0.01 | 0.00 |

## Bell 206B Ranger III - Rotary

| Downwind Distance (ft) | Acute ADD Adult (ug/kg/day) | |
|---|---|---|
| | Dermal | Inhalation |
| 0 | 196.88 | 13.56 |
| 25 | 59.14 | 6.76 |
| 50 | 34.24 | 5.06 |
| 100 | 17.77 | 3.69 |
| 250 | 7.52 | 2.43 |
| 500 | 4.54 | 1.46 |
| 1000 | 2.20 | 0.66 |

| Downwind Distance (ft) | Acute ADD Child (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal | Inhalation | Oral | | |
| | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 288.59 | 41.53 | 11.83 | 0.36 | 0.00 |
| 25 | 86.69 | 17.85 | 3.55 | 0.11 | 0.00 |
| 50 | 50.19 | 12.76 | 2.06 | 0.06 | 0.00 |
| 100 | 26.05 | 8.93 | 1.07 | 0.03 | 0.00 |
| 250 | 11.03 | 5.84 | 0.45 | 0.01 | 0.00 |
| 500 | 6.65 | 3.51 | 0.27 | 0.01 | 0.00 |
| 1000 | 3.23 | 1.58 | 0.13 | 0.00 | 0.00 |

## Bell 204B - Rotary

| Downwind Distance (ft) | Acute Adult (ug/kg/day) | |
|---|---|---|
| | Dermal | Inhalation |
| 0 | 106.87 | 9.58 |
| 25 | 44.23 | 6.01 |
| 50 | 28.40 | 5.78 |
| 100 | 16.08 | 3.66 |
| 250 | 7.52 | 2.40 |
| 500 | 4.67 | 1.50 |
| 1000 | 2.33 | 0.70 |

| Downwind Distance (ft) | Acute ADD Child (ug/kg/day) | | | | |
|---|---|---|---|---|---|
| | Dermal | Inhalation | Oral | | |
| | | | Hand-to-mouth | Object-to-mouth | Soil ingestion |
| 0 | 156.65 | 27.66 | 6.42 | 0.20 | 0.00 |
| 25 | 64.83 | 15.42 | 2.66 | 0.08 | 0.00 |
| 50 | 41.63 | 12.93 | 1.71 | 0.05 | 0.00 |
| 100 | 23.57 | 8.89 | 0.97 | 0.03 | 0.00 |
| 250 | 11.03 | 5.76 | 0.45 | 0.01 | 0.00 |
| 500 | 6.84 | 3.60 | 0.28 | 0.01 | 0.00 |
| 1000 | 3.42 | 1.68 | 0.14 | 0.00 | 0.00 |