PROPARGITE
(OMITE)

RISK CHARACTERIZATION DOCUMENT
OCCUPATIONAL AND AMBIENT AIR EXPOSURES

Medical Toxicology and Worker Health and Safety Branches

DEPARTMENT OF PESTICIDE REGULATION

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY

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SUMMARY

2-[4-(1,1-Dimethylethyl)phenoxy]cyclohexyl 2-propynyl sulfite (propargite) was first registered in 1969 as a miticide (U.S. EPA, 2001a). U.S. EPA issued a Registration Standard for propargite in 1986. In 1996, U.S. EPA and the registrant signed an agreement to voluntarily cancel certain uses due to unacceptable carcinogenicity dietary risk. In September 2001, U.S. EPA finalized their Reregistration Eligibility Document (RED) which resulted in proposed mitigation for worker exposure including changes in the packaging of some formulations, increased protective equipment (e.g., gloves, closed mixing systems, enclosed cabs and cockpits) and increased restricted entry intervals (REIs). The California Department of Pesticide Regulation completed a Risk Characterization Document (RCD) in 2004 which addressed the potential risk for human health effects from dietary and drinking water exposure to propargite in the general public (Lewis, 2004). This RCD addresses the potential risks for human health effects from occupational and ambient air exposure to propargite.

Toxicology

The pharmacokinetic and toxicology studies were reviewed and presented in the Toxicology Profile section. Included in the Toxicology Profile are guideline studies submitted to the Department of Pesticide Regulation DPR) and studies from open literature with the greatest weight generally given to guideline studies that met the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines. From the treatment-related effects identified in the studies, the highest dose, which did not cause any toxicological effect, known as No-Observed-Effect Level (NOEL), was established for each study. In the Hazard Identification section, the NOELs and effects at the Lowest-Observed-Effect Level (LOEL) from the available toxicity studies were evaluated to determine what would be the most appropriate NOEL, referred to as a critical NOEL, to evaluate particular exposure scenarios. The toxicity studies can be categorized as acute (< 7 days), subchronic (> 7 days to < 6 months), and chronic (1 or more years) in duration. For propargite, critical NOELs were identified for acute, subchronic, and chronic exposure scenarios. In addition, a potency factor was estimated for carcinogenicity. The critical NOELs were adjusted to absorbed doses because occupational and bystander exposures were expressed as absorbed doses. The oral and dermal adsorption rates for propargite were assumed to be 40% and 17%, respectively. A default absorption rate of 100% was assumed for inhalation exposure.

Propargite is an organosulfur miticide/acaricide whose pesticidal mechanism of action involves the inhibition of magnesium-stimulated ATPase. One of its primary mechanisms of toxicity in mammals is local irritation at the site of contact. However, reduction in body weights were seen with all routes of exposure which could either be due to metabolic effects of the chemical or may be a secondary response to the local irritation. Since larger uncertainty factors are used with systemic effects than local effects, the body weight reduction was assumed to be systemic without additional information as to cause. With acute exposure by the inhalation route, labored breathing, nasal discharge, moist rales, reduced body weights and discolored lungs were observed at the lowest dose tested. With acute oral exposure to propargite, gastrointestinal abnormalities, dark red adrenal glands, bright red lungs, jaundice, red and swollen paws, mouth

and urogenital area, decreased urination, abnormal defecation and reduced body weights were seen. With acute dermal exposure, severe dermal irritation was observed along with vocalization, abnormal defecation, decreased urination, inappetence, dehydration, hypothermia, ataxia, hypersensitivity to touch, moist rales, hair loss, scabbing, swelling and/or staining around mouth, nose, ears, and urogenital areas, and reddened lungs. NOELs were not observed in any of the acute toxicity studies. Therefore, an oral NOEL of 2 mg/kg/day from a rabbit development toxicity study was used to evaluate acute and subchronic inhalation exposure. The acute NOEL from this study was 0.8 mg/kg/day after adjusting for oral absorption (40%) based on anorexia in does (onset day 2) and delayed ossification in their fetuses. Using this NOEL, the RfC was 14 $\mu g/m^3$ for children and 29 $\mu g/m^3$ for adults. An acute dermal NOEL was seen in a 21-day dermal toxicity study based on the lack of any effects during the first week of exposure including clinical signs or reduced body weights. After adjusting for dermal absorption (17%), the acute dermal NOEL was 17 mg/kg. The acute dermal RfD (absorbed) is 170 $\mu g/kg$ after dividing by a default uncertainty factor of 100.

Severe dermal irritation was seen with acute dermal exposure to propargite. Since this endpoint is a local effect, concentration was considered the more appropriate expression of dosage rather than on a body weight basis. A NOEL for this endpoint was not observed in the available dermal studies, but was estimated to be 0.7 mg/cm^2 based on erythema that was observed in rabbits after the first 6-hr exposure in a 21-day dermal toxicity study. Generally, an acute RfC for dermal irritation is estimated by dividing the NOEL by an uncertainty factor of 10 for intraspecies variation. However, propargite also produced dermal sensitization, so an additional uncertainty factor of 3 was recommended to protect against dermal sensitization as well. Therefore, the proposed RfC for acute local dermal effects is 23 $\mu g/cm^2$.

The most common systemic effect with subchronic exposure to propargite, regardless of route, was reduced body weights. Reductions in food consumption were also seen. Changes in hematological and clinical chemistry values (↓ serum albumin and calcium, ↑ serum globulin, ↑ WBC count, segmented neutrophils, monocytes and platelets) were observed in a dermal study in rabbits. The veterinary pathologist for this study suggested that the hematological and clinical chemistry changes may be related to the dermal irritation. Increased relative liver, kidney, adrenal gland and/or gonad weights were observed in several studies. It is unclear if these organ weight changes are related to reduced body weights or organ toxicity. Pathological findings in these subchronic studies included increased pigment in reticuloendothelial cells of the liver and hemosiderosis of the spleen in dogs and chronic nephritis, liver inflammation and necrosis in rabbits. There were no subchronic inhalation studies available for propargite, so the lowest subchronic oral NOEL (2 mg/kg/day) from a rabbit developmental toxicity study was used after adjusting for oral absorption of 40%, resulting in absorbed NOEL of 0.8 mg/kg/day. The lowest subchronic dermal NOEL in an acceptable 21-day dermal toxicity study was 1 mg/kg/day based on reduced body weights (F: 14-20%), changes in clinical chemistry and hematology values, and increased relative liver and kidney weights in rabbits. After adjusting for dermal absorption, the subchronic dermal NOEL was 0.17 mg/kg/day. The subchronic RfD for dermal exposure was 1.7 $\mu g/kg/day$. A subchronic NOEL for dermal irritation was estimated at 0.21 mg/cm^2 from another 21-day dermal toxicity study. The subchronic RfC for dermal irritation was 7 $\mu g/cm^2$.

Several developmental and reproductive effects were seen in repeat dosing studies. These effects included increased abortions, increased resorptions, reduced fetal viability, delayed ossification, malaligned or fused sternebrae, hydrocephaly and reduced body weights. The NOELs for fetal or pup effects were usually equal to or higher than the maternal or parental NOELs, except in one rat developmental toxicity study in which delayed ossification was seen at a lower dose level than maternal toxicity suggesting there may be some increased pre-natal sensitivity to propargite.

The effects observed in laboratory animals with chronic exposure to propargite were similar to those observed with subchronic exposure, including reductions in body weights and food consumption, and changes in clinical chemistry, hematological values and organ weights. The lowest NOEL in a chronic oral study of acceptable quality was 3.8 mg/kg/day based on reduced body weights and food consumption in rats fed propargite in the diet for 2 years. This study was used to evaluated inhalation exposure with an NOEL of 1.5 mg/kg/day after adjusting for oral absorption. Therefore, the chronic inhalation RfC for propargite was 25 and 54 $\mu g/m^3$ for children and adults, respectively, based on this oral NOEL. No chronic dermal studies were available for propargite; therefore, the subchronic dermal NOEL (0.17 mg/kg/day) was used for evaluating chronic exposure. No additional uncertainty factor for extrapolating from subchronic to chronic was applied since the chronic oral NOELs were similar to the subchronic oral NOELs. Therefore, the chronic dermal RfD is the same as the subchronic RfD (1.7 μg/kg/day).

There is evidence that propargite is oncogenic based on an increase in undifferentiated sarcomas of the jejunum in Sprague-Dawley rats. The weight of evidence was considered sufficient to do a quantitative assessment of the oncogenic potential for propargite because 1) jejunal sarcomas are a rare tumor type; 2) sarcomas of the intestine and other tissues were observed in two other supplemental studies; and 3) there was a shortening of the time to tumor. There was some evidence to suggest that propargite may be acting by a threshold mechanism: 1) transient increase in cell proliferation and 2) essentially all negative genotoxicity studies. However, by itself, this evidence was not considered sufficient to justify using a threshold approach. Therefore, a non-threshold mechanism was assumed as a default. Although there was a dose-related increase in deaths at the high dose, which suggests that the Weibull time-to-tumor model would be the most appropriate model to estimate oncogenic potency, the registrant showed that the Weibull time-to-tumor model was not the best model to use based on its poor fit. Apparently, the poor fit with the Weibull time-to-tumor model was due to its inability to optimize the model parameters. The best fit for the jejunal sarcomas in male rats was obtained with the multistage model. The estimated oncogenic potency for propargite ranged from 2.4×10^{-2} $(mg/kg/day)^{-1}$ for the maximum likelihood estimate (MLE) to 3.4×10^{-2} $(mg/kg/day)^{-1}$ for the 95th percent upper bound (95% UB). To evaluate occupational and ambient air exposure the potency was adjusted for oral absorption, 40%. The adjusted oncogenic potencies were 5.9×10^{-2} $(mg/kg/day)^{-1}$ for the MLE and 8.4×10^{-2} $(mg/kg/day)^{-1}$ for the 95% UB. Generally, RfDs/RfCs are not calculated for a non-threshold effect like cancer. However, it is possible to calculate a dose or air concentration at which the carcinogenic risk is negligible (less than one in a million excess cancer cases). The dermal exposure dosage or RfD corresponding to a negligible risk using the 95% UB potency estimate is 12 ng/kg/day (absorbed). This corresponds to an air concentration of 43 ng/m^3 (3.0 ppt) below which there is no regulatory concern for carcinogenic effects.

Table 1. Critical No-Observed-Effect Levels (NOELs), Reference Doses or Concentrations, And Cancer Potency For Propargite

Exposure Scenario	NOEL/ENEL[a]	Effects on LOEL	RfD/RfC		Ref.[b]
Inhalation Exposure					
Systemic Acute / Seasonal	0.8 mg/kg (absorbed[c])	Maternal: Anorexia, adipsia, reduced body wt. gain, reduced survival Fetal: Delayed ossification	Children 8 µg/kg (14 µg/m^3)	Adults 8 µg/kg (29 µg/m^3)	1
Systemic Chronic	1.5 mg/kg/day (absorbed[c])	↓ Body weights and food consumption	Children 15 µg/kg/day (25 µg/m^3)	Adults 15 µg/kg/day (54 µg/m^3)	2
Dermal Exposure					
Local Acute	0.7 mg/cm^2	Erythema in rabbits after 6-hr exposure	23 µg/cm^2		3
Local Seasonal/ Chronic	0.21 mg/cm^2	Erythema, edema, eschar, exfoliation, atonia, desquamation, fissuring, blanching, coriaceous-ness in rabbits	7 µg/cm^2		3
Systemic Acute	17 mg/kg (absorbed[d])	No clinical signs or ↓ body weight during first week (no reddened lungs after 3 weeks) in rabbits	170 µg/kg (absorbed)		4
Systemic Seasonal/ Chronic	0.17 mg/kg/day (absorbed[d])	↓ Body weights, changes in clinical chemistry and hematology values, ↑ relative liver and kidney weights in rabbits	1.7 µg/kg/day (absorbed)		4
Lifetime Exposure - Inhalation and Dermal					
Cancer Potency	8.4 x 10^{-2} $(mg/kg/day)^{-1}$ (absorbed)	Jejunal sarcomas in male rats	12 ng/kg/day (absorbed)		2

a ENEL = estimated no effect level
b References: 1. Serota *et al.*, 1983; 2. Trutter, 1991; 3. Goldenthal, 1989; 4. Bailey, 1987.
c Oral NOEL converted to absorbed dose to evaluate inhalation exposure assuming 40% oral absorption.
d Dermal NOEL converted to absorbed dose assuming for 17% dermal absorption.

Exposure

Occupational

There were no acceptable chemical-specific occupational exposure studies for propargite, so handler exposure was estimated using the Pesticide Handler Exposure Database (PHED). Daily, seasonal, chronic and lifetime exposure dosages were estimated for 17 handler exposure scenarios covering aerial, airblast, groundboom, high and low-pressure handwand and backpack application with two different formulations: emulsifiable concentrate (EC) and water soluble bags (WSB). The estimated acute dermal concentrations of propargite for handlers ranged from 0.06 to 47.8 μg/cm^2 on their body and 0.03 to 1,691 μg/cm^2 on their hands. The Absorbed Daily Dosage (ADD) represented the upper confidence limit on the 95th percentile assuming 17% dermal absorption and 100% inhalation absorption. The dermal ADDs for handlers ranged from 15.6 to 5,194 μg/kg/day. The inhalation ADDs were between 0.6 and 110 μg/kg/day. The estimated seasonal dermal concentrations of propargite for handlers ranged from 0.02 to 12.4 μg/cm^2 on their body and from 0.01 to 564 μg/cm^2 on their hands. The Seasonal Average Daily Dosage (SADD) was the upper confidence limit on the mean daily exposure during the high-end use months. The dermal SADDs for handlers ranged from 3.9 to 1,731 μg/kg/day. The inhalation SADDs were between 0.2 and 44 μg/kg/day. The Annual Average Daily Dosage (AADD) was calculated by multiplying the SADD by the annual use months per year and dividing by 12 months. The seasonal exposures for handlers were estimated to occur over 4 months. The dermal AADDs for handlers ranged from 1.3 to 577 μg/kg/day. The inhalation ADDs were between 0.07 and 14.7 μg/kg/day. The Lifetime Average Daily Dosage (LADD) was estimated by multiplying the AADD by 40 years of work in a lifetime and dividing by 75 years in a lifetime. The LADDs for handlers ranged from 1.0 to 315 μg/kg/day. Aerial applicators using WSB formulations had the highest dermal exposure while aerial applicators with the EC formulations had the highest inhalation exposures.

The exposure dosages were calculated for field workers using dislodgeable foliar residues (DFRs) and transfer factors (TFs). Twenty field worker exposure scenarios were also evaluated for propargite. The DFRs were those anticipated at the end of the restricted entry interval (REI) for acute exposure and at the end of the REI plus 3 days for subchronic exposure for most activities. The REIs ranged from 7 to 42 days with most equal or greater than 21 days. The estimated acute dermal concentrations for fieldworkers ranged from 0.02 to 1.3 μg/cm^2 on their body and 0.6 to 68.7 μg/cm^2 on their hands. Assuming a dermal absorption of 17%, the dermal ADDs for fieldworkers were between 5.6 and 340 μg/kg/day. The estimated seasonal dermal concentrations for field workers ranged from 0.02 to 0.8 μg/cm^2 on their body and from 0.4 to 44.2 μg/cm^2 on their hands. The dermal SADDs for fieldworkers were between 4.5 and 218 μg/kg/day. For fieldworkers, seasonal exposure was annualized over 3-7 months. The dermal AADDs for fieldworkers ranged from 1.9 to 99 μg/kg/day. The LADDs were between 1.0 and 53 μg/kg/day. The field worker scenarios with the highest exposure were rose harvesters/cutters followed by corn detasselers.

Bystander Air

Application site and ambient air was monitored in Fresno County between June and August of 1999 to coincide with its use on cotton and grapes. The application site monitoring study for propargite was conducted over 3 days following an application to grapes. Bystander exposure estimates were calculated using the application site air monitoring data which represented a worse case scenario for the general public from agricultural drift exposure to propargite. The exposure estimates were adjusted for the maximum application rate of propargite (3 lbs/acre). The 1-hr acute bystander ADDs were 0.22 and 0.11 μg/kg for infants and adults, respectively, using the highest measured concentration and assuming a default inhalation absorption of 100%. The 24-hr bystander ADDs were 1.36 μg/kg for infants and 0.65 μg/kg for adults. The SADDs for the application site represented the average air concentration over the 3 days of monitoring. The bystander SADD for infants was 0.59 μg/kg/day and 0.28 μg/kg/day for adults. The AADDs were calculated assuming 4 months of exposure over a year. The bystander AADDs were 0.20 μg/kg/day for infants and 0.09 μg/kg/day for adults. Due to their higher respiratory rate relative to their body weight, infants consistently had the highest exposure.

Aggregate

The occupational exposure for agricultural workers represented 80-99.9% of the aggregate exposure while the dietary and drinking water exposure was usually less than 10% and the residential air exposure was usually less than 5%. Therefore, the aggregate exposure for agricultural workers was not further analyzed since the aggregate MOEs would not be significantly lower than their occupational MOEs. The aggregate exposure for the general public to propargite through the diet, drinking water and residential (application site) air was evaluated. The acute aggregate exposure estimates were 1.05 and 0.69 μg/kg for 1-hr and 3.85 and 2.39 μg/kg for 24 hours in infants and adults, respectively. The seasonal aggregate exposure estimates were 0.71 μg/kg/day for infants and 0.35 μg/kg/day for adults. The chronic aggregate exposure estimates were 0.31 and 0.21 μg/kg/day for infants and children, respectively. Unlike workers, dietary exposure represented a significant portion of the aggregate exposure to propargite for the general public, ranging from 16% (seasonal) to 79% (1-hr acute) of the total exposure for infants and from 20% (seasonal) to 89% (1-hr acute) of the total exposure for adults.

Risk Characterization

The risk for non-oncogenic adverse health effects is expressed as a margin of exposure (MOE) which is the ratio of the NOEL from the animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable for systemic effects assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower range of the normal distribution of the overall population and the sensitive subgroup. For local irritation from dermal exposure, a MOE of 10 is considered adequate when the NOEL is based on dermal irritation in rabbits since rabbits appear to be the most sensitive species to dermal irritation. However, an additional uncertainty factor of 3 is recommended for local

dermal effects to also protect against dermal sensitization. The negligible carcinogenic risk level is generally considered one excess cancer case in a million people.

Occupational

Occupational exposure for propargite handlers is of concern since many of the dermal MOEs for systemic effects with acute, seasonal and chronic exposure were less than the target of 100. The acute dermal MOEs for systemic effects were less than 100 for most applicators, for mixer/ loaders with aerial and airblast application of WSB formulations, for flaggers with WSB formulations and for mixer/loader/applicators (M/L/As) with high pressure equipment. Due to the significantly lower subchronic NOEL, the subchronic dermal MOEs were less than 10 for most handlers. The chronic dermal MOEs for handlers were higher due to the amortization of seasonal exposure over the year, but they were still less than 100 for most scenarios. The acute inhalation MOEs were less than the target of 100 for all applicators regardless of formulation, for mixer/loaders with all application methods of WSB formulations and with aerial application of EC formulations, for all flaggers and for M/L/As with low and high pressure sprayers. The subchronic inhalation MOEs were less than 100 for applicators with aerial or airblast application of both formulations, for mixer/loaders with aerial application of WSB formulations and for M/L/As with high pressure sprayers. The chronic inhalation MOEs were all greater than 100. The acute and subchronic MOEs for local dermal effects were greater than the target of 30 on the body of most handlers, but were less than 30 on the hands of many handlers (most applicators, mixer/loaders for aerial application with EC formulations and flaggers with WSB formulations). The cancer risk estimates for handlers all exceeded the negligible risk level, ranging from 5.9 excess cancer cases in 100,000 to 2.6 excess cancer cases in 100. Aerial applicators using WSB formulations had the highest estimated cancer risk for handlers.

There is less concern about the occupational exposure for fieldworkers since the acute dermal MOEs for systemic effects for fieldworkers were all greater than the target of 100 except for corn detasselers and rose harvesters/cutters. As with handlers, the seasonal dermal exposures for fieldworkers were a concern since all subchronic MOEs were less than 100. The chronic dermal MOEs were higher, but still less than 100 for all scenarios. The acute and subchronic MOEs for local dermal effects were all greater than the target of 30 for the body, but the acute and/or subchronic MOEs were less than 30 for the hands for some scenarios including corn harvesters and detasselers, nectarine and citrus pruners/ leaf thinners, rose harvesters/cutters and jojoba harvesters. The cancer risk estimates for fieldworkers were between 5.9 in 100,000 and 4.4 in 1,000. Corn detasselers had the highest cancer risk estimates.

Bystander Air

For propargite, the acute, seasonal and chronic MOEs for bystander inhalation exposure near the application site were all greater than the conventional target of 100. However, the MOE for children's 24-hr exposure was less than 1,000 and would meet the criteria for consideration as a possible toxic air contaminant. The cancer risk estimates for bystanders near the application site ranged from 5.5 to 7.8 excess cancer cases in a million are just above the level indicative of negligible risk suggesting mitigation should be considered. The cancer risk level is also high

enough to meet the criteria for consideration as a possible toxic air contaminant (greater than 10^{-7} risk level).

Aggregate

The aggregate MOEs for the general public from dietary, drinking water and ambient air exposure were all greater than 100. The dietary and drinking water exposure was a major contributor to the aggregate exposure for the general population. Consequently, the aggregate MOEs for the general public were significantly lower than the MOEs for bystander air exposure alone.

Conclusions

The MOEs for occupational exposure to propargite were generally low, especially for systemic effects from seasonal and chronic dermal exposure, suggesting mitigation should be considered. Inhalation exposure was also a concern for some handler scenarios, especially applicators for aerial and airblast application. There is some concern about the risk for local dermal effects (irritation and sensitization) with occupational exposure, especially to the hands of applicators and mixer/loader/applicators. Cancer risk estimates for all occupational exposure scenarios were high enough to suggest mitigation should be considered.

The MOEs for bystanders from acute, seasonal and chronic exposure to propargite in application site air are high enough that mitigation does not appear to be an issue, but the 24-hr MOE for children was low enough to meet the criteria for listing propargite as a toxic air contaminant. Cancer risk estimates for bystanders near the application site were also high enough to meet the criteria for listing propargite as a toxic air contaminant.

I. INTRODUCTION

I.A. REGULATORY BACKGROUND

2-[4-(1,1-Dimethylethyl)phenoxy]cyclohexyl 2-propynyl sulfite (propargite) was first registered in 1969 as a miticide (U.S. EPA, 2001a). U.S. EPA issued a Registration Standard for propargite in 1986. In 1995, U.S. EPA issued a data call-in. In 1996, U.S. EPA and the registrant signed an agreement to voluntarily cancel certain uses including its use on apricots, apples, peaches, pears, plums, figs, cranberries, strawberries, green beans, and lima beans. These uses were eliminated due to unacceptable carcinogenicity dietary risk. In July 2000, U.S. EPA had a conference call with USDA, the registrant and stakeholders to discuss risk concerns. U.S. EPA incorporated information from this call in their Reregistration Eligibility Document (RED) that they finalized in September of 2001. At the same time the RED was finalized, U.S. EPA held a close-out conference call with many of the same participants from the July 2000 conference call to discuss proposed mitigation which included changes in the packaging of some formulations, increased protective equipment (e.g., gloves, closed mixing systems, enclosed cabs and cockpits) and increased restricted entry intervals (REIs). DPR completed a Risk Characterization Document in 2004 which addressed potential health risks for the general public through dietary and drinking water exposure to propargite (Lewis, 2004). No mitigation was needed for dietary or drinking water exposure based on that risk assessment.

The purpose of this Risk Characterization Document is to address the potential adverse health effects for occupational and ambient air exposure to propargite. An aggregate risk assessment was included to address combined exposure to propargite through diet, drinking water, occupation and ambient air.

I.B. CHEMICAL IDENTIFICATION

Propargite is an organosulfur miticide/acaricide for controlling mites on a variety of bearing and non-bearing agricultural crops, as well as non-food agricultural sites (U.S. EPA, 2001a). Its pesticidal mechanism of action involves the inhibition of magnesium-stimulated ATPase (IRAC, 2002). The primary mechanism of toxicity in mammals involves local irritation at the site of contact.

I.C. TECHNICAL AND PRODUCT FORMULATION

The only registrant for propargite is Chemtura Corp. which acquired Crompton Manufacturing Co. Inc. in 2005 who had acquired Uniroyal Chemical Company in 1996, the original registrant for propargite. It is registered under the trade names Omite or Comite. Currently, there are only three actively registered products in California. Two are emulsifiable concentrates with propargite concentrations of 73.6% (Comite) and 69.2% (Omite-6E). The other product is a wettable powder (WP) packaged in water soluble packages (WSBs) with a propargite concentration of 32% (Omite-30WS).

I.D. USAGE

Propargite may be sprayed on crops by ground or air application. Chemigation is not allowed. From Pesticide Use Reprots from 2007 to 2013, 1,905,513 lbs. of propargite were applied. Most of the use was on corn (forage, 44.4%), almonds (19.5%), walnuts (15.0%), corn (human, 4.2%), grapes (wine, 2.5%), alfalfa (2.2%), bean (dried, 2.2%), cherry (2.0%), grapes (1.7%), cotton (1.6%), and corn (grain, 1.1%). Other crops had uses less than one percent of the total.

I.E. ILLNESS REPORTS

From 1982 to 2010, there were 1,057 illness/injury cases in California reported to the Pesticide Illness Surveillance Program (PISP) database maintained by DPR that were associated with the use of propargite, either alone and in combination with other pesticides (Dong, 2013). Nearly all of these cases (98%) were due to occupational exposure. Among the occupational cases attributed to propargite exposure alone, skin irritation was the only symptom reported in 75% of the cases.

Since 1982, there were 16 priority investigations of incidents associated with propargite use. The largest of which occurred in 1986 involving 114 of 198 orange harvesters (six crews) in Tulare County exposed to a CR (controlled release) formulation which was formulated for use on citrus to prevent leaf burn (Saunders *et al.*, 1987, Saiz and Schneider, 1987). The initial symptoms of the dermatitis included redness, itching and burning followed by a variable course including small papules, small vesicles, weeping, crusting, peeling (exfoliation) and a change of skin color (usually hyperpigmentation). Eye irritation was reported in 88 workers. The propargite dislodgeable foliar residues (DFRs) ranged from 0.82 to 5.49 $\mu g/cm^2$ with median values of 1.65, 1.52, 2.46, 1.51, 3.33 and 1.88 $\mu g/cm^2$ for the six crews. It should be noted that the CR formulation was promptly suspended after this outbreak, but then extended in 1988. However, it has not been registered since 2009.

In 1988, another large outbreak of dermatitis occurred among 46 of 57 nectarine harvesters (three crews) in Tulare County in California (O'Malley et al., 1989 &1990). The predominant lesion noted by medical examination in this outbreak was fine erythematous papules (blisters) in the antecubital fossae (fold of elbow), with the right arm usually more affected than the left. The propargite DFRs associated with this incident ranged from 0.55 to 1.91 $\mu g/cm^2$ with median values of 0.61, 0.64 and 0.68 $\mu g/cm^2$ for the three affected crews. In contrast, propargite DFRs for one unaffected crew ranged from 0.14 to 0.82 $\mu g/cm^2$ with a median value of 0.15 $\mu g/cm^2$. The authors suggested that 0.2 $\mu g/cm^2$ is a DFR NOEL for dermatitis based on this outbreak.

A third large incident occurred in 1995 involving 65 of 202 workers (8 crews) turning canes in a vineyard in Fresno County that had been treated twice during a 10 day interval at 6.25 lb/acre more than a month prior to the incident (O'Malley, 1998). Sixty-four of the 65 cases had skin irritation ranging from mild to moderately severe erythema. No blistering or post-inflammatory changes were observed. The propargite DFRs ranged from 0.37 to 0.66 $\mu g/cm^2$. In

each of these three major outbreaks, the DFRs correlate well with the severity of dermal irritation observed.

I.F. PHYSICAL AND CHEMICAL PROPERTIES (Agrochemical Handbook, 1992)

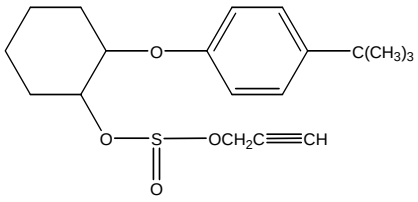
1. Common Name: Propargite

2. Chemical Name: 2-(4-(1,1-Dimethylethyl)phenoxy)cyclohexyl 2-propynyl sulfite

3. Trade Names: Omite®, Comite®

4. CAS Registry No.: 2312-35-8

5. Structural Formula:



6. Empirical Formula: $C_{19}H_{26}O_4S$

7. Molecular Weight: 350 g

8. Specific Gravity : 1.085 – 1.115 g/ml

9. Physical Form: Dark reddish-brown viscous liquid

10. Solubility: Water at 25°C: 1.93 µg/ml (McManus and Spare, 1987)
Acetone at 25°C: > 1 g/ml
Hexane at 25°C: > 1 g/ml

11. Vapor pressure: 4.49×10^{-8} mmHg at 25°C (Schofield and Blasberg, 1989)

12. Octanol/water partition coefficient: 5313 (log K_{ow} = 3.66) at 25°C (Smilo, 1986)

13. Henry's law constant: 1.088×10^{-8} atm-m^3/mol at 25°C
(Schofield and Blasberg, 1989)

I.G. ENVIRONMENTAL FATE

Summary

Air: Propargite has very negligible vapor pressure, therefore, it is not readily volatilized into the atmosphere. However, based on its very low vapor pressure, greater than 80% of propargite could become associated with particulate matter in the air (Bidleman, 1988). This particle associated propargite could exist in the air for days and travel over a great distance. The low Henry's law constant indicates that propargite is unlikely to volatilize into air from an aqueous solution. The low Henry's law constant also suggests that most of the propargite would be washed out of the air by rain during the winter months in California.

Water: Propargite is an extremely hydrophobic compound with very low water solubility. Its organic adsorption coefficient (K_{oc}) values indicate that propargite moderately binds to soils with low organic matter (OM) content and strongly binds to soils with rich OM content. It also has a high octanol/water partition coefficient suggesting that this compound readily binds to soils and other suspended matters in water. Therefore, propargite has a low potential to leach in soil and reach ground water. Propargite was not detected in well monitoring conducted in California between 1984 and 1991. However, propargite was found in approximately 10% of the surface water samples tested in California between 1993 and 1998.

Soil: The fate of propargite in soil can be affected by many factors including its physical-chemical properties, application rate, soil type, moisture content, climate and runoff. The K_{oc} values of propargite suggest that propargite moderately binds to soil particles and strongly to soils with rich organic contents. The photodegradation half-life of propargite on a sandy loam soil is approximately 75 days. The anaerobic metabolism half-lives for propargite ranged from 4.5 to 12 months. Under aerobic conditions, the half-life is 40 days. In field dissipation studies, no residues were detected below 6 inches and the estimated half-lives ranged from 64 to 122 days, indicating that propargite is moderately persistent in soil.

Hydrolysis

The hydrolysis half-lives of propargite are pH dependent. Experiments were conducted at concentrations of 0.6-0.7 ppm at 25°C (Nowakowski, 1987a). The half-lives at pH 5, 7 and 9 were 120, 78 and 3 days, respectively, when the concentration of tetra-n-butylammonium phosphate buffer was 0.5 M. When the buffer concentration was 0.005M, the half-lives at pH 5, 7 and 9 were 702, 48, and 2 days, respectively. The only identified hydrolysis product was 2-[4-(1,1-dimethylethyl)phenoxy]-cyclohexanol (propargite glycol ether).

Photolysis

Aqueous photolysis studies on propargite were performed at 0.97 ppm and pH 5, which was the most stable pH of those tested for hydrolysis (Nowakowski, 1987b). Samples were exposed to natural sunlight for 12 hours every day. The observed photolysis half-life was approximately 134-140 days. This result was almost identical to the result obtained from an aqueous dark control, meaning that hydrolysis is the major degradation pathway for propargite in

water as opposed to photolytic degradation. The identified degradation products were propargite glycol ether and *p*-*t*-butylphenol.

Soil photolysis of Omite was investigated on a sterilized sandy loam soil using a Xenon arc burner over 15 days (Korpalski, 1990). The estimated soil photolysis half-life for Omite was 75 days and the only identified degradate was glycol ether.

Soil Metabolism

The aerobic soil metabolism of 4.9 ppm [^{14}C]Omite was investigated on sandy clay loam in darkness at 25°C (Dzialo, 1988). After 90 days, 31% of applied radioactivity was extractable from the soil, of which 77% was unreacted propargite. Thirty percent of the original radioactivity was found to be bound residues and another 31% was converted to carbon dioxide. The estimated half-life of Omite under aerobic conditions was 40 days.

Anaerobic soil metabolism of [^{14}C]Omite was studied at concentrations of 1 and 10 ppm on sandy loam soil (Meck and Campbell, 1977). The half-lives of 1 and 10 ppm Omite were approximate 4.5 months and 12 months, respectively. The major degradation product was glycol ether. Large amounts of bound residues were also found in the study.

Soil Adsorption

Caplan and Lu (1978) determined the Freundlich constants (K_f) for adsorption and desorption in two soil types, eastern North Carolina loamy sand (86.1 and 292, respectively) and Kansas silt loam (698.2 and 6,918, respectively). Based on the K_f values for adsorption, propargite was categorized as intermediate in mobility in these soil types. The K_f values for desorption categorized its mobility as intermediate in loamy sand and low silt loam.

A batch soil adsorption/desorption study on Omite was conducted on four soils: a Wisconsin potato soil (OM 0.71%, pH 6.7), a California sand (OM 0.30%, pH 7.7), a Hesperia sandy loam (OM 1.70%, pH 6.9) and a clay loam (OM 5.36%, pH 6.3) (Korpalski and Nowakowski, 1988). The 48 hours K_d values was experimentally obtained via ^{14}C measurements. The soil adsorption coefficient values (K_d) were 17, 11, 55 and 266 for potato soil, sand, sandy loam and clay loam, respectively. Their organic adsorption coefficient values (K_{oc}) were 4128, 6322, 5578 and 8553 cm^3/g, respectively. These data showed that propargite moderately binds to soils of low OM content and strongly bind to soils of high OM content.

Soil Dissipation

Field dissipation tests have been performed for propargite in many locations and conditions. Propargite and glycol ether residues did not penetrate to below 6 inches in tested sites (Korpalski and Nowakowski, 1988; Harned, 1989). Comite was applied at a rate of 4.1 lbs a.i. per acre in a cotton field situated in Kerman, California (Harned, 1989). The soil type was a sandy loam (OM 0.7%, pH 7.9) and the total rainfall during this period was 49 inches. After 1, 4, 7, and 14 days and 1, 2, 3, 4, 6, 9, 12 months of application, soil was sampled for analysis. The propargite residues in the top 6 inches ranged from 0.22 ppm to 0.54 ppm during the first 4

months of the study. After 6 months, residues in all soil samples were below the minimum detection level of 0.10 ppm and no residues were found below 6 inches.

In another experiment, Omite 30W was applied onto two unplanted sites in California to investigate the dissipation of propargite and its metabolite glycol ether in soils (Lengen, 1989). The total rainfall was 8-9 inches during the study and the application rate was 4.5 lb active ingredient per acre. The monitoring period was 375 days. Propargite was only found in the top 6 inches of soil on both sites with residues ranging from 5.35 to 0.14 ppm on first site and 2.23 to 0.14 ppm on second site. The estimated half-lives in first and second site were 64-100 and 83-122 days, respectively. Propargite glycol ether was only detected in the top 6 inches with the concentrations from 0 to 0.35 ppm and from 0 to 0.30 ppm on first and second site, respectively.

Surface Water Monitoring

Although propargite has low water solubility and medium to high soil adsorption, its relatively long soil dissipation half-lives make it a possible contaminant for surface water. From January 1993 through August 1998, 295 samples were examined for propargite in California and there were 15 detections ranging from 0.018 to 20 parts per billion (ppb) with a limit of quantitation of 0.013 ppb (Starner, 2003). The estimated 95th percentile for the residues was 2.42 ppb and the mean residue level was 0.089 ppb.

Groundwater Monitoring

Propargite has low water solubility and medium to high soil adsorption. DPR does not consider propargite a potential groundwater contaminant since its physicochemical properties do not exceed the specific numerical values (SNVs) for solubility (SNV>3 ppm), K_{oc} (SNV <1,900 cm^3/g), hydrolysis (SNV > 14 days) or aerobic and anaerobic soil metabolism (SNVs > 610 and 9 days, respectively) (DPR, 2000a). Of 405 wells sampled for propargite in California during 1984 through 1991, no detection was reported at minimum detection levels ranging from 0 to 80 ppb (DPR, 2000b).

II. TOXICOLOGY PROFILE

II.A. PHARMACOKINETICS

Summary

The oral absorption of propargite was estimated to be approximately 40% in rats and mice based on a bioavailability study using plasma concentration curves with oral and intravenous administration. This estimate is similar to the amount of propargite excreted in the urine and bile in several elimination studies (20-40%). The elimination studies were not used to estimate oral absorption because either the recovery was low or the bile duct was not cannulated. Dermal absorption in rats varied with the formulation and concentration of propargite ranging from 3 to 20%. The elimination half-lives were between 8 and 11 hrs for rats and mice, respectively. The proposed metabolic pathway for propargite involves the hydrolysis of the propynyl sulfite side chain of propargite and the subsequent oxidation of the tert-butyl moiety and hydroxylation of the cyclohexyl moiety. After oral administration, the majority of propargite appears to be excreted unabsorbed, ranging from 33% to 64%, depending on the species and the amount administered. The amount excreted in the bile also varied with the dosage and species, ranging from 0.1% to 16% . The amount of propargite in the urine did not vary as much, ranging only between 4 and 11%.

Absorption

Oral: A pharmacokinetic study was conducted in both sexes of Sprague-Dawley rats and CD-1 mice following a single oral dose (150 mg/kg) or intravenous dose (20 mg/kg) of ^{14}C-propargite (Gay, 1994). Blood samples were collected at 30 minutes, and 1, 2, 4, 8, 12, 24, 36 and 48 hours after oral administration and 2, 5, 10, 15 and 30 minutes, and 1.5, 4, 12, 24 and 48 hours after intravenous administration. Although blood samples were taken only during the first 48 hours, the area under the plasma concentration curve was extrapolated out to infinity. Oral bioavailability (F) was calculated by comparing the area under the plasma concentration curve (AUC) with oral and intravenous administration after normalizing for dose and clearance:

$$F = \left[\frac{AUC_{oral}}{AUC_{iv}} \times \frac{Dose_{iv}}{Dose_{oral}} \times \frac{Clearance_{oral}}{Clearance_{iv}} \right] \times 100$$

Table 2 shows the AUC and clearance values the investigators reported for each species and sex. Using this formula, the investigators estimated the oral bioavailability was approximately 80% in rats and 75% in mice. However, this estimate of oral absorption appears to be in conflict with the urinary, biliary, and fecal excretion data which suggest that a large portion of propargite (45-75%) is excreted by rats in the feces, especially at high doses, possibly as unabsorbed material (see Excretion section). In some elimination studies the recoveries were less than 100%, probably because the blood or excreta were only monitored for 24 to 48 hours after dosing. Also, in most of these elimination studies, the bile duct was not cannulated, so it is unclear how much of the radioactivity in the feces is absorbed material. However, a more likely explanation for the contradictory results between the bioavailability study and the elimination studies, is that

Table 2. Estimated Area Under Plasma Concentation (AUC) Curve and Clearance (Cl) With Oral and Intravenous Administration of Propargite to Rats and Mice[a]

Species/Sex	AUC_{oral}	AUC_{iv}	Cl_{oral}	Cl_{iv}	F^{b}	F_{-Cl}
Rats/male	16200	5840	8.44	4.37	78.7	37.0
Rats/female	16100	5960	9.46	4.20	79.7	36.0
Mice/male	10000	3190	15.2	8.56	73.5	41.8
Mice/female	12500	3110	12.3	8.59	75.5	53.6

a Gay (1994)
b Reported F values from Gay (1994). When calculated independently using the values they reported for AUC and Cl, slightly lower F values were derived for male rats, female rats, male mice and female mice, respectively: 71.4, 81.1, 74.2 and 76.7. The reason for the discrepancies is not clear even when taking the actual administered dose into consideration.

bioavailability was calculated incorrectly due to a "flip-flop" phenomenon (Gilbaldi and Perrier, 1982). The slopes for the elimination rates with oral and intravenous administration should be parallel. However, in the "flip-flop" situation, the elimination rate is slower with oral administration than intravenous administration indicating that oral absorption is the rate limiting step during the elimination phase. Consequently, estimates of clearance are not considered accurate in this situation. In this case, it is more accurate to estimate bioavailability without taking clearance into consideration (expressed as F_{-Cl} in Table 2). When calculated this way, the bioavailability ranged from 36.0% in female rats to 53.6% in female mice. These adjusted bioavailability estimates are more consistent with the eliminations studies. The oral absorption was assumed to be 40% based on an average estimated bioavailability of 42% in rats and mice.

Dermal: Two sets of dermal absorption studies of various propargite formulations (Omite technical, Omite 30W, Omite 6E and Comite) were conducted in male Sprague-Dawley rats at 0.05, 0.5 and 5.0 mg/kg (Chadwick, 1989a-c; Andre et al., 1989&1990a-c; Mizens et al., 1990). These dosages correspond to concentrations of 1, 11 and 112 $\mu g/cm^2$, respectively, based on an application site of 10 cm^2. The test material was left on the application sites for 2, 4, 8 or 24 hours with 4 rats used for each exposure period. In the first set of studies, the dermal absorption for the various formulations (Comite, Omite 6E and Omite 30W) after the 24-hour exposure ranged from 3 to 17% after correction for recovery (Chadwick, 1989a-c; Andre et al., 1989). The lowest dermal absorption was with the Omite 30W formulation at 5.0 mg/kg. The highest dermal absorption was with Comite at 0.05 mg/kg. In the second set of experiments, the corrected dermal absorption of the various formulations (Omite technical, Omite 30W, Omite 6E and Comite) ranged from 6 to 20% (Andre et al., 1990a-c; Mizens et al., 1990). The lowest dermal absorption was with Omite 6E at 5.0 mg/kg and Comite at 0.5 mg/kg. The highest absorption, 20%, was observed with the technical material at 0.05 mg/kg. The dermal absorption for propargite was assumed to be 17% based on the highest dermal absorption with a non-technical formulation at a dermal concentration that was comparable to the actual worker exposure (Dong, 2013).

Distribution

In the pharmacokinetic study conducted by Gay (1994), the plasma concentration curve after oral administration best fit a one-compartment model for both species and sexes with first-order oral absorption and elimination. The C_{max} values were 11.4, 9.34, 14.3 and 11.7 μg/mL for male rats, females rats, male mice and female mice, respectively. The T_{max} values ranged from 4 to 8 hours for rats and 2 to 4 hours for mice. The elimination half-life (β $t_{1/2}$) ranged from 10 to 11 hours for rats and 8 to 9 hours for mice. After intravenous administration, the plasma concentration curve best fit an open two-compartment model for both species and sexes with a first order elimination phase. The distribution half-life (α $t_{1/2}$) ranged from 11 to 24 minutes for both species and sexes. The elimination half-lives were 4, 2 and 5.5 hours for both sexes of rats, male mice and female mice, respectively. The area under the concentration curve was two-fold greater for rats than mice. Clearance values were approximately 4 and 9 mL/min/kg for rats and mice, respectively. The volume of distribution (V_d) values ranged from 0.5 to 0.7 L/kg, which was similar to the total body water volumes, indicating distribution of propargite throughout the body.

The pharmacokinetics of propargite were also evaluated in another study where rats and mice had their bile ducts and duodenum cannulated (Gay, 1994). A single oral dose of ^{14}C-propargite was administered to 5 rats and 5 mice per sex at 150 mg/kg. The bile was collected at 1, 2, 4, 8, 12, 24, 36 and 48 hours. While bile was collected, an infusion pump delivered replacement bile salt via the duodenal cannula. The area under the concentration curve (AUC), C_{max}, T_{max}, and $t_{1/2}$ were estimated for the bile concentration curve. No gender-related differences in the bile elimination parameters were seen in either species. The values for AUC and C_{max} were greater for mice (11639 μg-equiv./g x h and 713 μg-equiv./g, respectively) than rats (8836 μg-equiv./g x h and 326 μg-equiv./g, respectively) while the $t_{1/2}$ was less (9.2 hrs vs. 21.4 hrs).

Biotransformation

Banijamali and Tortora (1988a) conducted a study in which male rats were administered 1.5 g/kg of ^{14}C-propargite (labeled on the phenyl ring). Urine and feces were collected for 72 hours. Five major metabolites in urine were identified: 1-[4-(2,x-dihydroxycyclohexoxy)-phenyl]-2,2-dimethyl acetic acid (Metabolite #1), 1-[4-(2,x-dihydroxycyclohexoxy)phenyl]-2,2-dimethylethyl sodium sulfate (Metabolite #2), 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,4,5-cyclohexane-triol (Metabolites #3), 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,x,x′-cyclohexane-triol (Metabolites #4) and 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2,x-cyclohexane-diol (Metabolite #5). Based on these urinary metabolites, these investigators proposed a metabolic pathway for propargite shown in Figure 1. In a subsequent study, Banijamali and Nag (1990) identified fecal metabolites in rats administered a single oral dose of ^{14}C-propargite at 1) 25 mg/kg, 2) 25mg/kg after 14 days of administration of unlabeled propargite at 25 mg/kg/day and 3) 200 mg/kg. The metabolites included 1-[4-(1,1-dimethylethyl)phenoxy]-2-cyclohexanol (propargite glycol ether), Metabolite #1, Metabolite #3 and Metabolite #5. Banijamali and Nag (1991) also examined the fecal metabolites of propargite in mice after a single oral dose of ^{14}C-propargite at 200 mg/kg. The metabolite profile was similar to rats qualitatively with 3 zones of radioactivity corresponding to the parent compound, the glycol ether

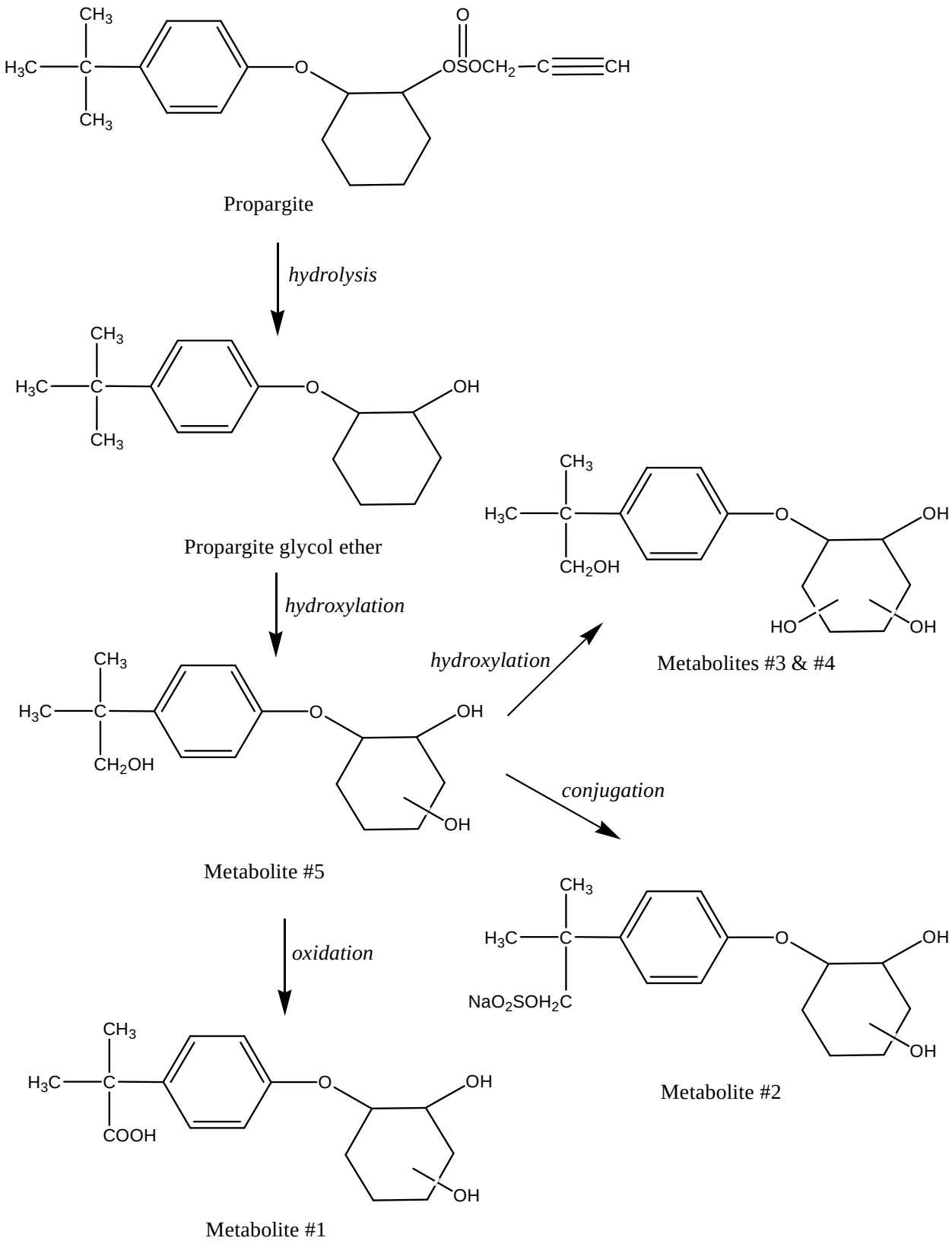


Figure 1. Proposed metabolic pathway for propargite (Banijami and Tortora, 1988).

metabolite and polar metabolites. Rats had a higher percentage of the parent compound in the feces while mice had a higher percentage of polar metabolites indicating more absorption and metabolism of propargite in mice.

The metabolism of propargite was evaluated *in vitro* and *in vivo* in female rats, rabbits, and monkeys due to apparent differences in toxicity (Doweyko and Tortora, 1989). The oral LD_{50} was reported to be significantly lower in rabbits than in rats and monkeys. The *in vitro* metabolism was evaluated by incubating liver homogenates and S-9 preparations with ^{14}C-propargite (labeled on the phenyl ring) at 8 and 80 nmol/mL. Three major components were observed in all analyses: the parent compound, propargite glycol ether and propargite bis-glycol ether sulfite. Two polar metabolites representing oxidation products were also present in all samples. No clear species differences in metabolism were seen. The *in vivo* metabolism was evaluated by analyzing urinary, biliary and liver metabolites after oral administration of ^{14}C-propargite at 18 mg/kg (4 rabbits, 2 monkeys) or 105 mg/kg (4 rats, 2 monkeys). Half of the animals for each species were placed in metabolism cages and excreta were collected. Selected tissues were also collected at the end of the 24-hour in-life period. The other half of the animals had a cannula inserted in the bile duct and had bile collected. Only liver samples were taken from these animals at the end of the 24-hour in-life period. It appears the rabbit tends to produce less polar metabolites than the rat or monkey. In addition, some unique metabolites were found, but their significance is unknown.

Plasma and bile samples from rats and mice were analyzed for metabolites by Gay (1994). Metabolism was rapid and extensive with similar metabolite profiles in both species. No parent compound was found in the bile of either species at any collection period. The parent compound was found in the plasma at less than 4% of the radioactive residue except in male mice which had approximately 10%. Generally, the proportion of more polar biliary metabolites increased with time. Six metabolites were detected in the biliary samples. Metabolites #1, #3 and #5 were identified. The biliary metabolites were reported to be similar to urinary metabolites identified in another study, except for two metabolites which were tentatively identified as different hydroxy-cyclohexyl isomers of TBPC. Four major metabolites were identified in plasma. The major plasma metabolite was 1-[4-(1,1-dimethyl-2-hydroxyethyl)phenoxy]-2-cyclohexanol or hydromethyl-TBPC. Metabolite #5 was also prominent in all the plasma samples. It was proposed that the plasma and biliary metabolites of propargite are the result of hydrolysis of the propynyl sulfite side chain of propargite and the subsequent oxidation of the tert-butyl moiety and hydroxylation of the cyclohexyl moiety.

An additional metabolism study analyzed the metabolites of the 2-propynyl sulfite side chain of propargite (Banijamali and Fang, 2000). [1,2,3-^{13}C, 2,3-^{14}C-Propargyl]Propargite was administered to male rats and mice at 150 mg/kg. Six major urinary metabolites were isolated and identified in rats: 2-(acetylamino)-3-(2-propynylthio)-propanoic acid (peak 1), 2-(carboxy-methylthio)-2-propenoic acid (peak 2), 3-(carboxymethylthio)-2-propenoic acid (peak 3), 3-[(2-carboxy-2-hydroxyethyl)thio]-2-propenoic acid (peak 4), 3-(N-formylglutamylcysteinyl)-2-propenoic acid (peak 5), and 2-(N-formylglutamylcysteinyl)-2-propenoic acid (peak 6). Two pathways of metabolism were proposed for propargite in rats based on this study. The first pathway involves direct conjugation of propargite to yield the peak 1 metabolite. The second pathway involves the hydrolysis of the propynyl sulfite side chain to the hypothetical intermediate, 2-propargyl alcohol, presumably followed by its oxidation to 2-propynoic acid.

The acid subsequently undergoes conjugation with glutathione with further metabolism to yield the remaining metabolites identified in rats. In feces, 80% of the total radioactive residue (TRR) was the parent compound. The other metabolites isolated were each less than 1% of the TRR. Some of these metabolites were intermediates in the biosynthesis of the urinary metabolites while others were diconjugates, probably formed by the addition of 2 glutathione molecules followed by further degradation, analogous to the pathways described for the urinary metabolites. Seven major urinary metabolites were identified in mice. The first 4 peaks were the same as in rats, but the remaining peaks were different: 3-[(2-acetylamino-2-carboxyethyl)thio]-3-[(2-amino-2-carboxyethyl)thio]-1-propanol (peak 5), 3-[(2-amino-2-carboxyethyl)thio]-2-propenoic acid (peak 6), and 3,3-bis[(2-amino-2-carboxyethyl)thio]-1-propanol (peak 7). Similar metabolic pathways were proposed for mice, except that some metabolites (peaks 5 and 7) were formed from the conjugation of the propargyl alcohol before it underwent further oxidation. In feces, propargite represented 68% of the TRR. The most abundant polar metabolite in mouse feces was 3-(carboxymethylthio)-2-propenoic acid, which represented 1.94% of the TRR. The other 7 fecal metabolites were each less than 1% of the TRR and were closely related to the mouse urinary metabolites.

Excretion

Banijamali and Tortora (1988b) conducted a pharmacokinetic study in which a single oral dose of ^{14}C-propargite was administered at 25, 60 or 200 mg/kg. Urine, feces and blood samples were collected for 96 hours after dosing. Findings from this study were compared with a satellite pharmacokinetic study that was conducted in conjunction with a subchronic toxicity study in which 12 rats/sex/dose were fed unlabeled propargite in the diet for 13 weeks at 100, 1000 or 2000 ppm. After 13 weeks, 2 rats/sex/dose were administered 12.5 μCi of ^{14}C-propargite by oral gavage. With a single dose of propargite, the mean urinary excretion was 40, 37 and 22% of the applied dose at 25, 60 and 200 mg/kg, respectively. The mean fecal excretion was 56, 74 and 73% of the applied dose at 25, 60 and 200 mg/kg, respectively. By comparison, the mean urinary excretion was 28, 34 and 28% after 13 weeks of feeding at 100, 1000 and 2000 ppm, respectively. The mean fecal excretion was 35, 31 and 29% at 100, 1000 and 2000 ppm, respectively. The highest tissue residues in both studies were found in the gastrointestinal tract, liver, muscle, fat and blood, but represented less than 5% of the applied dose at all dose levels. The recovery in the single dose study ranged from 97-114%. The recovery was lower in the subchronic study with only 68-79% of the radioactivity recovered. The low recoveries were attributed to no fecal or urine samples collected from some rats at certain time points. It is unclear whether the investigators were suggesting the lack of urine or fecal samples at these time points was due to experimental errors or other biological phenomena.

The fecal excretion increased with repeated exposure in another study conducted by Banijamali and Nag (1990). In this study, ^{14}C-propargite was given to rats at 25 mg/kg after pretreatment for 14 days with unlabeled propargite at 25 mg/kg/day. Another group was administered a single dose of ^{14}C-propargite at 25 mg/kg with no pretreatment. The fecal excretion increased from 51.3% to 63.3% of the applied dose in males and 61.2% to 71.7% of the applied dose in females with repeated exposure. As with the previous study, these investigators also found that the fecal excretion increased with dose. After administering a single dose of ^{14}C-propargite at 200 mg/kg, 74.5% and 69.9% of the applied dose was excreted in the feces by males and females, respectively. In mice administered a single oral dose of

propargite at 200 mg/kg, 41.5% and 52.9% of the applied dose was excreted in the feces by males and females, respectively (Banijamali and Nag, 1991).

In the comparative metabolism study in rats, rabbits, and monkeys, half the animals were maintained in metabolism cages for 24 hours (Doweyko and Tortora, 1989). The amount of radioactivity in the feces, stomach and GI chyme were added together to estimate the amount of unabsorbed material. Rabbits had the highest amount of unabsorbed material (59.9%) relative to rats (43.7%) and monkeys (33.5%). The amount excreted in the urine was similar between these species, ranging from 7% (rabbits) to 11% (rats) of the applied dose. The amount excreted in the bile ranged from 0.1% (rabbits) to 8.2% (rats) of the applied dose. However, due to the short collection period and incomplete analysis of all tissues, the apparent recoveries in this study were relatively low, ranging from 50% in monkeys to 70% in rabbits.

In the pharmacokinetic study conducted by Gay (1994), the animals were maintained in metabolism cages for 48 hours while their bile and excreta were collected. Urine and feces were collected at 12, 24 and 48 hours. In both rats and mice, the majority of the radioactivity was found in the feces (approximately 64 and 45% of the applied dose, respectively), presumably as unabsorbed material. The percentage of the applied dose that was eliminated in the bile was similar for rats and mice (16 and 15%, respectively). Only 11 and 4% of the applied dose was excreted in the urine in rats and mice, respectively. Due to the short collection period and lack of tissue analysis, the recoveries in this study were usually less than 100%, especially for mice. For rats, the recoveries were relatively high, ranging from 88% in males to 99% in females. It is unclear if the lower recoveries in mice are due to a slower digestive tract (i.e., not all unabsorbed radioactive material in digestive tract excreted yet) or slower metabolism (i.e., not all absorbed radioactive material excreted yet).

II.B. ACUTE TOXICITY

Summary

Acceptable acute toxicity tests were available for not only the formulations, but also the technical grade propargite. The inhalation LC_{50} for technical grade propargite was 0.89 mg/L. Reddening of the lungs was observed macroscopically in some animals that died. Clinical signs included labored breathing, anogenital stains, nasal discharge, moist rales, decreased activity and reduced body weights. The oral LD_{50} for technical grade propargite was 2800 mg/kg. Gastrointestinal abnormalities in most animals that died were considered to be due to the irritative properties of propargite. Other macroscopic findings in a few rats included dark red adrenal glands, bright red lungs and jaundice. Clinical signs included red and swollen paws, mouth and urogenital area, decreased urination and abnormal defecation. The dermal LD_{50} was greater than 4000 mg/kg, the only dose level tested. Severe dermal irritation was observed at this dose including erythema, edema, eschar, fissuring, desquamation, exfoliation and white-yellow exudate. Clinical signs included vocalization, abnormal defecation, inappetence, scabbing and swelling around the mouth, and staining around the nose and urogenital area. Technical grade propargite also caused severe eye irritation and dermal sensitization. The propargite emulsifiable concentrates were as toxic or more toxic than the technical grade material. Some formulations were corrosive to both the skin and eyes. The wettable powders

were considerably less toxic than the technical grade material by the inhalation, oral and dermal route. Only slight dermal irritation was observed; however, the wettable powders were still corrosive to the eyes and caused dermal sensitization.

Technical Grade Propargite

The acute toxicity tests for technical grade propargite (90.3% purity) are summarized in Table 3. In the acute inhalation study, 5 Sprague-Dawley rats/sex/dose were exposed (nose-only) to aerosolized propargite (90.3% purity) for 4 hours at 0.31, 0.80 and 1.3 mg/L (analytical) (Hoffman, 1992a). The mass median aerodynamic diameter was 1.6 µm. Twenty-two percent of the particles were less than 1 µm and 100% were less than 10 µm. Therefore, the respiratory uptake was assumed to be 100%. One male died at 0.31 mg/L 4 days after exposure. One male and one female at 0.80 mg/L died two and three days after exposure, respectively. All the animals at 1.3 mg/L died between one and seventeen days after exposure. The most common clinical signs during exposure were labored breathing and anogenital staining. Decreased activity was also observed at 0.31 mg/L. Upon removal from the chambers, nasal discharge, matted coats and moist rales were seen in addition to the labored breathing and anogenital staining. Animals at 0.80 and 1.3 mg/L were held an additional 7 days to allow for recovery. Substantial reductions in body weights (5-30%) were observed at all dose levels in the first week after exposure. Reddening of the lungs was observed macroscopically in some of the animals that died and in some of the animals that were sacrificed. Other postmortem findings were sporadic and not considered treatment-related. The LC_{50} was 0.89 mg/L when both sexes were combined. The NOEL appears to be less than 0.31 mg/L based on the death, clinical signs, reduced body weights and discoloration of the lungs. This study was found acceptable to DPR toxicologists based on the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) guidelines.

Table 3. The Acute Toxicity of Technical Grade Propargite (90.3% purity)

Species	Sex	Results	References[a]
		Acute Inhalation LC_{50}	
Rat	M/F	0.89 mg/L (4-hour, nose-only)	1*
		Acute Oral LD_{50}	
Rat	M	2639 mg/kg	2*
	F	2947 mg/kg	
		Acute Dermal LD_{50}	
Rabbit	M/F	>4000 mg/kg	3*
		Primary Dermal Irritation	
Rabbit	M/F	Severe Irritation	4*
		Primary Eye Irritation	
Rabbit	M/F	Severe Irritation	5*
		Dermal Sensitization	
Guinea Pig	M/F	Non-sensitization (Buehler)	6
	M/F	Sensitization (Maximization)	7*

a References: 1. Hoffman, 1992a; 2. Kiplinger, 1993a; 3. Kiplinger, 1993b; 4. Kiplinger, 1993c; 5. Kiplinger, 1993d; 6. Kiplinger, 1993e; 7. Morris, 2003.

* Study found acceptable to DPR toxicologists based on FIFRA guidelines.

In the acute oral toxicity study, technical grade propargite (90.3% purity) was administered to 5 Crl:CD®BR rats/sex/dose at 2000, 2800 and 3920 mg/kg by oral gavage (Kiplinger, 1993a). Five and 10 animals died at 2800 and 3920 mg/kg. Clinical signs were seen at all dose levels and included swollen paws, red and swollen mouth and ears, swollen urogenital area in females, swollen penis and prepuce and necrotic areas on scrotum in males, abnormal defecation, decreased urination, hypoactivity, hypothermia, hypersensitivity to touch, rales, ataxia, dehydration, prostration, scabbing on ears, hair loss on base of tail and paws, dried or wet material on paws, mouth and eyes, and staining/discoloration of abdomen and urogenital area. Gross pathological examination found gastrointestinal abnormalities (stomach: dark red areas or foci, dark red contents and thickened mucosa; intestine: red fluid contents and distended) in most of the rats that died which were considered to be due to the irritative properties of the test article. Dark red or reddened adrenal glands were observed in 6 rats that died, which is a typical agonal or stress-related change. Five rats had bright red lungs and 3 rats were icteric (affected by jaundice). Other findings observed in only one rat included a reddened pituitary gland, a dark red prostate gland and dark red streaks on the urinary bladder. A thickened mucosa in the stomach was observed in two rats that survived. One male at 2800 mg/kg had small, soft testes. The oral LD_{50} was 2800 mg/kg when both sexes were combined. The NOEL appears to be less than 2000 mg/kg based on the clinical signs and external findings (scabbing, hair loss, matting, swelling) at necropsy. DPR toxicologists found this study acceptable based on FIFRA guidelines.

In the acute dermal toxicity study, technical grade propargite (90.3% purity) was applied topically to the clipped backs of 5 New Zealand White rabbits/sex at 4000 mg/kg over an area that was approximately 23% (~ 380 cm^2) of their total body surface area[1] (Kiplinger, 1993b). This resulted in a concentration of approximately 23 mg/cm^2 based on an average weight of the rabbits at dosing of 2200 g. The application site was covered with gauze and secured with nonirritating tape. Collars were used during the exposure period (24 hours) to prevent ingestion of the test compound. No deaths or changes in body weights were observed. Systemic effects were noted including vocalization, abnormal defecation, inappetence, scabbing and swelling around the mouth, and staining around the nose and urogenital area. Severe dermal irritation was seen including severe erythema and edema, eschar, white-yellow area in the application site, fissuring, desquamation, exfoliation and white-yellow exudate. Thickened skin and desquamation were noted at necropsy in all rabbits. One rabbit had reddened lungs. The dermal LD_{50} was greater than 4000 mg/kg, the only dose level tested. The NOEL was less than 4000 mg/kg based on the systemic effects and dermal irritation. This study was acceptable based on FIFRA guidelines.

In a dermal irritation study with 3 New Zealand White rabbits/sex, technical grade propargite (90.3% purity) caused severe dermal irritation including moderate erythema and edema, eschar, fissuring and desquamation after a 4-hour exposure period under semi-occlusive wrapping (Kiplinger, 1993c). The concentration at the application site was estimated to be 85 mg/cm^2 based on 0.5 ml of propargite being applied to an area that was 1 inch square or 6.45 cm^2. Slight erythema and edema and desquamation were still present at study termination. This

[1] Assumed equal to 9.5 x (body weight in grams)$^{2/3}$ (Harkness and Wagner, 1995).

study was acceptable to DPR toxicologists based on FIFRA guidelines. Technical grade propargite (90.3% purity) caused severe eye irritation in 6 New Zealand White rabbits including mild corneal opacity and iritis that cleared by 10 days, discharge that cleared by 14 days and moderate redness and swelling of the conjunctiva that persisted through day 21 (Kiplinger, 1993d). DPR toxicologists found this study acceptable based on FIFRA guidelines. The sensitization potential of technical grade propargite (90.3% purity) was tested in 6 Hartley guinea pigs/sex using a modified Buehler method (Kiplinger, 1993e). The animals were induced with a 0.1% solution and rechallenged with both a 0.1% and 0.2% solution. There was no reaction with either concentration that was attributed to sensitization, although the 0.2% solution caused slight irritation at the naive site. The sensitization potential of technical grade propargite (91.9%) was also tested in guinea pigs with the Guinea Pig Maximization Test (Morris, 2003). The animals were administered propargite at 5 and 15% for the intradermal and topical induction, respectively. A sensitization response was seen in 16 of 20 animals based on a grade reaction of 2 after the challenge dose at 5%. The same number of animals still responded with reactions of grade 1 or 2 with a rechallenge dose at 0.5%.

Propargite Formulations

Acute toxicity studies for two propargite emulsifiable concentrates, Comite (73.6%) and Omite 6E (68.1%), are summarized in Table 4. Comite and Omite 6E were slightly more acutely toxic by the inhalation route compared to the technical grade material based on the LC_{50} values (Hoffman, 1992b&c). The clinical signs and macroscopic findings were similar to those seen with the technical grade material except that excessive salivation was also observed with both formulations. The acute oral toxicity of both emulsifiable concentrates were significantly more toxic than the technical grade material, presumably due to the inert ingredients in these formulations (Blaszcak, 1992a&b). Clinical signs observed after oral administration of these formulations included oral discharge or excessive salivation, watery or soft stool, urogenital staining, hypoactivity (Comite only), decreased food consumption and decreased fecal volume. Discoloration of the lungs and gastrointestinal tract was observed macroscopically after oral administration of both formulations. In addition, thickened stomach walls were seen with Comite. Omite 6E produced red nasal turbinates, fluid in the trachea and dark brown fluid in the urinary bladder in rats that died. The relative toxicity of the emulsifiable concentrates by the dermal route could not be compared with the technical grade material because only one dose level was tested with each of these formulations (Blaszcak, 1992c&d). Severe dermal irritation was observed with Omite 6E in the dermal toxicity study, but no systemic effects. Systemic effects were observed in the dermal toxicity study with Comite in part due to the higher dose level tested with Comite vs. Omite 6E (5000 mg/kg vs. 2000 mg/kg). The systemic effects included decreased food consumption and fecal volume, soft stools, fecal staining, hypothermia, nasal discharge, irregular breathing and emaciation. Comite also produced severe dermal irritation. In the dermal irritation studies, Comite and Omite 6E produced slight to moderate erythema and slight to moderate edema in the first 72 hours which progressed to necrosis and eschar formation with exfoliation (Blaszcak, 1992e&f). Comite produced severe eye irritation including severe conjunctival irritation, iridial damage, and corneal opacity, stippling and ulceration (Blaszcak, 1992g). Pannus and alopecia around the eye were observed at later

Table 4. The Acute Toxicity of Propargite Emulsifiable Concentrates[a,b]

Species	Sex	Results	References[c]
		Acute Inhalation LC_{50}	
Rat	M/F	0.75 mg/L (4-hr, nose-only)[a]	1*
	M/F	0.83 mg/L (4-hr, nose-only)[b]	2*
		Acute Oral LD_{50}	
Rat	M/F	600 mg/kg[a]	3*
	M/F	593 mg/kg[b]	4*
		Acute Dermal LD_{50}	
Rabbit	M/F	>5000 mg/kg[a]	5*
		>2000 mg/kg[b]	6*
		Primary Dermal Irritation	
Rabbit	M/F	Corrosive[a]	7*
	M/F	Severe Irritation[b]	8*
		Primary Eye Irritation	
Rabbit	M/F	Corrosive[a]	9*
	M/F	Moderate Irritation[b]	10*
		Dermal Sensitization	
Guinea Pig	M/F	No sensitization[a] (Buehler)	11
	M/F	No sensitization[b] (Buehler)	12

a Comite (73.60% purity)
b Omite 6E (69.92% purity)
c References: 1. Hoffman, 1992b; 2. Hoffman, 1992c; 3. Blaszcak, 1992a; 4. Blaszcak, 1992b; 5. Blaszcak, 1992c; 6. Blaszcak, 1992d; 7. Blaszcak, 1992e; 8. Blaszcak, 1992f; 9. Blaszcak, 1992g; 10. Blaszcak, 1992h; 11. Blaszcak, 1992i; 12. Blaszcak, 1992j.
* Acceptable study to DPR toxicologists based on the FIFRA guidelines

intervals in the study. Ocular effects were still present at day 21. Eye irritation was also seen with Omite 6E, but it was less severe and had cleared by day 21 (Blaszcak, 1992h). Neither Comite or Omite 6E caused dermal sensitization with the Buehler test (Blaszcak, 1992i&j). Both were tested at 5%, 0.05%, 0.05% and 0.025% for the induction, challenge and rechallenge (2 concentrations), respectively.

The acute toxicity tests for two propargite wettable powder formulations, Omite CR (30.02% purity) and Omite 30W (28.99% purity), are summarized in Table 5. The inhalation LC_{50} values of the wettable powders were significantly higher than the emulsifiable concentrates; however, the clinical signs observed were similar (Hoffman, 1993a & 1994a). The only macroscopic finding was thinning hair on the facial, ventral cervical/thoracic areas and forepaws which was observed with Omite CR, but not Omite 30W. The oral LD_{50} values for the wettable powders were also significantly higher than the emulsifiable concentrates. Clinical signs anogenital staining, watery stool, ulcerations at the base of the tail, moist rales (Omite included CR) and excessive salivation (Omite 30W). Red discoloration of lungs, fluid in the lungs and trachea (Omite 6E), urinary bladder distended with yellow fluid (Omite 6E) and intestine distended with gas (Omite 6E) were seen at necropsy in rats that died. Dilated renal pelvis, thickening of the stomach walls, white nodules on the spleen and enlarged lymph nodes were

Table 5. The Acute Toxicity of Propargite Wettable Powders[a,b]

Species	Sex	Results	References[c]
		Acute Inhalation LC_{50}	
Rat	M/F	> 6.4 mg/L (4-hour, nose-only)[a]	1*
	M/F	> 5.0 mg/L (4-hour, nose-only)[b]	2*
		Acute Oral LD_{50}	
Rat	M/F	> 5000 mg/kg[a]	3*
	M/F	>5200 mg/kg[b]	4*
		Acute Dermal LD_{50}	
Rabbit	M/F	> 2000 mg/kg[a]	5*
	M/F	> 5000 mg/kg[a]	6*
	M/F	> 5000 mg/kg[b]	7*
		Primary Dermal Irritation	
Rabbit	M/F	Moderate Irritation	8*
	M/F	Slight Irritation[a]	9*
	M/F	Slight Irritation[b]	10*
		Primary Eye Irritation	
Rabbit	M/F	Corrosive[a]	11*
	M/F	Corrosive[b]	12
		Dermal Sensitization	
Guinea Pig	M/F	Sensitization[a] (Buehler)	13*
	M/F	No Sensitization[a] (Buehler)	14
	M/F	No Sensitization[b] (Buehler)	15
	M/F	Sensitization[b] (Buehler)	16*

a Omite CR (30.02% purity)

b Omite 30W (28.99% purity)

c References: 1. Hoffman, 1993a; 2. Hoffman, 1994a; 3. Hoffman, 1993b; 4. Hoffman, 1994b; 5. Busch and Biesemeier, 1986; 6. Hoffman, 1993c; 7. Hoffman, 1994c; 8. Goodband, 1982; 9. Hoffman, 1993d; 10. Hoffman, 1994d; 11. Hoffman, 1993e; 12. Hoffman, 1994e; 13. Kreuzman, 1986; 14. Hoffman, 1993f; 15. Berman *et at*., 1989; 16. Hoffman, 1994f.

* Acceptable study to DPR toxicologists based on the FIFRA guidelines.

seen with Comite in rats that survived. The relative dermal toxicity of the wettable powders could not be compared with the emulsifiable concentrates or technical grade material since both formulations were only tested at 5000 mg/kg (Hoffman, 1993c & 1994c). No deaths or systemic effects were seen in these studies, only severe dermal irritation. Only slight erythema was observed in the dermal irritation studies for both wettable powders (Hoffman, 1993d & 1994d). On the other hand, both wettable powders were still corrosive with ocular effects still present on day 21 (Hoffman, 1993e & 1994e). Omite CR produced slight to moderate sensitization in Buehler test where it was applied at 33.3%, 5.0% and 5.0% (vehicle: water) during the induction, challenge and rechallenge, respectively (Kreuzman, 1986). However, no dermal sensitization was seen with Omite CR in another Buehler test where it was tested at 100%, 10%, 10% and 2.5% (vehicle: water) during the induction, challenge and rechallenge (2 concentrations), respectively (Hoffman, 1993f). It is unclear why no sensitization was observed in the second study with the same formulation at higher concentrations. Dermal sensitization was also not seen with Omite 30W when guinea pigs were tested with Buehler test at 0.1% of the formulation (Berman *et al.*, 1989). However, a positive sensitization response was produced with Omite

30W in the Buehler test using the neat formulation during the induction. Three of 20 animals had scores of 1 or greater when challenged at 0.75%. Five of 20 animals had positive reactions when rechallenged at 0.25%.

II.C. SUBCHRONIC TOXICITY

Summary

Two oral studies (rats and dogs) and two dermal studies (rabbits) were available for propargite. Only one of the dermal studies in rabbits was found acceptable based on FIFRA guidelines. The most common systemic effect with exposure to propargite, regardless of route, was reduced body weights. In addition, a slight increase in the incidence of several histopathological findings, including chronic nephritis, inflammation of the liver and hepatic necrosis, were seen in the 21-day dermal studies in rabbits. An increase in pigment in the reticuloendothelial cells of the liver and hemosiderosis of the spleen was observed in the dogs fed propargite for 13 weeks. Changes in hematological and clinical chemistry values were observed in another dermal study in rabbits. The lowest NOEL for systemic effects was 1 mg/kg/day based on the changes in hematological and clinical chemistry values. Dermal irritation was observed in both dermal studies. The NOEL for dermal irritation was less than 0.1 mg/kg/day.

Diet-Rat

Rats (number, sex and strain not reported) were fed technical grade propargite (purity not reported) in the diet at 10, 20, 40, 100 and 200 mg/kg/day for 90 days (Carson, 1964). No clinical signs were reported, although it is unclear if observations were made. Body weights and food consumption were reduced (percentage not reported) at 100 and 200 mg/kg/day. No abnormal hematological or clinical chemistry values were seen. No gross pathological lesions were found. Relative (to body), but not absolute weights of the liver, kidneys, adrenals and gonads were elevated in most groups probably due to body weight reductions. At 200 mg/kg/day major organs (not specified) were reduced in size. No microscopic lesions were found in the liver, kidneys, adrenals and gonads. The NOEL for this study appears to be 40 mg/kg/day. This study was unacceptable since only summary information was provided.

Diet-Dog

Three beagle dogs/sex/dose were fed technical grade propargite (purity not reported) in the diet at 2000 to 2500 ppm (dose intervals not specified) for 13 weeks (Hazleton, 1968). Three dogs/sex served as controls for this study and two other studies run simultaneously. The dogs had reduced food consumption and body weights. No effects were reported for clinical signs, hematology, clinical chemistry, organ weights or gross pathological lesions, except for a tendency for elevated serum glutamic-oxalacetic transaminase (SGOT or more currently referred to as aspartate aminotransferase or ASAT) activity and relative (to body) liver weight. An increase in pigment in the reticuloendothelial cells of the liver and hemosiderosis of the spleen were observed in the treated dogs. A NOEL could not be established due to insufficient information. This study was unacceptable since only summary information was provided.

Dermal-Rabbit

Technical grade propargite (purity not reported) was applied to the shaved backs of 5 HRA:(NZW)SPF rabbits/sex/dose at 0 (vehicle: acetone), 0.1, 1, 10 or 100 mg/kg/day for 6 hours/day, five days/week for 3 weeks (Bailey, 1987). Propargite was applied under a 2 inch square (25 cm^2) gauze patch and held in place with tape for 6-hours. The concentration on the skin was estimated to be 0, 0.01, 0.1, 1.0 and 10 mg/cm^2 based on an average weight during the study of 2.5 kg. Rabbits wore plastic collars 24 hrs/day to avoid ingestion of the test material. Some signs of dermal irritation, such as erythema, thickening, epidermal scaling and fissuring were observed in all the dose groups, including the controls, which the investigators attributed to the vehicle (acetone). Atonia was observed in the skin in all treatment groups. More severe dermal effects were also observed at 10 mg/kg/day and higher including necrosis, sloughing and eschar. Dermal microscopic findings in untreated and/or treated skin included acanthosis, hyperkeratosis, subepidermal inflammatory infiltrate, necrosis, erosion/ulceration, subepidermal edema and hemorrhage at 0.1 mg/kg/day or higher (Table 6). The severity of these dermal lesions increased with dosage with the dermal lesions being minimal to slight at 0.1 mg/kg/day, slight to moderate at 1 mg/kg/day, moderate at 10 mg/kg/day and moderate to moderately severe at 100 mg/kg/day. Erosion and ulceration were only observed at 100 mg/kg/day. The acanthosis resulted in papillary projections into the epidermis in some rabbits at 10 and 100 mg/kg/day, but the incidence was not dose-related. The NOEL for dermal irritation was less than 0.1 mg/kg/day based on dermal observations (very slight to well-defined erythema, thickening, epidermal scaling, fissuring and atonia) and microscopic lesions (acanthosis, hyperkeratosis, subepidermal inflammatory infiltrate and necrosis).

No treatment-related clinical signs were seen. One male rabbit at 100 mg/kg/day with an intussusception of the ileum into the cecum was sacrificed in a moribund condition. The mean body weights were significantly depressed at 10 mg/kg/day (F: 14-20%) and 100 mg/kg/day (M: 12-16%; F: 14-18%) during the second and third weeks of the study (Table 6). There was no significant effect on food consumption. Increases in several hematological values were seen in one or both sexes at 10 and/or 100 mg/kg/day including white blood cell count, segmented neutrophils, monocytes and platelets. Changes in several clinical chemistry values were also seen in both sexes at 10 and 100 mg/day including a decrease in serum albumin and calcium and an increase in serum globulin. The veterinary pathologist for the study suggested that the hematological and clinical chemistry changes may be related to the dermal irritation. The decrease in albumin may be due to loss through exudate. The calcium may be reduced because it binds to albumin. The increased globulin may be due to increased immunoglobulins. An increase in relative (to body) liver and kidney weights was seen at 10 mg/kg/day (F: 24% and 26%, respectively) and 100 mg/kg/day (liver - M: 24%, F: 14%; kidney - M: 24%, F: 16%). The investigator suggested these relative organ weight changes may be related to reduced body weight changes; however, the histopathological lesions in the liver and kidney at 100 mg/kg/day in this study and the other 21-day dermal study conducted by Goldenthal (1989) suggest they may be related to organ toxicity. Histopathological examination revealed focal hepatic necrosis in one male and one female at 100 mg/kg/day. The NOEL for systemic effects was 1 mg/kg/day

Table 6. Possible Adverse Effects in Rabbits Treated Topically with Propargite in Acetone for 21 Days[a]

Possible Adverse Effect	Sex	Dose Level (mg/kg/day)				
		0	0.1	1	10	100
Acanthosis	M	0/5	5/5*	5/5*	5/5*	4/5*
	F	0/5	4/5*	5/5*	5/5*	5/5*
Hyperkeratosis	M	0/5	4/5*	4/5*	4/5*	4/5*
	F	0/5	0/5	4/5*	5/5*	5/5*
Subepidermal infiltrate	M	0/5	5/5*	5/5*	5/5*	5/5*
	F	0/5	5/5*	3/5	4/5*	5/5*
Skin, edema	M	0/5	0/5	1/5	3/5	4/5*
	F	0/5	0/5	2/5	2/5	5/5*
Skin, necrosis	M	0/5	2/5	1/5	1/5	2/5
	F	0/5	0/5	2/5	0/5	1/5
Body weights wk 3 (kg)	M	2.61±0.15[b]	2.43±0.20	2.64±0.12	2.40±0.15	2.18±0.15*
	F	2.67±0.23	2.58±0.15	2.52±0.15	2.14±0.22*	2.20±0.20*
Platelets (1,000/µl)	M	352±53	435±73	559±158	687±203*	747±98*
	F	319±46	346±41	492±129	797±133*	949±186*
Neutrophils (1,000/µl)	M	1.8±1.0	1.9±0.6	3.2±1.0	4.3±1.9*	7.0±4.4*
	F	2.3±2.0	1.5±0.8	2.7±1.1	9.8±7.0*	7.7±3.8*
Monocytes (1,000/µl)	M	0.0±0.0	0.1±0.2	0.0±0.1	0.1±0.1	0.3±0.3
	F	0.0±0.0	0.0±0.1	0.0±0.0	0.3±0.3*	0.2±0.2*
Albumin (g/dl)	M	3.7±0.1	3.5±0.2	3.7±0.1	3.3±0.1*	3.2±0.2*
	F	3.7±0.1	3.6±0.1	3.6±0.1	3.3±0.2*	3.1±0.2*
Globulin (g/dl)	M	1.6±0.2	2.2±1.0	1.8±0.1	2.1±0.2*	1.9±0.2
	F	1.5±0.3	1.5±0.2	1.7±0.1	2.2±0.3*	2.0±0.3*
Calcium (mg/dl)	M	12.5±0.4	12.7±0.4	12.4±0.2	11.8±0.4*	11.6±0.7*
	F	12.1±0.2	12.3±0.5	12.4±0.2	11.8±0.4	11.9±0.5
Liver weights (% body)	M	2.03±0.11	2.05±0.17	2.08±0.11	2.18±0.26	2.52±0.17*
	F	2.04±0.23	1.96±0.17	2.07±0.22	2.53±0.28*	2.33±0.40
Kidney weights (% body)	M	0.58±0.05	0.83±0.55	0.60±0.03	0.67±0.06	0.72±0.08*
	F	0.58±0.07	0.57±0.03	0.63±0.04	0.73±0.10*	0.67±0.03
Hepatic necrosis	M	0/5	0/5	0/5	0/5	1/5
	F	0/5	0/5	0/5	0/5	1/5

a Bailey, 1987.
b Mean ± standard deviation.
* Significantly different from controls, $p \leq 0.05$.

based on reduced body weights, changes in clinical chemistry and hematology values and increases in relative liver and kidney weights. DPR toxicologists found this study acceptable based on FIFRA guidelines.

Dermal-Rabbit

Groups of 5 New Zealand White rabbits/sex/dose had technical grade propargite (86.6% purity) applied neat (undiluted) to their shaved backs at 0, 0.1, 1.0, 10 and 100 mg/kg (0, 2.1, 4.5, 12.5 or 28 mg/cm^2) for 6 hrs/day, 5 days/week for 3 weeks (Goldenthal, 1989). The test sites were covered with gauze and secured with tape. The rabbits wore collars during the 6-hr exposure periods. Erythema and edema were observed as early as day 2 before the 2nd application (Table 7). The severity of erythema and edema increased with dose and repeated exposure with only slight to moderate erythema at 0.1 mg/kg/day on day 2, but marked erythema and edema in most animals at 10 and 100 mg/kg/day by day 21. Other signs of severe dermal irritation were seen including eschar, exfoliation, atonia, desquamation, fissuring, blanching and/or coriaceousness (leatheriness) with dose-related increases in onset, severity and incidence. Microscopic lesions were observed in the treated skin at all dose levels, including acanthosis, hyperkeratosis, inflammation, necrosis and abscess. The dermal inflammation did not show a dose-related trend in the incidence and severity, unlike acanthosis and hyperkeratosis. The NOEL for dermal irritation was less than 0.1 mg/kg/day based on dermal observations (erythema, edema, eschar, exfoliation, atonia, desquamation, fissuring, blanching, coriaceousness) and microscopic lesions (acanthosis, hyperkeratosis, inflammation and necrosis).

There was no treatment-related effect on mortality or clinical signs. Treated males tended to have slightly lower mean body weights than controls; however, the differences were not statistically significant. Both sexes tended to have slightly lower mean food consumption in all the treatment groups, but the differences were only statistically significant for females at 0.1, 1.0 and 10 mg/kg/day in week 2 of the study and at 100 mg/kg/day in week 1 of the study. At necropsy, a statistically significant increase in segmented neutrophils was observed in males at 100 mg/kg/day. The investigator did not consider this finding biologically significant since it was an isolated finding; however, increased neutrophils were also observed in the 21-day dermal study conducted by Bailey (1987) who suggested it may be related to the dermal irritation. There were no other significant hematological or biochemical changes in the blood. An increase in chronic interstitial nephritis (0: 2/10 vs. 100: 5/10) and inflammation of the liver (0: 2/10 vs. 100: 4/10) was observed in both sexes at 100 mg/kg. Mild hepatic necrosis was also observed in 2 females at 100 mg/kg. The NOEL for these lesions was uncertain since the kidney and liver were not examined microscopically at 0.1, 1 or 10 mg/kg/day. This study was unacceptable for evaluating systemic toxicity due to the incomplete histopathology in the low and intermediate treatment groups. It was considered acceptable for evaluating dermal effects since the skin was examined microscopically at all treatment levels.

Table 7. Possible Adverse Effects in Rabbits Administered Propargite Neat Dermally for 21 Days[a]

Possible Adverse Effect	Severity/ Sex	Dose Level (mg/kg/day)				
		0	0.1	1	10	100
Erythema day 2	Slight Moderate	0/10[b] 0/10	6/10 4/10	1/10 9/10	0/10 10/10	0/10 10/10
Erythema day 21	Moderate Marked	0/10 0/10	5/10 5/10	3/10 7/10	0/10 10/10	0/10 10/10
Edema day 2	Slight Moderate Marked	0/10 0/10 0/10	0/10 0/10 0/10	8/10 2/10 0/10	0/10 9/10 0/10	0/10 0/10 10/10
Edema day 21	Slight Moderate Marked	0/10 0/10 0/10	2/10 8/10 0/10	4/10 6/10 0/10	0/10 5/10 5/10	0/10 1/10 9/10
Acanthosis	mild moderate	0/10 0/10	6/10 4/10	3/10 7/10	3/10 7/10	3/10 7/10
Hyperkeratosis	mild moderate severe	0/10 0/10 0/10	10/10 0/10 0/10	8/10 2/10 0/10	6/10 4/10 0/10	1/10 7/10 2/10
Skin, inflammation	mild moderate	7/10 0/10	1/10 9/10	0/10 10/10	0/10 10/10	0/10 10/10
Skin, necrosis	mild moderate	0/10 0/10	0/10 0/10	5/10 0/10	3/10 0/10	3/10 4/10
Body weights wk 3 (kg)	M F	2.93±0.20[b] 3.08±0.09	2.82±0.13 3.14±0.09	2.84±0.25 3.13±0.11	2.79±0.30 3.15±0.05	2.82±0.28 2.96±0.21
Neutrophils (1,000/µl)	M F	1.4±0.3 1.2±1.4	1.1±0.4 1.1±0.3	1.0±0.2 1.7±0.7	1.6±0.7 3.0±2.0	4.1±1.4* 3.1±1.6
Liver inflammation	M F	1/5 1/5	----- -----	----- -----	----- -----	2/5 2/5
Liver necrosis	M F	0/5 0/5	----- -----	----- -----	----- -----	0/5 2/5
Chronic nephritis	M F	1/5 1/5	----- -----	----- -----	----- -----	2/5 3/5

a Goldenthal, 1989.
b Mean ± standard deviation.
* Significantly different from controls, $p \leq 0.05$.

II.D. CHRONIC TOXICITY/ONCOGENICITY

Summary

One mouse, two rat and two dog studies were available for propargite. All five studies were oral studies. Only the mouse, one rat and one dog study were found acceptable based on FIFRA guidelines. Reduced body weights and food consumption were the most prevalent effects observed. Reduced survival was observed in both rat studies. Changes in hematological values were seen in both rats and dogs. Changes in clinical chemistry values were also seen in rats. Most of these changes were of uncertain toxicological significance. Changes in organ weights (usually increases in relative and decreases in absolute), seen in several studies, were probably related to body weight reductions. An increase in sarcomas of the jejunum was observed in Sprague-Dawley rats, but not Wistar rats or mice. Several supplemental studies were conducted to ascertain the mechanism for tumor formation. The stabilizer, propylene oxide, does not appear to be responsible. One study suggests that increased cell proliferation may be the mechanism for the tumor formation. Microscopic lesions in the lungs (congestion or inflammation), thymus (involution) and bone marrow (atrophy) were seen in one dog study at 1250 ppm and higher. The lowest NOEL in the chronic studies appears to be 80 ppm (M: 3.8 mg/kg/day: F: 4.7 mg/kg/day) based on slight reductions in body weights and food consumption in rats.

Diet-Mouse

Groups of 60 CD-1 mice/sex/dose were administered propargite (purity 84.3 - 88.5%) in the diet at 0, 50, 160, 500 or 1000 ppm (0, 24, 75 or 150 mg/kg/day[2]) for 18 months (Block I) (Cox and Re, 1979). An additional 15 mice/sex/dose were fed propargite at 0, 500 or 1000 ppm for 12 months (Block II). There was no effect on survival except for a greater survival of Block I males at 160, 500 and 1000 ppm during the first 12 months. There was no effect on clinical signs, body weights, food consumption and hematology. Changes in some absolute (A) or relative (R) organ weights were observed in the kidney (160 ppm - M: R ↓11%; 1000 ppm - F: A ↓11%) and uterus (160 ppm - F: R ↑53%; 1000 ppm - F: A ↑75%, R ↑84%) in Block I animals. Increased organ weights were also seen in the kidney (1000 ppm - M: R 10%), adrenal (500 ppm - F: A 50%, R 46%; 1000 ppm - F: A 46%, R 46%) and thyroid (500 ppm - F: A 60%, R 64%) in Block II animals. Microscopic examination revealed no treatment-related pathologic lesions in these organs; therefore, the toxicological significance of these findings is uncertain. There was no treatment-related increase in neoplasms. The NOEL for this study is equal to or greater than 1000 ppm, the highest dose tested (HDT). DPR toxicologists initially found this study unacceptable due to the lack of effects at the HDT; however, after submission of additional data (test article characterization, homogeneity and stability and U.S. EPA's review of this study), this study was upgraded to acceptable.

[2] Estimated assuming for a mouse that 1 ppm in the diet is equivalent to 0.150 mg/kg/day (FDA, 1959).

Diet-Rat

In a combined chronic toxicity/reproductive toxicity study, 37 (controls) or 25 (treated) FDRL (Wistar-derived) rats/sex/dose were fed propargite (purity not reported) in the diet at 0, 100, 300, or 900 ppm (nominal compound intake: 0, 5, 15 or 45 mg/kg/day) for 2 years (FDRL, 1966). After 6 months, two more groups were added which were fed propargite at 0 (15 rats/sex) or 2000 ppm (25 rats/sex; nominal compound intake: 100 mg/kg/day) for 1.5 years. To avoid excessive dosages in the weanlings, the dietary concentrations were increased biweekly during the first 10 weeks of exposure starting at 42, 125, 380 and 833 ppm to reach the adult levels of 100, 300, 900 and 2000 ppm. When rats were 100 days old, 20 pairs of male and female rats from the control and 100 ppm groups were mated. At weaning, 10 pups/sex from the second litters were designated as the F_1 generation and maintained on the same diet as their parents for 12 weeks. The F_2 pups were then mated as above. At weaning, the dose level for F_2 pups was increased to 300 ppm. The F_3 generation reached maturity about the same time the 2-year test period of the F_0 generation was terminated. There was no effect on reproductive performance or survival and growth of offspring. In the chronic toxicity study, the survival of males at 2000 ppm was lower than controls at 18 months (68% vs. 93%). There was no significant effect on body weights and food consumption at 100, 300 and 900 ppm. Significantly lower body weight gains and cumulative food consumption were seen in males (30% and 10%, respectively) and females (34% and 25%, respectively) at 2000 ppm at termination. There was no effect on hematology, clinical chemistry or urinalysis including the descendent generations. Initial review of the gross and histopathological findings suggested there were no treatment-related effects. After reviewing the chronic toxicity/oncogenicity study conducted by Trutter (1991), the pathological findings in this study were reevaluated. The pathology findings were difficult to interpret since the cell type or organ of origin or other details were often missing. Although not definitive, there was an apparent dose-related increase in sarcomas of the intestine with characteristics resembling the undifferentiated sarcomas observed in the jejunum of rats in the Trutter (1991) study. These sarcomas included spindle cell sarcomas, myosarcomas and osseous sarcomas. These sarcomas were seen in 1 male at 300 ppm, 3 males and 1 female at 900 ppm and 3 males and 1 female at 2000 ppm. The incidence in males was significant by the Cochran-Armitage trend test ($p < 0.001$) and by Fisher's exact at 2000 ppm ($p= 0.02$). A NOEL was not clearly established in this study due to insufficient information, but appears to be 900 ppm (45 mg/kg/day) based on the reduced survival, body weight gains and cumulative food consumption at 2000 ppm (100 mg/kg/day). This study was unacceptable to DPR toxicologists due to major deficiencies including an inadequate number of animals per group, incomplete histopathological examination and no analysis of the diets.

Diet-Rat

Technical grade propargite (87.2% purity) was fed to 60 Crl:CD®BR rats/sex/dose in the diet at 0, 50, 80, 400 or 800 ppm (M: 0, 2.4, 3.8, 19.2 or 38.9 mg/kg/day; F: 0, 2.9, 4.7, 23.6 or 49.4 mg/kg/day) for 103 weeks (males) or 104 weeks (females) (Trutter, 1991). Ten rats/sex/dose were sacrificed at week 53. There was a reduction in survival of males at 400 and 800 ppm with a positive linear trend in mortality for the male test groups. However, mortality rates were not significantly different between the control and test groups for either sex, except for a significantly lower mortality rate for males at 50 ppm. Reduced body weights were observed in both sexes at 400 ppm (M: 4-6%; F: 2-4%) and 800 ppm (M: 12-17%; F: 10-20%),

although females at 400 ppm recovered over time (Table 8). A reduction in food consumption was also observed at 400 ppm (M: 2-5%; F: 2-4%) and 800 ppm (M: 12-17%; F: 12-13%). There were no treatment-related differences in clinical signs, ophthalmologic findings or urinalysis. There was a significant increase in reticulocyte counts in males at 800 ppm that was associated with non-significant decreases in erythrocyte counts, hemoglobin and hematocrit values and an increase in nucleated erythrocyte count. A significant increase in platelet counts was also seen in females at 800 ppm at weeks 26 and 52, but it is of uncertain toxicological significance. A significant decrease in glucose level was observed in females at 800 ppm at week 78. Total protein and calcium values were significantly lower in males at 400 and 800 ppm and in females at 800 ppm at week 26. The reduction in calcium levels may be related to the reduction in protein levels since a large portion of the calcium is protein-bound. Significant decreases in globulin and increased albumin to globulin ratios were also seen at week 26 in males at 800 ppm. Non-significant decreases in total protein and globulin persisted until the study termination in males at 800 ppm. Significant reductions in aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) activities were seen in females at 400 and 800 ppm. The reductions in glucose, total protein, globulin, ASAT and ALAT levels may be related to the decreased food consumption. Significant increases in relative (to body) organ weights were seen at week 53 for the liver at 400 and 800 ppm (F: 17% and 38%, respectively) and for the kidney (M: 12%, F: 35%) and brain (M: 12%, F: 33%) at 800 ppm. These increases may be related to the body weight reductions. Many of the unscheduled deaths after week 65 at 800 ppm were in animals with abdominal masses which were associated with the small intestine. Histopathological examination revealed that these masses were undifferentiated sarcomas in the jejunum (Table 9). The increases in this rare tumor were statistically significant by pairwise comparison with controls in males at 400 ppm and in both sexes at 800 ppm. There was also a significant positive trend for these tumors in both sexes. Ulceration and ectatic mucosal glands at the tumor site were often associated with these tumors. No other treatment-related increases in histopathological lesions were seen. The NOEL for this study was 80 ppm (M: 3.8 mg/kg/day; F: 4.7 mg/kg/day) based on the slight reductions in body weights and food consumption. DPR toxicologists found this study acceptable based on the FIFRA guidelines.

The registrant had a consultant pathologist, Dr. R.A. Squire, analyze the data from the Trutter study (1991) in an attempt to determine the cause of the unanticipated increase in undifferentiated sarcomas (Cardona et al., 1991). He agreed with the original diagnosis as undifferentiated sarcomas. He proposed that the propylene oxide stabilizer in the technical grade material may be responsible since it is genotoxic. He also suggested that propargite is ulcerogenic at the doses that are carcinogenic, allowing lumenal exposure of the submucosal mesenchymal cells. Examination of the tumors revealed that most were ulcerated, suggesting that epithelial erosion and ulceration may have preceded and been required for tumor formation. To further evaluate the possible role of ulceration in the development of these tumors, Dr. Squire examined 10 additional jejunal step sections in 26 males that did not have tumors at 0 and 800 ppm. Among the males at 800 ppm, 5 had focal epithelial necrosis and 2 of these were large ulcers with submucosal stromal and inflammatory responses. The smallest lesions were crypt abscesses filled with necrotic cell debris and surrounded by attenuated epithelium, portions of which were necrotic. No crypt abscesses, ulcers, epithelial necrosis or other similar lesions were found in the control animals.

Table 8. Possible Adverse Effects in Rats Fed Propargite in the Diet for 104 Weeks[a]

Possible Adverse Effect		Dose Level (ppm)				
		0	50	80	400	800
Body wt. change wks 0-24 (g)	M	422±78[bT]	424±75	402±90	372±102*	346±53*
	F	279±101[T]	291±90	303±108	280±76	237±52
Total food cons. wks 0-24 (g)	M	3331±298[T]	3336±272	3301±262	3156±249*	2773±171*
	F	2467±205[T]	2495±218	2459±228	2375±167*	2136±156*
Reticulocytes wk 104 (10^6/µl)	M	0.25±0.16	-----	-----	0.25±0.18	0.54±0.25*
	F	0.13±0.12	-----	-----	-----	0.16±0.12
Platelets wk 52 (10^3/µl)	M	1305±114[M]	1256±154	1392±176	1367±151	1320±190
	F	1129±136[M]	1176±120	1152±110	1196±182	1350±136*
Glucose wk 78 (mg/dl)	M	112±13	111±13	112±14	113±13	106±19
	F	110±20[T]	106±15	100±16	99±16	83±16*
Total protein wk 26 (g/dl)	M	7.3±0.3[T]	7.1±0.4	7.5±0.3	7.0±0.4*	6.7±0.3*
	F	8.1±0.4	7.6±0.5	7.8±0.6	8.2±0.6	7.4±0.4
Globulin wk 26 (g/dl)	M	2.6±0.2[T]	2.5±0.4	2.8±0.4	2.5±0.3	2.1±0.3*
	F	2.1±0.2[M]	2.1±0.3	2.1±0.2	2.1±0.4	2.0±0.3
Calcium wk 26 (mg/dl)	M	10.3±0.3[T]	10.1±0.2	10.4±0.4	10.0±0.3*	10.0±0.3*
	F	10.9±0.3	10.8±0.6	10.6±0.5	10.9±0.4	10.3±0.3*
ASAT wk 26 (U/l)	M	132±34[T]	136±48	116±29	118±30	99±18
	F	214±154[T]	117±25*	171±109	112±38*	106±32*
ALAT wk 26 (U/l)	M	42±7[T]	48±16	42±15	38±16	34±5
	F	105±105[M]	40±10*	89±110	38±9*	38±17*
Liver wt. wk 53 (% body)	M	2.64±0.38[M]	2.69±0.83	2.54±0.27	2.65±0.32	2.94±0.38
	F	2.43±0.17[T]	2.62±0.14*	2.79±0.66	2.83±0.32*	3.35±0.32*
Kidney wt. wk 53 (% body)	M	0.63±0.07	0.62±0.08	0.62±0.05	0.65±0.07	0.71±0.06*
	F	0.59±0.06[T]	0.65±0.08	0.71±0.18*	0.66±0.11	0.79±0.08*
Brain wt wk 53 (% body)	M	0.36±0.04	0.34±0.03	0.36±0.03	0.36±0.03	0.41±0.04*
	F	0.50±0.05[T]	0.53±0.09	0.53±0.10	0.55±0.08	0.66±0.07*

a Trutter, 1991.
b Mean ± standard deviation.
T Significant trend, $p \leq 0.05$.
* Significantly different from controls, $p \leq 0.05$.
M Significant monotonic trend, $p \leq 0.05$.

Table 9. Histopathological Lesions in Jejunum of Rats Fed Propargite in the Diet for 104 Weeks[a]

Lesion	Dose Level (ppm)				
	0	50	80	400	800
MALES					
Sarcoma	0/44[b+++] (0%)	0/47 (0%)	0/44 (0%)	11/46*** (24%)	24/46*** (52%)
Ulceration, tumor site	0/49[c+++] (0%)	0/47 (0%)	0/46 (0%)	3/49 (6%)	10/50*** (20%)
Ectatic mucosal glands, tumor site	0/49[c+++] (0%)	0/47 (0%)	0/46 (0%)	3/49 (6%)	6/50* (12%)
FEMALES					
Sarcoma	0/45[b+++] (0%)	1/49 (2%)	1/49 (2%)	1/47 (2%)	12/45*** (27%)
Ulceration, tumor site	0/47[c++] (0%)	1/49 (2%)	0/49 (0%)	0/47 (0%)	3/47 (6%)
Ectatic mucosal glands, tumor site	0/47[c+] (0%)	1/49 (2%)	0/49 (0%)	0/47 (0%)	2/47 (4%)

a Trutter, 1991.
b The denominator is the number of animals at risk (excluding those that died before week 52); the first tumor observed week 65; the number in the parentheses represents the incidence in percentage.
c The denominator is the number examined.
+,++,+++ Significant trend based on the Cochran-Armitage trend test at $p < 0.05$, 0.01 and 0.001, respectively.
*,*** Significantly different from controls based on the Fisher's exact test at $p < 0.05$ and 0.001, respectively.

To address the possible role of the stabilizer, propylene oxide, in the oncogenic response in the Trutter (1991) study, a new oncogenicity study was conducted with a reformulated technical grade propargite that contained epoxidized soybean oil as the stabilizer. Sixty male CD® rats /dose were fed the reformulated technical grade propargite (89.1% purity) in the diet at 0 or 800 ppm (0 or 36.3 mg/kg/day) for 2 years (Goldenthal, 1993). Ten rats/dose were sacrificed at 1 year. There was an increase in mortality in the treated males in the second year. No treatment-related clinical signs were observed. There was a significant reduction in food consumption (up to 23%) and body weights (up to 18%) in treated males. Increases in relative (to body) organ weights were seen in the brain, kidney, liver and testis that were probably related to the decreased body weights. Macroscopic and microscopic examination of the animals revealed an increase in undifferentiated sarcomas in the duodenum (2/47), jejunum (23/47) and soft tissue of the abdomen (1/1) of treated animals relative to controls (duodenum: 0/50; jejunum: 0/49; soft tissue, abdomen: 0/0). Most of the treated rats that died or were killed in a moribund condition on the study had undifferentiated sarcomas (19/28) compared to the survivors (4/17). This study indicates that the propargite itself, not the stabilizer, is responsible for the oncogenic response. This supplemental study was not intended to be a FIFRA guideline study and did not have enough dose levels to establish a NOEL.

To evaluate the possible role that necrosis and ulceration had in the oncogenic response in the Trutter (1991) study, a cell proliferation study was conducted (Eldridge, 1994). Technical grade propargite (88.64% purity) was administered in the diet to male CD rats at 0, 80 or 800 ppm, female CD rats at 0, 40 or 800 ppm and male CD-1 mice at 0 or1000 ppm up to 4 weeks. Twelve and 22 animals/sex were assigned to each of the control and treatment groups, respectively. At 1 and 4 weeks, half the animals were sacrificed and sections of the jejunum were collected for cell proliferation analysis. Three different smooth muscle layers were evaluated: the muscularis mucosa, and both the inner circular layer and the outer longitudinal layer of smooth muscle from the tunica muscularis. One week prior to sacrifice, osmotic pumps containing 5-bromo-2'-deoxyuridine (BrdU) were placed under the skin of the rats. Cells that incorporated BrdU were identified by staining of their nuclei. Cell proliferation was expressed as a unit length labeling index (ULLI; number of labeled cells per mm). The total ULLI for all three smooth muscle layers was significantly elevated (3-4 fold over controls) in both sexes at 800 ppm at week 1. The increase in the total ULLI was also statistically significant in males at 800 ppm at week 4; however, the investigators did not consider this increase biologically significant since the increase was less than two-fold over controls. There was no significant increase in the total ULLI in the male rats at 80 ppm, female rats at 40 ppm or male mice at 1000 ppm at either week 1 or week 4. The investigator noted that although the increase in cell proliferation was transient, that a transient increase in cell proliferation has been observed with mitogenic nongenotoxic carcinogens (Eldridge *et al.* 1992; Tilbury *et al.*, 1993). Furthermore, a NOEL was established for cell proliferation in this study at 80 ppm (4 mg/kg/day) in male rats and 40 ppm (2 mg/kg/day) in female rats. This was not a guideline study, but was conducted according to Good Laboratory Practice (GLP) regulations and provided useful information regarding the possible mechanism of action for the oncogenicity.

In order to understand the apparent lack of an oncogenic response in the Wistar rat, a second cell proliferation study was conducted in which Wistar (WKY) rats were fed technical grade propargite (88.64% purity) for 1 week at 0 ppm (6 rats/sex) or 900 ppm (11 rats/sex) (Eldridge, 1995). As before, osmotic pumps containing BrdU were implanted under the skin in the rats one week before the animals were sacrificed. The same three layers of smooth muscle from the jejunum were examined for cell proliferation. There was a statistically significant increase (200%) in the outer longitudinal layer of the tunica muscularis in females at 900 ppm, but the investigator did not think this was biologically meaningful since cell proliferation in the total smooth muscle was not significantly increased. The investigators suggested that this study may explain the apparent negative response in the FDRL (1966) study in Wistar rats.

Diet-Dog

Eight beagle dogs/sex/dose were fed propargite (purity not reported) in the diet at 0, 100, 300 or 900 ppm (0, 2.5, 7.5 or 22.5 mg/kg/day)[3] for 2 years (FDRL, 1966). At one year one dog/sex/dose was sacrificed and was examined for gross pathological lesions. Two dogs (1 male at 100 ppm and 1 female at 300 ppm) died from causes unrelated to treatment. There was no effect on body weights, food consumption, hematology, clinical chemistry, urinalysis, or gross or histopathological findings. The NOEL appears to be 900 ppm. This study was unacceptable to

[3] Estimated assuming for a dog that 1 ppm in the diet is equivalent to 0.025 mg/kg/day (FDA, 1959).

DPR toxicologists due to major deficiencies including no analysis of the diet, inadequate pathological examination and no evidence of toxicity at the highest dose level.

Diet-Dog

Omite technical (88.6% purity) was fed to 6 beagle dogs/sex/group in the diet at 0, 160, 1250 and 2500 ppm (4, 31 and 62 mg/kg/day)[4] for 1 year (Atkinson, 1991). At day 57 (week 8), the high-dose level was decreased to 1875 ppm (47 mg/kg/day) due to excessive body weight losses. At 1875 ppm, one male and one female were sacrificed in moribund condition. Both animals had marked body weight losses which were considered treatment-related. Moderate to marked decreases in body weights were observed at 1250 ppm (M: 18%, F: 20%) and 1875 ppm (M: 58%, F: 50%). Food consumption was reduced during weeks 1-8 when the high dose was 2500 ppm (M: 42-60%, F: 43-67%). After the high dose was reduced to 1875 ppm, the food consumption was still reduced (M: 9-25%, F: 1-20%), but the difference was no longer statistically significant except for females at week 9. The investigator suggested that palatability of the high-dose diet may have been a factor in the reduced food consumption. The investigator attributed the decreased body weights to the decreased food consumption; however, this does not explain the body weight reduction at 1250 ppm since there was no reduced food consumption at this dose level. Significant reductions in several hematological parameters were observed at 1250 and 1875 ppm, including RBC counts, hematocrit and hemoglobin values. A significant increase in platelet counts was also observed at 1250 and 1875 ppm. Increases in various relative organ weights (to body weight) were observed primarily at 1875 ppm (adrenal glands - M: 55%, F: 53%; liver - M: 53%, F: 35%; kidney - F: 31%; testes - M: 68%; thyroid/ parathyroid - M: 53%, F: 44%), but occasionally at 1250 ppm (liver - M: 38%, F: 28%). The absolute organ weights were decreased at 1875 ppm for several organs (heart - M: 39%, F: 40%; kidney - M: 34%, F: 33%; ovaries - F: 52%). Both the increased relative organ weights and the decreased absolute organ weights were attributed to reduced body weights by the investigator. Microscopic lesions in the stomach (vacuoles in parietal cells), thymus (involution) and bone marrow (erythroid/myeloid depletion/atrophy) were observed at 1250 ppm (stomach - M: 6/6, F: 4/6; thymus - F: 5/6) and 1875 ppm (stomach - M: 6/6, F: 5/6; thymus - M: 6/6, F: 4/5; bone marrow - M: 6/6, F: 5/6). Microscopic lesions in the lungs (foci of congestion or serosal subacute/chronic inflammation) were also observed in females at 160 and 1275 ppm, but not at 1875 ppm and, therefore, were not considered treatment related. The NOEL was 160 ppm (4 mg/kg/day) based on reduced body weights, hematological changes, increased relative liver weights and involution of the thymus. DPR toxicologists found this study acceptable based on FIFRA guidelines.

[4] Ibid.

II.E. GENOTOXICITY

Summary

There was no evidence of an increase in gene mutation in reverse mutation assays with *Salmonella typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100), *Saccharomyces cerevisiae* (D4 strain) and *Escherichia coli* (WP2 *hcr* strain). None of these assays were found acceptable by DPR toxicologists. A significant increase in mutation frequency was observed in a marginally acceptable forward mutation assay with Chinese hamster ovary (CHO) cells that measured mutations in the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus. However, analysis of the dosing solutions revealed that the propargite had either broken down or reacted with the vehicle, DMSO. More recent, well-conducted studies with acetone or DMSO as the vehicle at similar concentrations were negative. No evidence of chromosomal aberrations was found in an *in vitro* cytogenetics assay with CHO cells and an *in vivo* micronucleus cytogenetics assay in mice. Both of these tests were acceptable. A rec assay with *Bacillus subtilis* H17 (rec^+) and M45 (rec^-) strains and an unscheduled DNA synthesis (UDS) assay with rat primary hepatocytes were also negative. The rec assay was not acceptable to DPR toxicologists, but the UDS assay was acceptable. Based on these studies, it appears that the genotoxic potential of propargite in humans is low.

Gene Mutation

In a reverse mutation assay, *Salmonella typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100) was exposed to propargite (purity 91%) at 0, 0.001, 0.01, 0.1, 1.0 or 5.0 µl/plate with and without metabolic (S-9) activation (Brusick, 1977). Brusick also exposed *Saccharomyces cerevisiae* D4 strain to the same concentrations of propargite. There was no increase in mutation frequency with any strain at any concentration. DPR toxicologists found this study unacceptable due to multiple deficiencies. In another reverse mutation assay, propargite (purity 90.9%) was tested with *S. typhimurium* strains TA1535, TA1537, TA1538, TA100 and TA98 and *Escherichia coli* strain WP2 *hcr* at 0, 10, 50, 100, 500, 1000 or 5000 µg/plate with and without S-9 (Shirasu *et al.*, 1979). No increase in mutation frequency was observed with any strain at any concentration. This study was also unacceptable to DPR toxicologists due to insufficient replicates and questionable culture characteristics.

Three forward mutation assays with Chinese hamster ovary (CHO) cells that measured mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus were submitted to DPR by the registrant. In the first assay submitted, technical grade propargite (purity not stated) was tested at 0.01 to 15 µg/ml with and without S-9 using DMSO as the vehicle (Godek, 1987). Concentrations of 1.0 µg/ml or greater without S-9 resulted in reduced cell survival. At 0.05 to 0.75 µg/ml statistically significant increases in the mutation frequency were observed. Analysis of the dosing solutions revealed that propargite had either broken down or reacted with the DMSO. Therefore, propargite was tested again at 0.005 to 1.0 µg/ml without S-9 and 0.75 to 15 µg/ml with S-9 using acetone as the vehicle. There was no increase in mutation frequency with or without S-9. DPR toxicologists considered this study marginally acceptable with a possible genotoxic effect without activation. The registrant submitted two more assays, one with acetone as the vehicle and the other with DMSO as the vehicle. In the assay with acetone as the vehicle, propargite technical (90% purity) was tested at 0.5 to 5 µg/ml without S-9 and at 5 to 50

μg/ml with S-9 (Bigger and Clarke, 1993a). No increase in mutation frequency was observed with or without S-9. DPR toxicologists found this study acceptable based on the guidelines. In the assay with DMSO as the vehicle, propargite technical (90% purity) was tested at 0.2 to 5 μg/ml without S-9 and at 10 to 75 μg/ml with S-9 (Bigger and Clarke, 1993b). No concentration related increase in mutation frequency was seen with or without S-9 in this study. This study was also found acceptable by DPR toxicologists based on the guidelines.

Chromosomal Aberrations

An *in vitro* cytogenetics assay was conducted using cultured Chinese hamster ovary (CHO) cells with propargite (purity not stated) at 25 to 100 μg/ml without S-9 and 25 to 200 μg/ml with S-9 (Kirkland, 1985). No increase in chromosomal aberrations was observed when tested up to the limits of cytotoxicity. DPR toxicologists found this study acceptable. In a micronucleus cytogenetic assay, ICR mice were given a single intraperitoneal injection of propargite (89.56% purity) at 0 (corn oil), 37.5, 75, or 150 mg/kg (Putman and Young, 1994). Five mice/sex/dose were sacrificed at 24, 48 and 72 hours. The proportion of polychromatic erythrocytes to total erythrocytes was reduced in male and female mice at 75 and 150 mg/kg at 48 and 74 hours after treatment; however, there was no increase in micronucleated erythrocytes. This study was found acceptable by DPR toxicologists based on the FIFRA guidelines.

Other Genotoxic Effects

Shirasu *et al.* (1979) also conducted a rec-assay in which *Bacillus subtilis* H17 (rec^+) and M45 (rec^-) strains were exposed to propargite (90.9% purity) at 1 to 100% (v/v in DMSO). Propargite did not induce any inhibitory zone around either strain at all doses tested. DPR toxicologists found this study unacceptable since there were no replicates or repeats. In an unscheduled DNA synthesis (UDS) assay, rat primary hepatocytes were exposed to technical grade propargite (purity not stated) at 0.0167 to 5000 μg/ml for 18-20 hrs in triplicates (Barfknecht, 1987). UDS was quantified by autoradiography using ^{3}H-thymidine in 50 nuclei per slide. No evidence of treatment-related UDS was observed. This study was found acceptable by DPR toxicologists.

II.F. REPRODUCTIVE TOXICITY

Summary

Two reproductive toxicity studies in rats were available for propargite, the main study and an ancillary cross-fostering study. The main study was found acceptable based on FIFRA guidelines. The primary effect observed in the main study was a reduction in the body weights of both the adults and pups. Propargite had no effect on mating, fertility or gestation. There was also no treatment-related effect on macroscopic and microscopic lesions. The NOEL was 80 ppm (4 mg/kg/day) for both reproductive effects (reduced pup weights) and parental effects (reduced parental weights). The cross-fostering study was conducted to determine if the pup weight reduction was due to maternal toxicity or direct consumption of propargite in breast milk or the diet. The investigators suggested that the weight reductions are due to direct consumption of propargite in the diet by the pups since they were not observed until the latter half of the

lactation period, but DPR toxicologists concluded that dam-mediated effects could not be ruled out.

Diet-Rat

Propargite (87.2% purity) was administered to 25 Crl:CD BR (Sprague-Dawley) rats/sex/dose at 0 (corn oil and chow), 80, 400 or 800 ppm (0, 4, 20 or 40 mg/kg/day)[5] for two generations with 2 litters per generation (Kehoe, 1990). Body weights were significantly lower in both sexes of the F_0 generation during the premating phase and the gestation and lactation phases (postmating phase in males) for both matings at 400 ppm (M & F: 5-7%) and 800 ppm (M: 9-19%; F: 5-18%). Similar significant reductions were also observed in the F_{1b} generation, although the reductions were greater (M & F: 5-10% at 400 ppm and M: 26-29%, F: 15-22% at 800 ppm). Food consumption was also significantly reduced in both sexes during these periods at 400 ppm (M: 5-8%; F: 7-19%) and 800 ppm (M: 8-25%; F: 11-31%) in both generations, with the reductions being greater in the F_{1b} generation. Propargite had no effect on male fertility, mating, female fertility and gestation indices. Pup weights were significantly reduced at 400 ppm starting on lactation day 7 and at 800 ppm starting on lactation day 0. By lactation day 21, the pup weights were 8-14% lower (M & F) at 400 ppm and 36-43% lower (M & F) at 800 ppm. There were no treatment-related differences in macroscopic or microscopic lesions. The reproductive NOEL was 80 ppm (4 mg/kg/day) based on the postnatal growth reductions in pups. The parental NOEL was also 80 ppm (4 mg/kg/day) based on reduced parental body weights. This study was considered acceptable to DPR toxicologists based on the FIFRA guidelines.

Diet-Rat

In an ancillary cross-fostering reproduction study, 100, 60 and 120 Crl:CD VAF/Plus® rats/sex were exposed to propargite (89.87% purity) at 0, 400 or 800 ppm (0, 20 or 40 mg/kg/day)[6], respectively, for 70 days prior to delivery (York, 1992). On lactation day 0, litters were cross-fostered to dams in different groups or to other dams within the group. The dams were reassigned to smaller groups of 20, where possible, on the basis of the groups into which their offspring were born. There were 7 groups during the lactation period: 1) untreated dams with their own untreated litters, 2) untreated dams cross-fostered to untreated litters, 3) untreated dams cross-fostered to 400 ppm litters, 4) untreated dams cross-fostered to 800 ppm litters, 5) 400 ppm dams cross-fostered to untreated litters, 6) 800 ppm dams cross-fostered to untreated litters and 7) 800 ppm dams with their own 800 ppm litters. Treatment of dams continued for 3 weeks following cross-fostering. Pup weights were significantly reduced in untreated litters cross-fostered to dams treated at 400 ppm (M: 11-14%; F: 10-12%) on lactation days 14-21 and at 800 ppm (M: 17-30%; F: 17-29%) on lactation days 7-21. Reduced pup weights were not observed in treated litters cross-fostered to control dams. Pups weights were significantly reduced (M & F: 2%) on day 0 in litters of dams receiving 800 ppm who also had significantly reduced maternal weights (8%). This suggests that the reduced weights in pups at 800 ppm that were not cross-fostered during lactation was due to a combination of maternal toxicity and the

[5] Estimated assuming for a rat that 1 ppm in the diet is equivalent to 0.05 mg/kg/day (FDA, 1959).
[6] Ibid.

direct consumption of the diet by the pups during the latter half of the lactation period. On the other hand, pup weights were not reduced on day 0 in litters of dams treated at 400 ppm; therefore, reductions in pup weights at this dose level were primarily due to direct consumption of the treated diet by the pups. Since the reduction in pup weights did not occur in the untreated litters cross-fostered to treated dams in the early lactation period when the pups were too young to ingest the diet, the investigators suggested that the reduced pup weights was due to the direct consumption of the treated diet by pups rather than indirect exposure through nursing. However, DPR toxicologists concluded that dam-mediated effects could not be ruled out. Therefore, the NOEL for reproductive toxicity from the previous study was not changed; however, the extent of the concern for reproductive toxicity was reduced since there was no indication of reproductive toxicity during prenatal development.

II.G. DEVELOPMENTAL TOXICITY

Summary

Two rat and two rabbit teratology studies were available for propargite. All four studies were found acceptable by FIFRA guidelines. Maternal effects included mortalities, clinical signs (bloody nasal discharge, urinary incontinence, diarrhea, soft stools, abnormal respiration, vaginal discharge, adipsia, anorexia, alopecia, depression) and reduced body weights. The lowest maternal NOEL was 2 mg/kg/day based on reduced survival, body weight losses, anorexia and adipsia in rabbits. Developmental effects included abortions, resorptions, reduced fetal viability, minor skeletal variations related to delayed ossification, malaligned or fused sternebrae, hydrocephaly and reduced pup weight. The lowest developmental NOEL was also 2 mg/kg/day based on delayed ossification in rabbits.

Gavage-Rat

Propargite (84-88% purity) was administered by oral gavage to at least 20 pregnant female BLU:(SD) rats/dose at 0 (corn oil), 6, 25 or 105 mg/kg/day on gestation days (GDs) 6-15 (Knickerbocker, 1979). There was evidence of maternal toxicity at 105 mg/kg/day including 2 deaths and numerous clinical signs (bloody nasal discharge - onset GD 6, diarrhea - onset GD 7, soft stools - onset GD 8, urinary incontinence - onset GD 8, vaginal discharge - onset GD day 8, abnormal respiration - onset GD 8 and alopecia - onset GD 9). The deaths occurred on GDs 15 and 16. In addition, one dam at 105 mg/kg/day was sacrificed due to aggressive behavior. Terminal body weights were slightly reduced (3%) at 105 mg/kg/day, but the difference was not statistically significant. No treatment-related increase in external, skeletal or visceral malformations was seen. There was a slight increase in minor skeletal variations at 25 mg/kg/day (missing sternebrae, incomplete ossification of vertebrae and extremities, incomplete closure of skull and reduced or missing hyoid bones). DPR toxicologists considered the minor skeletal variations to be a result of delayed ossification which were possible developmental effects because they occurred in the absence of apparent maternal toxicity. The maternal NOEL was 25 mg/kg/day based on the deaths and clinical signs. The developmental NOEL was 6

mg/kg/day based on the skeletal variations. The study was considered acceptable to DPR toxicologists based on the FIFRA guidelines.

Gavage-Rat

In a subsequent study, 45 mated female Sprague-Dawley CRL:CD VAF/Plus rats were administered propargite (85% purity) by oral gavage at 0 (corn oil), 6, 12, 18, 25 and 105 mg/kg/day on GDs 6-15 (Schardein, 1990). Twenty litters per group were collected by C-section on day 20 and the remainder were delivered and raised to weaning. Anogenital and body staining and significantly reduced body weights (5-7%) were observed in the dams at 105 mg/kg/day on GDs 9-20. A reduction in the percentage of live pups delivered and an increase in the number of litters with dead pups during lactation occurred at 105 mg/kg/day. The maternal NOEL was 25 mg/kg/day based on reduced body weights and anogenital staining. The developmental NOEL was also 25 mg/kg/day based on the decreased number of live pups at delivery and reduced survival of pups during lactation. DPR toxicologists found this study acceptable based on FIFRA guidelines.

Gavage-Rabbit

Groups of 17 pregnant female New Zealand White rabbits/dose were administered propargite (85% purity) by oral gavage at 0 (corn oil), 2, 6, 10 or 18 mg/kg/day from GDs 6 through day 18 (Serota *et al.*, 1983). There was an increase in deaths at 6, 10 and 18 mg/kg/day, but was only statistically significant at 18 mg/kg/day (Table 10). There were also two deaths at 0 and 2 mg/kg/day which appear to be related to misdosing based on pathological findings in the trachea (dark red lining or material, thick foamy material) and/or thoracic cavity (red fluid). One rabbit that died at 18 mg/kg/day may have also been misdosed based on dark red material in the trachea. Clinical signs were observed within the first 3 days of dosing at these same dose levels, including adipsia (absence of thirst or abnormal avoidance of drinking of water - onset GD 8) and anorexia (onset GD 7). Since food or water consumption were not measured in this study, these observations were presumably based on full feeders and water bottles. A dose-response relationship was apparent by GD 9 for anorexia and by GD 14 for adipsia. Depression (onset GD 11) and soft feces (onset GD 10) was also observed at 10 and 18 mg/kg/day. Dose-related maternal body weight losses were seen between days 6 and 18 at 6, 10 and 18 mg/kg/day (3%, 8% and 18%, respectively), but they were only statistically significant at 18 mg/kg/day. These body weight losses were seen as early as GD 11[7], but were not as severe (3%, 4% and 9% at 6, 10 and 18 mg/kg/day, respectively). The percentage of resorptions was twice as high at 10 and 18 mg/kg/day compared to controls. The percent fetal viability (number of live fetuses divided by the number of implantations multiplied by 100) was reduced at 10 and 18 mg/kg/day (73.5% and 78%, respectively) relative to controls (88.5%). The differences were not statistically significant, but the investigators considered them treatment-related. The mean pup body weights were also reduced (M: 9%; F: 14%) relative to controls at 18 mg/kg/day. A significant increase in delayed ossification of the skull (Grade 3) occurred at 6 and 10 mg/kg/day. Three fetuses had enlarged, domed heads or hydrocephaly, one at 10 mg/kg/day and the other two at 18 mg/kg/day.

[7]GD11 was the next time maternal body weights were taken after the first day of dosing, GD6.

Table 10. Possible Adverse Effects in a Pregnant Rabbits Administered Propagite By Gavage During Gestation Days 6-18.[a]

Possible Adverse Effect	Dose Level (mg/kg/day)				
	0	2	6	10	18
Doe Death (%)	2/17 (12%)	2/17 (12%)	3/17 (18%)	4/17 (24%)	13/17* (76%)
Adipsia	6/17 (35%)	3/17 (18%)	7/17 (41%)	11/17 (65%)	15/17* (88%)
Anorexia	6/17 (35%)	5/17 (29%)	8/17 (47%)	11/17 (65%)	15/17* (88%)
Body weight gain days 6-18 (g)	8±257	61±94	-110±308	-313±387	-683±178*
Pups Resorptions (mean #/litter)	1.0±1.6	1.0±1.0	0.7±1.0	1.8±1.5	1.5±1.7
Live pups (mean #/litter)	7.7±2.8	6.6±2.4	6.7±2.1	5.6±2.8	5.3±1.7
Body weights (g) M	41.3±6.1	44.3±5.1	39.7±7.8	41.9±8.4	37.7±1.8
F	39.6±7.2	42.3±7.6	40.2±8.4	42.3±9.2	34.2±3.3
Hydrocephaly (pups affected) (litters affected)	 0/115 0/15	 0/92 0/14	 0/74 0/12	 1/62 1/11	 2/21* 1/4
Delayed ossification of skull (pups affected) (litters affected)	 5/115 3/15	 4/92 3/14	 9/74* 6/12	 8/62* 4/11	 2/21 1/4
Malaligned or fused sternabrae (pups affected) (litters affected)	 0/115 0/15	 2/92 2/14	 2/74 2/12	 5/62* 3/11	 0/21 0/4

a Serota *et al.*, 1983.
b Incidence on dosing day 4 (GD 9) was 3/16, 0/16, 3/17, 1/17 and 3/16 at 0, 2, 6, 10 and 18 mg/kg/day, respectively.
c Incidence on dosing day 4 (GD 9) was 2/16, 2/16, 4/17, 6/17 and 11/16 at 0, 2, 6, 10 and 18 mg/kg/day, respectively.

The two fetuses at 18 mg/kg/day occurred in the same litter, so the increase at 18 mg/kg/day was only statistically significant when expressed on a pup basis. One of the fetuses at 18 mg/kg/day also had dilated lateral and third ventricles. The other two fetuses (1 at 10 mg/kg/day and 1 at 18 mg/kg/day) had severe delayed ossification of the skull (Grade 2) which was considered an anomaly, rather than a variant. This would suggest that the hydrocephaly may be secondary to the delayed skull ossification, at least in some instances. A significant increase in malaligned or fused sternebrae was found at 10 mg/kg/day. The low incidence rate and lack of statistical

significance, of the delayed ossification of the skull and malaligned or fused sternebrae at 18 mg/kg/day was considered to be due to the small number of fetuses available for examination at this dose level. The investigators considered all these developmental effects, except possibly the hydrocephaly, to be related to maternal toxicity. The delayed ossification in the skull and fused or malaligned sternebrae were usually associated with reduced maternal weight gain or weight loss during treatment. The maternal NOEL was 2 mg/kg/day based on body weight losses and clinical signs. The developmental NOEL was also 2 mg/kg/day based on delayed ossification of the skull. DPR toxicologists found this study to be acceptable based on FIFRA guidelines.

Gavage-Rabbit

In a second rabbit teratology study, 25 inseminated female New Zealand White (SPF) rabbits/dose were administered propargite (85% purity) by gavage at 0 (corn oil), 2, 4, 6, 8 or 10 mg/kg/day on GDs 7 through 19 (Schardein, 1989). One female each died at 6 mg/kg/day (day 28) and 8 mg/kg/day (day 22) after they aborted. Eight other does were killed after they aborted on days 18-25 (Table 11). No abortions occurred below 4 mg/kg/day. The study investigators considered only the abortions at 10 mg/kg/day to be treatment related because they occurred at the highest dose level and they were accompanied by other signs of toxicity. DPR toxicologists initially considered the abortions at 4, 6 and 8 mg/kg to also be treatment-related, however, the study investigator provided additional information that one doe at 6 mg/kg/day that had red material in pan did not abort since all implantation sites were accounted for by resorptions and that one abortion at 8 mg/kg/day occurred when the doe died and was probably secondary to the death. Therefore, these abortions are not included in Table 11. The study investigator also argued that the 3 abortions at 4 mg/kg/day were spontaneous providing historical control data from studies conducted between 1988 and 1990 showing several studies with at least 2 abortions in control animals, although none with 3 abortions. The lack of a dose response at the lower doses and the absence of abortions in Serota *et al.* study in which rabbits were dosed up to 18 mg/kg/day also supports that the 3 abortions at 4 mg/kg/day were spontaneous. It is unclear if the one abortion at 8 mg/kg/day that was not associated with maternal death was treatment-related. Based on this supplemental information, DPR toxicologists then revised the maternal NOEL to 6 mg/kg/day based on the body weight reductions. However, on further review for this risk assessment it was noted that there was a noticeable dose-related reduction in the mean body weight gain even at 6 mg/kg/day, although the differences in the body weight gain were not statistically significant at any dose level (due to the large variation). When examining the individual animal data, it was noted that the number of does with weight loss were significantly increased by trend analysis, but the differences were not significant by Fisher's exact test. It was also noted that there was an increase in the incidence of decreased defecation at 6 mg/kg/day and higher which may be related to the reduced body weight gains (Table 11). The incidence was significantly different from controls at 6, 8 and 10 mg/kg/day. The earliest onset (GD 9) was at the lowest dose. Due to the later onset in the other groups (GDs 13-14), the decreased defecation was considered a cumulative effect. One rabbit at 10 mg/kg/day was noted as emaciated which may also be related to the reduced body weight gains. Food consumption was not monitored in this study so it is not possible to confirm that the reduced body weight gain and decreased defecation was due to reduced food consumption. However, since a dose-related increase in anorexia was seen in the Serota *et al.* study, it seems very likely that there was reduced food consumption and/or anorexia in this study, too. The only other treatment related effect was an increase in fused sternebrae at 10 mg/kg/day. Therefore, the maternal NOEL for this study was

identified as 4 mg/kg/day based on decreased defecation and reduced body weight gains at 6 mg/kg/day and higher. The developmental NOEL was 8 mg/kg/day based on the increased fused sternebrae. The study was found acceptable by DPR toxicologists based on the FIFRA guidelines.

Table 11. Possible Adverse Effects in a Pregnant Rabbits Administered Propargite By Gavage During Gestation Days 7-19.[a]

Possible Adverse Effect	Dose Level (mg/kg/day)					
	0	2	4	6	8	10
Doe Aborted	0/25[+] (0%)	0/25 (0%)	3/25 (12%)	0/25 (0%)	1/25 (8%)	4/25[b] (16%)
Decreased defecation	5/25[+++] (20%)	6/25 (24%)	9/25 (36%)	12/25* (48%)	14/25* (56%)	13/25* (52%)
Emaciated	0/25 (0%)	0/25 (0%)	0/25 (0%)	0/25 (0%)	0/25 (0%)	1/25 (4%)
Mean body weight gain - GDs 7-20 (g)	114±188	165±133	119±253	38±291	9±267	-20±308
No. with body weight loss - GDs 7-20	4/19[++] (21%)	1/16 (6%)	3/18 (17%)	6/19 (31%)	9/20 (45%)	7/17 (41%)
Pups - Fused sternebrae (pups affected) (litters affected)	0/106[+++] 0/17[++]	2/101 1/15	1/121 1/17	0/139 1/18	2/125 2/18	9/116** 6/16**

a Schardein, 1989.
b Based on Fisher's exact test p= 0.055.
*, ** Significantly different from controls by Fisher's exact test at $p < 0.05$ and 0.01, respectively.
+,++,+++ Significant trend based on the Cochran-Armitage trend test at $p < 0.05$, 0.01 and 0.001, respectively.

III. RISK ASSESSMENT

III.A. HAZARD IDENTIFICATION

III.A.1 Acute Toxicity

The studies considered in the selection of the acute NOELs for propargite are summarized in Table 12. The studies included LD_{50}/LC_{50} studies and the developmental toxicity studies. The effects observed in the LD_{50}/LC_{50} studies included death, clinical signs, reduced body weights, dermal irritation with dermal exposure, gastrointestinal abnormalities, dark red adrenal glands and jaundice with oral exposure and discoloration or red lungs with all routes of exposure. The clinical signs included vocalization, abnormal defecation, decreased urination, inappetence, dehydration, hypothermia, ataxia, hypersensitivity to touch, moist rales, hair loss, scabbing and swelling around mouth, ears, and urogenital areas and staining around nose and urogenital area. Dermal irritation included severe erythema and edema, eschar, fissuring, desquamation, exfoliation and white-yellow exudate. The dose levels were too high in the LD_{50}/LC_{50} studies to establish NOELs for these effects.

Some of the effects observed in the developmental toxicity studies were considered acute, including maternal signs observed within the first 4 days of exposure and fetal effects that could be the result of one or two days of exposure, such as pre- and post-implantation losses, and skeletal and visceral malformations. Various clinical signs were seen in dams/does in several developmental toxicity studies during the first 4 days of treatment. These signs included bloody nasal discharge, diarrhea, soft stools, urinary incontinence, vaginal discharge, abnormal respiration and alopecia in rats, and anorexia and adipsia in rabbits (Knickerbocker, 1979; Serota *et al.*, 1983). Reduced maternal body weight gains were observed in one rat developmental toxicity study and in both rabbit developmental toxicity studies; however, it was unclear if these were acute effects since the maternal body weights were often not measured frequently enough to determine the onset. However, in the one rat study, reduced maternal body weights (5-7%) were observed by treatment day 4 at 105 mg/kg/day (Schardein, 1990). Several fetal effects were noted in the developmental toxicity studies including delayed or incomplete ossification of the vertebrae, extremities, skull and hyoid bones, fused or malaligned sternabrae, hydrocephaly, abortions and reduced fetal viability. It is possible that the skeletal variations, such as delayed ossification, were the result of repeated dosing and/or related to maternal toxicity, but the assumption was made that these variations, especially the delayed ossification, were due to one or two doses since the maternal anorexia occurred very early on in the treatment period. Some fetal effects, late abortions (earliest occurrence on treatment day 13 at 10 mg/kg/day) and dead fetuses at term, were not considered acute. It appears from the developmental toxicity studies that rabbits are more sensitive to propargite than rats. The lowest NOEL in the developmental toxicity studies was 2 mg/kg based on anorexia in pregnant rabbits that was observed as early as treatment day 2 at 6 mg/kg/day (Serota *et al.*, 1983). A dose-related trend in the incidence of anorexia was observed by day 4 of dosing. Although adipsia was observed as early as day 3 of treatment, a dose-related trend in the incidence was not apparent until day 9 of dosing; therefore. it was considered a subchronic rather than an acute effect. The treatment-related trend in

Table 12. Acute and Short-term Effects of Propargite and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg)	LOEL (mg/kg)	Ref.[a]
Inhalation					
Rat[b]	Single, 4-hour nose only	Death, clinical signs, ↓ body wts., discolored lungs	-----	50	1*
Oral					
Rat[b]	Single, gavage	Numerous clinical signs[c]	-----	2000	2*
Rat[d]	10 days, gavage	Maternal: Clinical signs[e] Fetal: Skeletal variations related to delayed ossification	25 6	105 25	3*
Rat[d]	10 days, gavage	Maternal: ↓Body weight (day 4)	25	105	4*
Rabbit[d]	**13 days, gavage**	**Maternal: Anorexia (day 2), Fetal: Delayed ossification**	**2**	**6**	5*
Rabbit[d]	13 days, gavage	Fetal: Fused sternebrae	8	10	6*
Dermal					
Rabbit[f]	Single, 4-hr	Severe dermal irritation	-----	85[g]	7*
Rabbit[b]	Single, 24-hr	Clinical signs[h], reddened lungs Severe dermal irritation	----- -----	4000 23[g]	8*
Rabbit[i]	**6-hrs/day, 5 days/wk, 3 wks**	**No clinical signs or ↓ body weight during first week**	**100**	**HDT**	**9***
Rabbit[i]	**6-hrs/day, 5 days/wk, 3 wks**	**Slight to moderate erythema (day 1)**	**(0.7)[g,j]**	**2.1[g]**	**10**

a References: 1.Hoffman, 1992a; 2.Kiplinger, 1993a; 3. Knickerbocker, 1979; 4. Schardein, 1990; 5. Serota *et al*., 1983; 6. Schardein, 1989; 7. Kiplinger, 1993c; 8. Kiplinger, 1993b; 9. Bailey, 1987; 10. Goldenthal, 1989.

b LC_{50}/LD_{50} study

c Clinical signs include vocalization, abnormal defecation, decreased urination, inappetance, dehydration, hypothermia, ataxia, hypersensitivity to touch, moist rales, hair loss, scabbing and swelling around mouth, ears, and urogenital areas, staining around nose and urogenital area.

d Developmental toxicity study: All fetal effects were considered acute effects; however, only maternal effects observed within the first few days of exposure were considered acute exposure.

e Bloody nasal discharge (day 1), diarrhea (day 2), soft stools (day 3), urinary incontinence (day 3), vaginal discharge (day 3), abnormal respiration (day 3) and alopecia (day 4).

f Dermal irritation study

g NOEL and LOEL for dermal irritation was expressed in mg/cm^2 since it was local effect.

h Vocalization, abnormal defecation, decreased urination, inappetance, dehydration, hypothermia, ataxia, hypersensitivity to touch, moist rales, hair loss, scabbing and swelling around mouth, ears, and urogenital areas, staining around nose and urogenital area

i 21-Day dermal toxicity study

j NOEL estimated by dividing by an uncertainty factor of 3 due to the mild effects at the LOEL.

* Acceptable study based on FIFRA guidelines

anorexia was supported by maternal body weight losses in this study between treatment days 1 and 6. Delayed ossification was also observed at this dose level in the fetuses. The delayed ossification may be related to the maternal weight losses. A higher NOEL was observed in a similar rabbit developmental toxicity study that was conducted later by Schardein (1989), but there were no major deficiencies in the Serota *et al.* study that would justify dismissing the findings in this study.

Ideally, a NOEL from an inhalation study would be preferable to use for evaluating inhalation exposure. However, the only inhalation study was an LC_{50} study where a NOEL was not established. Furthermore, one death was observed at the lowest dose level so that there is more uncertainty in extrapolating from the LOEL to a NOEL. The other option is to evaluate inhalation exposure using a NOEL from an oral study and perform route-to-route extrapolation. There is also uncertainty associated with this extrapolation, but the uncertainty associated with the route-to-route extrapolation seemed smaller when compared to extrapolating to a NOEL when death was observed at the LOEL. The lowest NOEL in an oral study was 2 mg/kg in a rabbit developmental toxicity study where anorexia was observed at 6 mg/kg on day 2 of exposure (Serota *et al.*, 1983). In addition, delayed ossification was observed in the fetuses. After adjusting for oral absorption (40%), the critical NOEL selected to evaluate all acute inhalation exposures to propargite was 0.8 mg/kg. The acute RfC for propargite was estimated to be 14 and 29 $\mu g/m^3$ for children and adults, respectively, assuming 0.59 and 0.28 m^3/kg/day for their respective breathing rates.

The dermal LD_{50} study was the only acute dermal study that evaluated systemic effects. A BMD analysis could not be performed on this study because the rabbits were only tested at one dose level. A number of clinical signs (vocalization, abnormal defecation, decreased urination, inappetence, dehydration, hypothermia, ataxia, hypersensitivity to touch, moist rales, hair loss, scabbing and swelling around mouth, ears, and urogenital areas, staining around nose and urogenital area) and reddened lungs were observed at 4000 mg/kg, the only dose level tested. A NOEL of 400 mg/kg was estimated for systemic effects by dividing the LOEL by a default uncertainty factor of 10. However, with only one dose level tested it unclear if this default uncertainty factor is adequately protective. Therefore, the 21-day dermal toxicity studies for propargite were examined for signs acute toxicity. In both studies systemic effects were observed by the study termination, but there were no effects at any dose level that could be considered acute, including clinical signs or reduced body weights during the first week of exposure. Furthermore, no reddened lungs were seen at study termination which had been seen in the acute toxicity study. Therefore, the highest dose level tested in these two 21-day dermal toxicity studies, 100 mg/kg/day, was selected as the critical NOEL for evaluating acute dermal exposure to propargite. Since dermal exposure estimates for agricultural workers are expressed as absorbed doses, the acute dermal NOEL was adjusted by the dermal absorption (17%). The adjusted acute dermal NOEL is 17 mg/kg. The acute RfD for dermal exposure is 0.17 mg/kg/day.

Propargite caused severe dermal irritation in various animals studies. There have also been a number of outbreaks of moderate to severe dermatitis among workers exposed to propargite (see section I.E. for details). Due to concern about these incidents, a NOEL was

estimated for this endpoint. Dermal irritation was observed in two acute studies, the dermal LD_{50} study and the dermal irritation study. Since dermal irritation is a local effect, concentration on the skin was considered the more appropriate expression of dosage rather than on a body weight basis. To estimate the concentration at the application site the dosage was multiplied by the weight of the animal and then divided by the area of the application site. NOELs were not observed for this endpoint in either study and only one concentration was tested in both studies. The LOEL in the dermal irritation study was 85 mg/cm^2 with severe dermal irritation after 4 hours of exposure. The LOEL in the dermal LD_{50} study was 23 mg/cm^2 with severe dermal irritation after 24 hours of exposure. Occupational exposure is assumed to be 8 hours, so a study with a more similar exposure duration would be preferable. Consequently, the 21-day dermal toxicity studies were examined to see if dermal irritation was observed after the first day of exposure since the daily exposure duration was 6 hours. The 21-day dermal study by Bailey (1987) was not used because the dermal observations were not made daily and the vehicle (acetone) caused dermal irritation in itself. In the 21-day dermal study conducted by Goldenthal (1989), observations were made daily before the application. Slight to moderate erythema was observed at the lowest dose level tested (0.1 mg/kg/day or 2.1 mg/cm^2) on day 2, presumably before the application. Since the dermal irritation after one exposure was so mild compared to after 21 days of exposure, the acute (6-hr) NOEL was estimated to be 0.7 mg/cm^2 by dividing the LOEL by an uncertainty factor of 3 instead of 10. Various studies have shown that rabbits are more sensitive than guinea pigs or humans with regards to dermal irritation and, therefore, the 10-fold uncertainty factor for interspecies variation was dropped when calculating the RfC for this endpoint (see Risk Appraisal section for further discussion of this issue).

Propargite also caused dermal sensitization in the guinea pig maximization test with the technical material (Morris, 2003) and in the Buehler patch test with the wettable powder formulations (Kreuzman, 1986; Hoffman, 1994). Recent reviews of contact sensitization conclude that there are thresholds for this endpoint (Kimber *et al.*, 1999; Boukhman and Maibach, 2001). Felter *et al.* (2003) proposed a method for quantitatively evaluating the risk for dermal sensitization using results from the mouse local lymph node assay which provides dose response data that can be used to estimate relative potency. Since this assay was not available for propargite, it was not possible to evaluate quantitatively the risk for this endpoint. It would appear from the animal data that propargite is probably a stronger irritant than a sensitizer since not all the dermal sensitization studies with the Buehler test were positive while severe dermal irritation was observed in the all of the dermal irritation studies. Furthermore, the investigators of the outbreak of dermatitis among nectarine harvesters in 1988 concluded the dermatitis was an irritation response not an allergic response. However, due to concerns about the dermal sensitization potential of propargite an additional uncertainty factor of 3 is recommended to be used in evaluating dermal exposure resulting in an acute RfC of 23 $\mu g/cm^3$ for local dermal effects.

III.A.2. Subchronic Toxicity

The studies considered in the selection of a subchronic NOEL for propargite are summarized in Table 13. In the subchronic toxicity studies, the most common systemic effect was reduced body weights or body weight gain, regardless of route. Reductions in food

consumption were also seen. Changes in hematological and clinical chemistry values were observed in a dermal study in rabbits, including increased ASAT, globulin, white blood cell count, segmented neutrophils, monocytes and platelets, and reduced albumin and calcium. The veterinary pathologist for one dermal study suggested that the hematological and clinical chemistry changes may be related to the dermal irritation (Bailey, 1987). The reduced body weights might also be secondary to the dermal irritation if the animals are stressed. Increased relative liver, kidney, adrenal gland and/or gonad weights were observed in several studies. It is unclear if these organ weight changes are related to reduced body weights or organ toxicity. Pathological findings in these subchronic studies included increased pigment in reticuloendothelial cells of the liver and hemosiderosis of the spleen in dogs and chronic nephritis, liver inflammation and necrosis in rabbits.

In addition to the standard subchronic toxicity studies, Table 13 includes several developmental toxicity studies where maternal effects were observed after short-term exposure for 1 to 2 weeks. The systemic maternal toxicity observed after short-term exposure to propargite included death, bloody nasal discharge, diarrhea, soft stools, urinary incontinence, anogenital staining, vaginal discharge, abnormal respiration, anorexia, adipsia and alopecia (Knickerbocker, 1979; Serota *et al.*, 1983; Schardein, 1990). Reduced maternal weight gain or weight loss were also seen (Schardein, 1989 & 1990; Serota *et al.*, 1983). Increased late-term abortions and dead fetuses were also seen and were considered the result of cumulative toxicity (Schardein, 1989 & 1990; Serota *et al*., 1983). The lowest NOEL in an acceptable developmental toxicity study was 2 mg/kg/day based on anorexia, adipsia, reduced body weight and reduced survival in pregnant rabbits (Serota *et al.*, 1983).

The effects observed in the reproductive toxicity study were considered subchronic and, therefore, included in Table 13. The effects observed in the parental generations of the reproductive toxicity study for propargite included reduced body weights and food consumption. The effects observed in pups were reduced postnatal growth. In the one acceptable study, the parental NOEL of 4 mg/kg/day (80 ppm) was based on reduced body weights (5-10%) (Kehoe, 1990). The pup NOEL in this study was also 4 mg/kg/day based on reduced postnatal growth.

No subchronic inhalation studies were available for propargite. Therefore, an oral study was selected to evaluate subchronic inhalation exposure to propargite. The lowest subchronic oral NOEL was 2 mg/kg observed in the rabbit developmental toxicity study conducted by Serota *et al*. (1983). Adipsia, reduced survival and body weight gain were seen in addition to the anorexia and delayed ossification at the LOEL(6 mg/kg/day), These effects were considered subchronic since they were not observed early in the exposure period. Therefore, the critical NOEL for evaluating subchronic inhalation exposure was 0.8 mg/kg, after adjusting for oral absorption (40%), based on reduced anorexia, adipsia, reduced body weight gain and reduced survival. The subchronic inhalation RfC for propargite was estimated to be 14 and 29 $\mu g/m^3$ for children and adults, respectively, assuming 0.59 and 0.28 m^3/kg/day for their respective breathing rates.

Table 13. Short-term or Subchronic Effects of Propargite and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[a]
Oral					
Rat[b]	10 days, gavage	Maternal: Deaths, clinical signs	25	105	1*
Rat[b]	10 days, gavage	Maternal: Anogenital staining, ↓body weights Fetal: ↓Survival	25	105	2*
Rabbit[b]	**14 days, gavage**	**Maternal: Anorexia, adipsia, ↓ body wt. gain, ↓ survival**	**2**	**6**	**3***
Rabbit[b]	14 days, gavage	Maternal: ↓Defecation, ↓ body weight gain	4	6	4*
Rat[c]	2-gen., 10 wks premating, diet	Parental: ↓Body weights Pups: ↓ Postnatal growth	4	20	5*
Rat	90-days, diet	↓ Body wt., ↓food consumption	40	110	6
Dog	13 weeks, diet	↓ Body wts. and food cons., ↑ASAT, ↑ liver wt., ↑ pigment in reticuloendothelial cells of liver	-----	50	7
Dermal					
Rabbit	**6 hrs/day, 5 days/wk, 3 wks**	**Systemic: ↓Body wts., changes in clinical chemistry and hematology values, ↑ relative liver and kidney wts.** Local: Dermal irritation	**1** (0.01)[d,e]	**10** 0.1	**8***
Rabbit	**6 hrs/day, 5 days/wk, 3 wks**	Systemic: Chronic nephritis, inflammation of liver **Local: Erythema, edema, eschar, exfoliation, atonia, desquamation, fissuring, blanching, coriaceousness**	-----[f] **(0.21)[d,e]**	100 **2.1**	**9**

a References: 1. Knickerbocker, 1979; 2. Schardein, 1990; 3. Serota *et al.*, 1983; 4. Schardein, 1989; 5. Kehoe, 1990; 6. Carson, 1964; 7. Hazelton, 1968; 8. Bailey, 1987; 9. Goldenthal, 1989.
b Developmental toxicity study: Only maternal effects observed after the first few days were included.
c Reproductive toxicity study
d NOEL estimated by dividing the LOEL by an uncertainty factor of 10.
e NOEL and LOEL for dermal irritation expressed in mg/cm^2 since it was a local effect.
f The liver and kidney were not examined microscopically at 0.1, 1 or 10 mg/kg/day.
* Acceptable study based on FIFRA guidelines

To evaluate subchronic dermal exposure, two 21-day dermal toxicity studies in rabbits were considered. A LOEL of 100 mg/kg/day was reported in a 21-day dermal study conducted by Goldenthal (1989), however, this study was not considered acceptable for evaluating systemic effects because the low and mid-dose level animals did not have their kidneys and livers examined microscopically even though chronic nephritis and inflammation of the liver were seen in the high-dose animals. Therefore, the 21-day dermal toxicity study conducted by Bailey (1987) was selected for evaluating subchronic dermal exposure to propargite. The systemic NOEL for this study was 1 mg/kg/day based on reduced body weights (F: 14- 20%), changes in clinical chemistry and hematology values, and increased relative liver and kidney weights in rabbits. After adjusting for dermal absorption (17%), the internal dermal NOEL is 0.17 mg/kg/day. The subchronic RfD for dermal exposure is 1.7 μg/kg/day applying a default 100-fold uncertainty factor to the NOEL.

Dermal irritation was also observed in the 21-day dermal toxicity studies. In the study conducted by Bailey (1987), dermal irritation was observed at all dose levels, however, acetone was used as a vehicle which may have exacerbated the dermal irritation. Dermal irritation was also observed at all dose levels in another study conducted by Goldenthal (1989) where propargite was applied neat. Although this study was not considered acceptable for identifying a systemic NOEL due to incomplete histopathological examination of the kidneys and liver, the skin was examined histopathologically at all dose levels. Therefore, this study was considered acceptable for evaluating dermal irritation. Slight to moderate erythema and edema, eschar, exfoliation, atonia, desquamation, fissuring, blanching and coriaceousness were seen at the lowest dose level, 0.1 mg/kg or 2.1 mg/cm^2 (concentration reported by the investigator). The estimated NOEL for dermal irritation with subchronic exposure was 0.21 mg/cm^2 by dividing by a default uncertainty factor of 10. The subchronic RfC for local dermal effects is 7 μg/cm^2 applying a 30-fold uncertainty factor, 10 for intraspecies variation and 3 to protect against dermal sensitization.

III.A.3. Chronic Toxicity

The studies considered for selecting the chronic NOEL for propargite are summarized in Table 14. Reduced body weights (M: 4-58%, F: 2-50%) and food consumption (M: 2-60%, F: 2-67%) were the most prevalent effects observed with chronic exposure. Reduced survival was observed in two rat studies. Changes in hematological values were seen in both rats and dogs. These included significant increases in platelets and reticulocytes and significant decreases in RBC counts, hematocrit and hemoglobin values. Changes in clinical chemistry values were also seen in rats. This included significant reductions in glucose, total protein, globulin, calcium, ASAT, ALAT and a significant increase in albumin levels. Most of these changes were of uncertain toxicological significance, although the reductions in many of the clinical chemistry values may be related to reduced food consumption. Increases in organ weights were observed in mice, rats and dogs, including absolute adrenal gland (F:46-50%), thyroid (F:60%), and uterus (F: 75%) weights and relative liver (M: 38-53%; F: 17-38%), kidney (M: 10-12%, F: 31-35%), brain (M: 12%, F: 33%), adrenal gland (M: 46-55%, F: 46-53%), testes (M: 68%) and thyroid/parathyroid (M: 53%, F: 44-64%) weights. Decreases in the absolute weight of a few

Table 14. Chronic Effects of Propargite and Their Respective NOELs and LOELs

Species	Exposure	Effect	NOEL (mg/kg/day)	LOEL (mg/kg/day)	Ref.[a]
Mouse	18 months, diet	None	150	-----	1*
Rat	2 years, diet	↓ Survival, ↓body wts., ↓food consumption (Miscellaneous sarcomas)	45 (15)	100 (45)	2
Rat	**2 years, diet**	**↓ Body wts., ↓food consumption, (Sarcomas of jejunum)**	**3.8 (3.8)**	**19.2 (19.2)**	**3***
Rat	2 years, diet	↓ Survival, ↓body wts., ↓food consumption, ↑ relative organ wts. (Sarcomas of sm. intestine and abdomen)	----- (-----)	36.3 (36.3)	4
Dog	2 years, diet	None	22.5	-----	5
Dog	1 year, diet	↓ Body wts., ↓ RBC, Hct and Hgb, ↑ platelets, ↑ relative liver wts., involution of the thymus	4	31	6*

a References: 1. Cox and Re, 1979; 2. FDRL, 1966; 3. Trutter, 1991; 4. Goldenthal, 1993; 5. FDRL, 1966; 6. Atkinson, 1991.

* Acceptable study based on FIFRA guidelines

organs were seen, including the heart (M: 39%, F: 40%), kidney (M: 34%, F: 33%) and ovaries (F: 52%). Most of these organ weight changes were probably related to body weight reductions. Microscopic lesions in the lungs (congestion or inflammation), thymus (involution) and bone marrow (atrophy) were seen in one dog study at 1250 ppm and higher. Mice appear to be less sensitive to long-term exposure to propargite than rats and dogs based on the available studies.

As with subchronic toxicity, no chronic inhalation studies available for propargite, therefore, a NOEL from an oral study was selected to evaluate inhalation exposure and route-to-route extrapolation was performed. The lowest NOEL in an oral chronic toxicity study was 3.8 mg/kg based on reduced body weights and food consumption in rats in the 2-year feeding study conducted by Trutter (1991). Therefore, this study was selected as the definitive study for evaluating chronic inhalation exposure with a critical NOEL of 1.5 mg/kg/day after adjusting for oral absorption (40%). The chronic inhalation RfC for propargite was estimated to be 26 and 54 $\mu g/m^3$ for children and adults, assuming breathing rates of 0.59 and 0.28 m^3/kg/day for their respective breathing rates.

The Trutter study was not used to evaluate chronic dermal exposure because a lower NOEL was observed in the acceptable 21-day dermal toxicity study in rabbits conducted by Bailey (1987). Therefore, the 21-day dermal toxicity study conducted by Bailey (1987) was selected as the definitive study for evaluating chronic dermal exposure to propargite after

adjusting for dermal absorption, 17%. No additional uncertainty factor for extrapolating from subchronic to chronic was applied since the lowest oral NOELs for the subchronic and chronic toxicity studies in rats were comparable. Therefore, the critical NOEL for evaluating chronic dermal exposure was the same as that used for evaluating seasonal exposure, 1.0 mg/kg/day, based on reduced body weights, changes in clinical chemistry and hematological values and increased liver and kidney weights in rabbits. The adjusted NOEL was 0.17 mg/kg/day. The chronic RfD for dermal exposure to propargite was estimated to be 1.7 μg/kg/day.

A chronic NOEL for dermal irritation was not established not only because there are no chronic dermal toxicity studies, but also because there is some question whether it was logical to amortize dermal exposure over the year to evaluate the risk for this endpoint. Dermal irritation is a local effect that was assumed to be concentration dependent. Therefore, the risk for dermal irritation should be the greatest during the peak season where there could be daily exposure for several months. Consequently, the risk for dermal irritation from chronic exposure was not evaluated assuming it would be less than the risk from seasonal exposure.

III.A.4. Oncogenicity - Weight of Evidence

There is evidence that propargite is oncogenic based on an increase in undifferentiated sarcomas of the jejunum in Sprague-Dawley rats (Table 9) (Trutter, 1991). The increases in this rare tumor were statistically significant by pairwise comparison with controls in males at 400 ppm and in both sexes at 800 ppm. There was also a significant positive trend for these tumors in both sexes. Ulceration and ectatic mucosal glands at the tumor site were often associated with these tumors. In another study with Wistar rats (FDRL, 1966), there was an apparent dose-related increase in sarcomas of the intestine with characteristics resembling the undifferentiated sarcomas observed in the jejunum of Sprague Dawley rats in the Trutter (1991) study. These sarcomas included spindle cell sarcomas, myosarcomas and osseous sarcomas. These sarcomas occurred in 1 male at 300 ppm, 3 males and 1 female at 900 ppm and 3 males and 1 female at 2000 ppm. The incidence of the undifferentiated sarcomas in the jejunum of Wistar rats was significant in males by trend analysis and by pairwise comparison at 2000 ppm.

There was a shortening of the time to tumor when males at 400 and 800 ppm from the Trutter (1991) study were compared. The average time to tumor at 400 and 800 ppm was 99.5 and 90.2 weeks, respectively. The shortest time to tumor (65 weeks) was in a male at 800 ppm. The jejunal sarcomas were considered the cause of death in 8 of 11 rats at 400 ppm and 20 of 24 rats at 800 ppm.

A consultant pathologist noted that propargite was ulcerogenic at the doses that caused tumors in the Trutter (1991) study, allowing the lumenal exposure of the submucosal mesenchymal cells. He examined 10 additional jejunal step sections in 26 males at 0 and 800 ppm from this study. At 800 ppm, 5 males had focal epithelial necrosis and 2 of these were large ulcers with submucosal stromal and inflammatory responses. The smallest lesions were crypt abscesses filled with necrotic cell debris and surrounded by attenuated epithelium, portions of which were necrotic. No crypt abscesses, ulcers, epithelial necrosis or other similar lesions were found in the control animals.

It should be noted that although no jejunal sarcomas were seen in the mouse oncogenicity study, this study was only 18 months long and may have reduced their sensitivity to detect increases in these tumors. In addition, no overt signs of toxicity were seen at the highest dose level.

To evaluate the possible role necrosis and ulceration had in the oncogenic process, a cell proliferation study was conducted (Eldridge, 1994). Male and female Sprague-Dawley rats and male CD-1 mice were fed propargite in the diet for up to 4 weeks. There was no significant increase in cell proliferation in the jejunum in male rats at 80 ppm, female rats at 40 ppm, or male mice at 1000 ppm at either week 1 or 4. However, there was a significant increase in cell proliferation in the jejunum in both sexes of rats at 800 ppm at week 1. The cell proliferation was also significantly increased in males at 800 ppm at week 4, but was not considered biologically significant by the investigator since the increase was less than 2-fold over the controls. The investigator noted that, although the increase in cell proliferation was transient, transient increases in cell proliferation have been observed with mitogenic nongenotoxic carcinogens. However, other researchers at the National Institutes of Health (NIH) maintain that transient increases in cell proliferation are not sufficient to induce liver cancer with nongenotoxic carcinogens like phenobarbital (Melnick and Huff, 1993). A second cell proliferation study was conducted to evaluate the apparent lack of response in the Wistar rat (Eldridge, 1995). There was a statistically significant increase (200%) in the outer longitudinal layer of the tunica muscularis in females at 900 ppm, although the investigator did not think this was biologically meaningful since cell proliferation in the total smooth muscle was not significantly increased.

The consulting pathologist also suggested that the propylene oxide stabilizer in technical grade propargite formulations may have been responsible for the tumors since it is genotoxic. To investigate this further, another 2-year chronic toxicity study was conducted in which 60 male Sprague-Dawley rats were fed reformulated technical grade propargite in the diet at 0 and 800 ppm. An increase in undifferentiated sarcomas in the duodenum, jejunum and soft tissue of the abdomen were observed. Most of the treated rats that died or were killed in a moribund condition had undifferentiated sarcomas (19/28) compared to controls (4/17).

The genotoxicity studies for propargite were all negative except one marginally acceptable HPRT gene mutation assay in CHO cells. In this study, the propargite in the dosing solution had either broken down or reacted with the vehicle, DMSO. More recent, well-conducted HPRT gene mutation assays were negative using either acetone or DMSO as the vehicle at similar concentrations. The other negative genotoxicity studies included reverse mutation assays with *Salmonella typhimurium* (strains TA1535, TA1537, TA1538, TA98 and TA100), *Saccharomyces cerevisiae* (D4 strain) and *Escherichia coli* (WP2 *hcr* strain), an *in vitro* cytogenetics assay with CHO cells, an *in vivo* micronucleus cytogenetics assay in mice, a rec assay with *Bacillus subtilis* H17 (rec^+) and M45 (rec^-) strains and an unscheduled DNA synthesis (UDS) assay with rat primary hepatocytes. The two chromosomal aberration studies and the UDS assay were found acceptable by DPR toxicologists, however, the UDS assay is relatively insensitive and there was no Comet assay or other oxidative DNA damage assay for propargite.

U.S. EPA did a structure activity analysis for propargite in their carcinogenicity peer review (U. S. EPA, 1992). The structure of propargite is similar to aramite (2-chloroethyl 1-methyl-2-(*p*-tert-butylphenoxy)ethyl sulfite). Exposure to aramite has been associated with various tumors in dogs (gallbladder and bile duct adenocarcinomas), rats (hepatocellular carcinomas), and mice (hepatomas). There was no indication that aramite caused an increased incidence of jejunal sarcomas. A computer analysis of the structure activity of propargite with two databases (CIS and TOXNET) did not indicate any additional toxicity information.

III.A.5. Quantitative Assessment of Oncogenic Effects

The weight of evidence for propargite was considered sufficient to do a quantitative assessment of the oncogenical potential because 1) the increase in jejunal sarcomas was statistically significant by pairwise comparison with controls in both sexes; 2) the incidence of the jejunal sarcomas exhibited a significant dose-related trend in both sexes; 3) jejunal sarcomas are a rare tumor type; 4) sarcomas of the intestine and other tissues were observed in two other supplemental studies (FDRL, 1966; Goldenthal, 1993); and 5) there was a shortening of the time to tumor. There was some evidence to suggest that propargite may be acting by a threshold mechanism: 1) an increase in cell proliferation and 2) essentially all negative genotoxicity studies. However, the increase in cell proliferation is only transient and it has been suggested that transient increases are not sufficient to cause cancer (Melnick and Huff, 1993). Furthermore, the incidence of ulceration at the tumor site was less than the incidence of jejunal sarcomas which is not what would be expected if increased cell proliferation was a precursor to tumor development. Therefore, the available evidence was not considered sufficient to assume a threshold mechanism was involved and a linear low-dose extrapolation approach was used as a default. The oncogenic potency of propargite was calculated using the incidence of jejunal sarcomas in male Sprague Dawley rats in the study conducted by Trutter (1991).

U.S. EPA classified propargite as a B_2 carcinogen based on the jejunal tumors in rats (U.S. EPA, 2001a). There was a dose-related increase in deaths at the high dose which suggests that the Weibull time-to-tumor model would be the most appropriate model. Although the registrant argued with U.S. EPA that the Weibull time-to-tumor model was not the most appropriate model when the deaths were due to tumors, their argument was not persuasive since no clear explanation was given as to why it was inappropriate (U.S. EPA, 2001b). The registrants had the K.S. Crump Group of ICF, the developers of the Weibull time-to-tumor model, evaluate the tumor data. These consultants compared the fit of the Weibull time-to-tumor model with a multistage quantal model from Tox_Risk software using the Akaike Information Criterion (AIC) values. The fit of the multistage quantal model was very good whereas the fit for the Weibull time-to-tumor model was poor. Because the fit was so poor for the Weibull time-to-tumor model, the confidence interval and corresponding upper confidence limit on risk were quite large. The consultants determined they were unable to get a good fit with the Weibull time-to-tumor model because the software was unable to optimize the model parameters. They were able to "reparameterize" the model and get a better fit; however, they found the AIC still indicated the multistage quantal model had a better fit. Based on this information, U.S. EPA decided to calculate the oncogenic potency of propargite using the multistage quantal model.

They calculated the Q_1* (i.e., 95th upper bound estimate for potency) for propargite to be 3.3 x 10^{-2} $(mg/kg/day)^{-1}$.

Since the developer of the software indicated that there is a poor fit with Weibull time-to-tumor model due to its inability to optimize the model parameters and it is not possible to "reparameterize" the model, the BMDS software developed by U.S. EPA (version 2.2) was used to estimate the potency. The U.S. EPA Guidelines for Carcinogen Risk Assessment recommends using a linear approach when the mode of action is not known (U.S. EPA, 2005). They also recommend using a benchmark dose as a point of departure from the observed data to do a linear extrapolation to the origin. The incidence of tumors was expressed in terms of rats at risk (i.e., rats that survived 52 weeks on the study). The dosages for male rats (0, 2.4, 3.8, 19.2 or 38.9 mg/kg/day) were first converted to human equivalent dosages (0, 0.7, 1.2, 5.8 or 11.8 mg/kg/day) by multiplying by an interspecies scaling factor of body weight to the 3/4 power $[(BWt_A/BWt_H)^{0.25} = (0.6 \text{ kg}/70 \text{ kg})^{0.25} = 0.304]$. All of the quantal models available on the BMDS software were run and the multistage model had the best fit for this data based on the AIC values. The ED_{10} (benchmark dose with an estimated excess lifetime tumor incidence of 10%) and LED_{10} (lower limit on ED_{10}) were estimated to be 4.23 and 2.97 mg/kg/day, respectively. The slope or potency factors were then estimated by dividing the risk at these dose levels (10% or 0.1) by ED_{10} and LED_{10}. The cancer potency estimates were 2.4 x 10^{-2} $(mg/kg/day)^{-1}$ for the maximum likelihood estimate (MLE) and 3.4 x 10^{-2} $(mg/kg/day)^{-1}$ for the 95th percent upper bound (95% UB). The 95% UB estimate is essentially the same that U.S. EPA estimated except U.S. EPA did not calculate a MLE. To evaluate dermal and inhalation exposure, the potencies were converted to an internal dose by dividing by the oral absorption (40%). The internal or absorbed potencies were 5.9 x 10^{-2} $(mg/kg/day)^{-1}$ for the MLE and 8.4 x 10^{-2} $(mg/kg/day)^{-1}$ for the 95% UB. Generally, RfDs/RfCs are not calculated for carcinogenicity since it is assumed there is no threshold for this endpoint. However, it is possible to calculate a dose or air concentration at which the carcinogenic risk is negligible. To do this, the negligible risk level (1 x 10^{-6}) is divided by the 95% UB estimate of carcinogenic potency. For propargite, the RfD corresponding to a negligible carcinogenic risk is 12 ng/kg/day (absorbed). This absorbed RfD was converted to an external dermal RfD of 70 ng/kg/day by dividing by the dermal absorption (17%). Assuming 100% inhalation absorption, the absorbed RfD for carcinogenicity was converted to an air concentration by dividing by the estimated breathing rate for an adult male (0.28 m^3/kg/day), to obtain an RfC for carcinogenicity of 43 ng/m^3 (3.0 ppt). This RfC is the air concentration below which there would be no regulatory concern for carcinogenic effects.

III.A.6. Critical Endpoints, NOELs and Reference Doses

The critical endpoints, NOELs, and reference concentrations/doses (RfDs/RfCs) used for evaluating occupational and ambient air exposure to propargite are presented in Table 15. When converting NOELs to RfDs, they are initially converted to absorbed doses by multiplying times an absorption factor (17% for dermal, 40% for oral) and amortizing exposure duration to daily exposure. To calculate the reference dose or concentration, the NOEL was divided by an uncertainty factor. For systemic effects, a total uncertainty factor of 100 was used for

Table 15. Endpoints, NOELs and Reference Concentrations Used for Evaluating Occupational and Residential Air Exposure to Propargite

Exposure Scenario	NOEL/ENEL[a]	Effects on LOEL	RfD/RfC		Ref.[b]
Inhalation Exposure					
Systemic Acute / Seasonal	0.8 mg/kg (absorbed[c])	Maternal: Anorexia, adipsia, reduced body wt. gain, reduced survival Fetal: Delayed ossification	Children 8 µg/kg (14 µg/m^3)	Adults 8 µg/kg (29 µg/m^3)	1
Systemic Chronic	1.5 mg/kg/day (absorbed[c])	↓ Body weights and food consumption	Children 15 µg/kg/day (25 µg/m^3)	Adults 15 µg/kg/day (54 µg/m^3)	2
Dermal Exposure					
Local Acute	0.7 mg/cm^2	Erythema in rabbits after 6-hr exposure	23 µg/cm^2		3
Local Seasonal/ Chronic	0.21 mg/cm^2	Erythema, edema, eschar, exfoliation, atonia, desquamation, fissuring, blanching, coriaceous-ness in rabbits	7 µg/cm^2		3
Systemic Acute	17 mg/kg (absorbed[d])	No clinical signs or ↓ body weight during first week (no reddened lungs after 3 weeks) in rabbits	170 µg/kg (absorbed)		4
Systemic Seasonal/ Chronic	0.17 mg/kg/day (absorbed[d])	↓ Body weights, changes in clinical chemistry and hematology values, ↑ relative liver and kidney weights in rabbits	1.7 µg/kg/day (absorbed)		4
Lifetime Exposure - Inhalation and Dermal					
Cancer Potency	8.4 x 10^{-2} (mg/kg/day)$^{-1}$ (absorbed)	Jejunal sarcomas in male rats	12 ng/kg/day (absorbed)		2

a ENEL = estimated no effect level

b References: 1. Serota *et al.*, 1983; 2. Trutter, 1991; 3. Goldenthal, 1989; 4. Bailey, 1987.

c Oral NOEL converted to absorbed dose to evaluate inhalation exposure assuming 40% oral absorption.

d Dermal NOEL converted to absorbed dose assuming for 17% dermal absorption.

intraspecies variation (10-fold) and interspecies variation (10-fold). For local effects, it was assumed the effects were concentration dependent only so there was no adjustment for exposure duration and humans were no more sensitive than animals. Therefore, only an intraspecies factor of 10 was applied. For local dermal effects, a 30-fold uncertainty factor was applied, 10 for intraspecies variation and 3 for skin sensitization concerns.

III.B. EXPOSURE ASSESSMENT

III.B.1 Occupational Exposure

All the products currently registered in California are for agricultural use, therefore, there should be no exposure to the general public in residential, recreational or other public settings, except from dietary and drinking water residues or drift from agricultural applications. There were only three chemical-specific exposure studies for propargite. All of these studies were found unacceptable for estimating handler exposure because only one worker was used as a test subject (Dong, 2012). Therefore, exposure estimates for handlers were derived using the Pesticide Handler Exposure Database (PHED) developed by U.S. EPA, Health Canada and the American Crop Protection Association. PHED provides mean exposure estimates, but does not provide sufficient information to allow calculation of an upper bound estimate. A method for approximating the upper bound from PHED data was developed by the Worker Health and Safety Branch which multiplied the mean by constants that increased as the number of observations decreased (Powell, 2002). The 95th percentile is used for acute exposure to estimate the highest exposure an individual may realistically experience while performing label-approved activities. When the acute exposure estimate is based on surrogate data (i.e., PHED), the 90% upper confidence limit on the 95th percentile is used to account for some added uncertainty with using surrogate data.

Nine exposure scenarios were identified for agricultural workers: application by aerial, airblast, and groundboom equipment, mixing/loading for aerial, airblast, and for groundboom application, flagging for aerial application and mixing/loading and application by handheld equipment and reentry by fieldworkers. The handler exposure scenarios were further divided by formulation type: emulsifiable concentrate (EC) and water soluble bags (WSB). The mean daily exposure estimate from PHED is referred to as the Absorbed Daily Dosage (ADD). Since separate dermal and inhalation NOELs were selected for evaluating acute, seasonal and chronic exposure to propargite, the ADDs were broken down into dermal and inhalation exposure. The dermal absorption rate was assumed to be 17%. The dermal absorption value is based on the upper end of the range calculated in reviews of several studies with non-technical formulations (Thongsinthusak, 1989&1990). Default assumptions of 100% inhalation absorption and 70 kg body weight were used in the calculation of the ADD. The default inhalation absorption was used in the absence of any chemical specific data. A multiplier was applied to the ADD to approximate the 90% upper confidence limit on the 95th percentile for acute exposure. For seasonal exposure estimates, the ADD is multiplied by a different constant that approximates the 90% upper confidence limit of the arithmetic mean. The seasonal exposure estimate is referred to as the Seasonal Absorbed Daily Dosage (SADD). The chronic exposure estimates were based on the SADD with an adjustment for number months of use per year. It was estimated that

propargite is used approximately 4 months out of the year. The chronic exposure estimates were referred to as the Annual Absorbed Daily Dosage (AADD). For evaluating cancer risk, chronic exposure estimates were adjusted for potential years of occupational exposure during a lifetime which was assumed to be 40 years out of lifetime of 75 years. The exposure estimates used for evaluating cancer risk were referred to as the Lifetime Absorbed Daily Dosage (LADD). The LADD was not divided into dermal and inhalation LADDs since all the animal cancer studies for propargite were oral studies. Therefore, the exposure from both routes was combined.

The exposure estimates for applicators are summarized in Table 16. The lowest dermal exposure for applicators was with groundboom application of EC formulations (acute ADD: 15.6 µg/kg/day; SADD: 3.9 µg/kg/day; AADDs: 1.3 µg/kg/day). The highest dermal exposures were with aerial application of WSB formulations (acute ADD: 5,193.6 µg/kg/day; SADDs: 1,731.2 µg/kg/day; AADDs: 577.1 µg/kg/day). Aerial application with the EC formulations resulted in the highest inhalation exposure (acute ADD: 110.0 µg/kg/day; SADDs: 44.0 µg/kg/day; AADDs: 14.7 µg/kg/day). Groundboom application had the lowest inhalation exposure, especially with the EC formulations (acute ADD: 16.8 µg/kg/day; SADDs: 4.2 µg/kg/day;

Table 16. Estimated Exposure Dosages of Propargite for Applicators[a]

Exposure Scenarios	Acute ADD[b] µg/kg/day		SADD[c] µg/kg/day		AADD[d] µg/kg/day		LADD[e] µg/kg/day
	Derm.[f]	Inhal.[f]	Derm.	Inhal.	Derm.	Inhal.	Combined
EC[g]							
Aerial	584.4	110.0	194.8	44.0	64.9	14.7	42.5
Airblast	361.6	69.6	90.4	17.4	30.1	5.8	19.2
Groundboom	15.6	16.8	3.9	4.2	1.3	1.4	1.4
WSB[g]							
Aerial	5,193.6	97.5	1731.2	39.0	577.1	13.0	314.7
Airblast	3,858.4	74.4	964.6	18.6	321.5	6.2	174.8
Groundboom	187.2	20.0	46.8	5.0	15.6	1.7	9.2

a The dermal and inhalation exposure estimates were calculated from Table 7 in the EAD for propargite by Dong (2012).

b ADD = Absorbed Daily Dosage. For handlers, average dermal ADD = [(dermal exposure - µg/lb AI handled) x (17% dermal absorption) x (acres/day) x (application rate lb AI/acre)] / (70 kg body weight). The average inhalation ADD = [(inhalation exposure - µg/lb AI handled) x (100% default inhalation absorption) x (acres/day) x (application rate - lb AI/acre)] / (70 kg body weight). Acres treated per day assumptions differed for each application method. The acres applied per day were 600, 50 and 100 for aerial, airblast and groundboom scenarios, respectively. The application rates were 3, 3 and 1.5 lbs/acre for aerial, airblast and groundboom scenarios, respectively, except for groundboom application of EC at 2.5 lbs/acre. The acute ADD = average ADD x acute multiplier. The multiplier represents the 90% upper confidence limit on the 95th percentile that was derived from Pesticide Handlers Exposure Database (PHED, 1995).

c SADD = Seasonal Absorbed Daily Dosage = average ADD x seasonal multiplier. The seasonal multiplier represents the 90% upper confidence limit on the mean estimate that was derived from PHED.

d AADD = Annual Average Daily Dosage which is the SADD x (4 annual use months per year) / 12 months.

e LADD = Lifetime Average Daily Dosage which is the AADD x (40 years of work in a lifetime) / (75 years in a lifetime).

f Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure

g EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

AADDs: 1.4 µg/kg/day). As with the dermal exposure, the combined LADDs were lowest for groundboom applicators of EC formulations (1.4 µg/kg/day) and highest for aerial applicators of WSB formulations (314.7 µg/kg/day). The inhalation exposure represented the highest percentage of total exposure with groundboom application of EC formulations (52%), probably because the dermal exposure was relatively low compared to other applicator scenarios. By comparison, the inhalation exposure was relatively low (2%) with aerial and airblast applicators of WSB formulations.

Table 17 summarizes the propargite exposure estimates for mixer/loaders (M/Ls). In general, the lowest exposure was seen in M/Ls with EC formulations. The dermal exposure for M/Ls was lowest for groundboom application of EC formulations (acute ADD: 17.6 µg/kg/day; SADDs: 4.4 µg/kg/day; AADDs: 1.5 µg/kg/day). The highest dermal exposure was seen in M/Ls for aerial application of WSB formulations (acute ADD: 536.2 µg/kg/day; SADDs: 214.0 µg/kg/day; AADDs: 71.3 µg/kg/day). M/Ls for groundboom application of EC formulations also consistently had the lowest inhalation exposures among M/Ls (acute ADD: 3.2 µg/kg/day; SADDs: 0.8 µg/kg/day; AADDs: 0.3 µg/kg/day). The highest inhalation exposure among M/Ls

Table 17. Estimated Exposure Dosages of Propargite for Mixer/Loaders[a]

Exposure Scenarios	Acute ADD[b]		SADD[c]		AADD[d]		LADD[e]
	µg/kg/day		µg/kg/day		µg/kg/day		µg/kg/day
	Derm.[f]	Inhal.[f]	Derm.	Inhal.	Derm.	Inhal.	Combined
EC[g]							
Aerial	95.6	18.4	23.9	4.6	8.0	1.5	5.0
Airblast	32.0	6.4	8.0	1.6	2.7	0.5	1.6
Groundboom	17.6	3.2	4.4	0.8	1.5	0.3	1.0
WSB[g]							
Aerial	536.2	48.0	214.0	19.2	71.3	6.4	41.5
Airblast	213.9	19.0	85.4	7.6	28.5	2.5	16.6
Groundboom	129.7	12.0	51.8	4.8	17.3	1.6	10.0

a The dermal and inhalation exposure estimates were calculated from Table 8 in the EAD for propargite by Dong (2012).

b ADD = Absorbed Daily Dosage. For handlers, average dermal ADD = [(dermal exposure - µg/lb AI handled) x (17% dermal absorption) x (acres/day) x (application rate lb AI/acre)] / (70 kg body weight). The average inhalation ADD = [(inhalation exposure - µg/lb AI handled) x (100% default inhalation absorption) x (acres/day) x (application rate - lb AI/acre)] / (70 kg body weight). Acres treated per day assumptions differed for each application method. The acres applied per day were 600, 100 and 100 for aerial, airblast and groundboom scenarios, respectively. The application rates were 3, 3 and 1.5 lbs/acre for aerial, airblast and groundboom scenarios, respectively, except for groundboom application of EC at 2.5 lbs/acre. The acute ADD = average ADD x acute multiplier. The multiplier represents the 90% upper confidence limit on the 95th percentile that was derived from Pesticide Handlers Exposure Database (PHED, 1995).

c SADD = Seasonal Absorbed Daily Dosage = average ADD x seasonal multiplier. The seasonal multiplier represents the 90% upper confidence limit on the mean estimate that was derived from PHED.

d AADD = Annual Average Daily Dosage which is the SADD x (4 annual use months per year) / 12 months.

e LADD = Lifetime Average Daily Dosage which is the AADD x (40 years of work in a lifetime) / (75 years in a lifetime).

f Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure

g EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

was with aerial application of WSB formulations (acute ADD: 48.0 µg/kg/day; SADDs: 19.2µg/kg/day; AADDs: 6.4 µg/kg/day). Not surprisingly, the M/Ls with the lowest LADDs were M/Ls for groundboom application of EC formulations (1.0 µg/kg/day) and the M/Ls for aerial application of WSB formulations have the highest LADDs (41.5 µg/kg/day). The inhalation exposure of M/Ls using the EC formulations was generally higher for all types of application as a percentage of their total exposure (18-20%) compared to the M/Ls using WSB formulations (~9%) due to the greater dermal exposure with the latter.

The exposure estimates for mixer/loader/applicators (M/L/As) using hand held equipment and human flaggers are summarized in Table 18. Hand-held equipment was only used with the WSB formulations, whereas the human flaggers could be used with the aerial application of both formulations. The highest dermal exposure was seen in flaggers with the aerial application of WSB formulations (acute ADD: 1,012.0 µg/kg/day; SADD: 253.0 µg/kg/day; AADD: 84.3 µg/kg/day). On the other hand, the lowest dermal exposure occurred in

Table 18. Estimated Exposure Dosages of Propargite for Mixer/Loaders/Applicators and Human Flaggers

Exposure Scenarios	Acute ADD[b]		SADD[c]		AADD[d]		LADD[e]
	µg/kg/day		µg/kg/day		µg/kg/day		µg/kg/day
	Derm.[f]	Inhal.[f]	Derm.	Inhal.	Derm.	Inhal.	Combined
Flagger							
EC[g]	113.6	30.8	28.4	7.7	9.5	2.6	6.4
WSB[h]	1012.0	27.6	253.0	6.9	84.3	2.3	46.2
M/L/A[i] with WSB							
Low Pressure	82.0	33.5	16.4	6.7	5.5	2.2	4.1
High Pressure	189.5	24.5	75.8	9.8	25.3	3.3	15.2
Backpack	146.5	0.6	48.8	0.2	16.3	0.07	8.7

a The dermal and inhalation exposure estimates were calculated from Table 9 in the EAD for propargite by Dong (2012).

b ADD = Absorbed Daily Dosage. For handlers, average dermal ADD = [(dermal exposure - µg/lb AI handled) x (17% dermal absorption) x (acres/day) x (application rate lb AI/acre)] / (70 kg body weight). The average inhalation ADD = [(inhalation exposure - µg/lb AI handled) x (100% default inhalation absorption) x (acres/day) x (application rate - lb AI/acre)] / (70 kg body weight). Acres treated per day assumptions differed for each application method. The acres applied per day were 600, 5 and 1 for flagger, high pressure M/L/A and low pressure and backpack M/L/A scenarios, respectively. The application rates were 3 and 0.45 lbs/acre for flagger and M/L/A scenarios, respectively. The acute ADD = average ADD x acute multiplier. The multiplier represents the 90% upper confidence limit on the 95th percentile that was derived from Pesticide Handlers Exposure Database (PHED, 1995).

c SADD = Seasonal Absorbed Daily Dosage = average ADD x seasonal multiplier. The seasonal multiplier represents the the 90% upper confidence limit on the mean estimate that was derived from PHED.

d AADD = Annual Average Daily Dosage which is the SADD x (4 annual use months per year) / 12 months.

e LADD = Lifetime Average Daily Dosage which is the AADD x (40 years of work in a lifetime) / (75 years in a lifetime).

f Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure

g EC = Emulsifiable Concentrate

h WSB = Water Soluble Bag

i M/L/A = Mixer/Loader/Applicator

M/L/As using low pressure equipment with WSB formulations (acute ADD: 82.0 μg/kg/day; SADD: 16.4μg/kg/day; AADD: 5.5 μg/kg/day). The inhalation exposure for flaggers was not that different from M/L/As with hand-held equipment. The lowest inhalation exposure was seen with backpack M/L/As of WSB formulations (acute ADD: 0.6 μg/kg/day; SADD: 0.2 μg/kg/day; AADD: 0.07 μg/kg/day). The M/L/As with low pressure equipment had the highest acute inhalation exposure (acute ADD: 33.5 μg/kg/day) while those using high-pressure equipment had the highest seasonal inhalation exposure (SADD: 9.8 μg/kg/day; AADD: 3.3 μg/kg/day). The scenarios with the highest and lowest LADDs (flaggers with WSB - 46.2 μg/kg/day and M/L/As with WSB using low pressure equipment - 4.1 μg/kg/day , respectively) were the same as those with the highest and lowest seasonal and chronic dermal exposure. Among these exposure scenarios, inhalation exposure represented the lowest percentage of the total exposure in M/L/As using backpack sprayers (0.4%) and highest percentage in M/L/As using low pressure equipment (29%).

To evaluate dermal irritation, the dermal ADD for the body and hands was converted to concentration by first multiplying the ADD by the body weight (i.e., 70 kg) and dividing by the dermal absorption. This dermal dose was then divided by surface area to get the dermal concentration. The surface area of the body minus the hands was assumed to be 20,290 cm^2. The surface area of the hands was assumed to 820 cm^2. Dermal concentrations were calculated for acute and seasonal exposure using this technique. No chronic dermal concentration was calculated because it was questionable whether it was logical to amortize dermal exposure over the year to evaluate the risk for this endpoint. Dermal irritation is a local effect that was assumed to be concentration dependent. Therefore, the risk for dermal irritation should be the greatest during the peak season where there could be daily exposure for several months. The dermal concentrations for applicators is summarized in Table 19. The concentration on the hands was always higher than the body, regardless of whether gloves were worn or not, although the concentration was usually higher by at least an order of magnitude when gloves were not worn.

The dermal concentration was lowest on the body with the EC formulations, especially with groundboom application (acute: 0.1 $\mu g/cm^2$; seasonal: 0.02 $\mu g/cm^2$). The highest dermal concentration among applicators was on the hands with aerial application of WSB formulations where no gloves were required (acute: 1,691.1 $\mu g/cm^2$; seasonal: 563.7 $\mu g/cm^2$). Table 20 summarizes the dermal concentrations for M/Ls. With M/Ls, the lowest dermal concentration was on the body using equipment for groundboom application with EC formulations (acute: 0.06 μg/kg/day; seasonal: 0.02 μg/kg/day). The highest dermal concentration among M/Ls was on the hands of those involved in aerial application of EC formulations (acute: 38.4 $\mu g/cm^2$; seasonal: 9.6 $\mu g/cm^2$). The dermal concentrations for M/L/As and human flaggers is summarized in Table 21. For M/L/As and flaggers, the highest dermal concentration was on the hands of flaggers with WSB formulations (acute: 70.5 $\mu g/cm^2$; seasonal: 17.6 $\mu g/cm^2$). The lowest dermal concentration was on the hands of M/L/As with backpack equipment (acute : 0.03 μg/kg/day; seasonal: 0.01 μg/kg/day).

Table 19. Estimated Dermal Concentrations of Propargite for Applicators[a]

Exposure Scenarios	Acute DC[b] µg/cm²		Seasonal DC[c] µg/cm²	
	Body[c]	Hand	Body	Hand
EC[d]				
Aerial	4.2	190.4	1.4	63.5
Airblast	4.5	70.7	1.1	17.7
Groundboom	0.1	5.4	0.02	1.4
WSB[d]				
Aerial	37.1	1691.1	12.4	563.7
Airblast	47.8	755.2	11.9	188.8
Groundboom	1.2	64.5	0.3	16.1

a Dermal concentration estimates from Tables 10 and 13 in the EAD for propargite by Dong (2012).

b DC = Dermal Concentration. For handlers, DC = [average body or hand ADD (µg/kg/day) x 70 kg body weight / 17% dermal absorption] / (surface area of body or hands) x multiplier for appropriate exposure duration. The surface area of the body (minus the hands) and the hands were assumed to be 20,290 and 820 cm^2, respectively.

c Body = Dermal concentration for the whole body, except the hands.

d EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

Table 20. Estimated Dermal Concentrations of Propargite for Mixer/Loaders[a]

Exposure Scenarios	Acute DC[b] µg/cm²		Seasonal DC[c] µg/cm²	
	Body[c]	Hand	Body	Hand
EC[d]				
Aerial	0.4	38.4	0.1	9.6
Airblast	0.1	12.8	0.03	3.2
Groundboom	0.06	7.1	0.02	1.8
WSB[d]				
Aerial	10.8	1.5	4.3	0.4
Airblast	4.4	0.6	1.7	0.2
Groundboom	2.6	0.4	1.0	0.08

a Dermal concentration estimates from Tables 11 and 14 in the EAD for propargite by Dong (2012).

b DC = Dermal Concentration. For handlers, DC = [average body or hand ADD (µg/kg/day) x 70 kg body weight / 17% dermal absorption] / (surface area of body or hands) x multiplier for appropriate exposure duration. The surface area of the body (minus the hands) and the hands were assumed to be 20,290 and 820 cm^2, respectively.

c Body = Dermal concentration for the whole body, except the hands.

d EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

Table 21. Estimated Dermal Concentrations of Propargite for Mixer/Loader/Applicators and Human Flaggers[a]

Exposure Scenarios	Acute DC[b] µg/cm^2		Seasonal DC[c] µg/cm^2	
	Body[c]	Hand	Body	Hand
Flagger				
EC[d]	2.0	7.9	0.5	2.0
WSB[e]	17.7	70.5	4.4	17.6
Mixer/Loader/Applicator[f]				
Low Pressure	1.3	9.3	0.3	1.9
High Pressure	3.7	4.8	1.5	1.9
Backpack	3.0	0.03	1.0	0.01

a Dermal concentration estimates from Tables 12 and 15 in the EAD for propargite by Dong (2012).

b DC = Dermal Concentration. For handlers, DC = [average body or hand ADD (µg/kg/day) x 70 kg body weight / 17% dermal absorption] / (surface area of body or hands) x multiplier for appropriate exposure duration. The surface area of the body (minus the hands) and the hands were assumed to be 20,290 and 820 cm^2, respectively.

c Body = Dermal concentration for the whole body, except the hands.

d EC = Emulsifiable Concentrate

e WSB = Water Soluble Bag

f With WSB

The dermal exposures for fieldworkers were calculated from dislodgeable foliar residues (DFRs) and transfer factors (TFs) taking into consideration the number of hours in a workday and the average body weight. For acute exposure, the DFR at the re-entry interval (REI) (or pre-harvest interval (PHI), if applicable) was used. For seasonal exposure, the DFR at the average REI was assumed to be the REI plus 3 days. The REIs varied from 7 days (corn detasselers, cotton/corn scouts, rose harvesters/cutters) to 42 days (citrus pruners and leaf thinners) although most REIs were equal to or greater than 21days (see Table 17 in Dong, 2012, for specific values). The default assumptions of an 8 hr workday and a 70 kg body weight were used in these calculations. The dermal exposure was then converted to an ADD by multiplying by the dermal absorption (17%). To estimate AADDs, the SADDs were amortized over the year. The number of months assumed for amortization ranged from 2 months (citrus) to 6 months (corn) with most being 4 or 5 months. The ADDs were estimated for 19 different field worker scenarios which are summarized in Table 22. Rose harvesters/cutters and corn detasselers had the highest dermal exposure (ADDs: 339.9 and 270.5 µg/kg/day; SADDs: 218.4 and 197.9 µg/kg/day; AADDs: 91.0 and 99.0 µg/kg/day; LADDs: 48.5 and 52.8 µg/kg/day, respectively) while Christmas tree/conifer transplanters consistently had the lowest dermal exposure (ADD: 5.6 µg/kg/day; SADD: 4.5 µg/kg/day; AADD: 1.9 µg/kg/day; LADD: 1.0 µg/kg/day). Due to the very low vapor pressure of propargite, it was assumed the inhalation exposure of fieldworkers was negligible, especially several days after application.

Table 22. Estimated Dermal Exposure Dosages of Propargite for Fieldworkers[a]

Scenario	ADD[b]	SADD[c]	AADD[d]	LADD[e]
	ug/kg/day	µg/kg/day	µg/kg/day	µg/kg/day
Corn harvesters	64.3	54.8	27.4	14.6
Corn detasselers	270.5	197.9	99.0	52.8
Corn (cotton) scouts	23.9	17.5	8.8 (5.8)[f]	4.7 (3.1)[f]
Grape cane turners/girdlers	36.4	29.2	9.7	5.2
Grape harvesters/cultivators	18.2	14.6	4.9	2.6
Nectarine harvesters	39.0	32.0	10.7	5.7
Nectarine pruners/leaf thinners	78.0	64.0	21.3	11.4
Citrus pruners/leaf thinners	72.9	67.9	11.3	6.0
Rose harvesters/cutters	339.9	218.4	91.0	48.5
Jojoba harvesters	57.6	50.5	12.6	6.7
Christmas tree/conifer transplanters	5.6	4.5	1.9	1.0
Strawberry transplanters	13.2	10.5	4.4	2.3
Dry bean harvesters	18.1	12.9	4.3	2.3
Almond sweepers/mech. harvesters	20.4	16.8	7.0	3.7
Walnut sweepers/mech. harvesters	31.8	26.3	11.0	5.8
Potato/peanut mech. harvesters	31.8	26.3	11.0	5.8
Alfalfa/clover seed mech. harvesters	31.8	26.3	11.0	5.8
Grain sorghum mech. harvesters	31.8	26.3	11.0	5.8
Irrigator and other cultivators	31.8	26.3	11.0	5.8

a Exposure estimates from Table 18 of the EAD by Dong (2012).

b ADD = Absorbed Daily Dosage. For fieldworkers, ADD = (hourly dermal transfer rate) x (dislodgeable foliar residue = DFR) x (8 hours/day) x (70 kg)$^{-1}$. For acute, the DFR is the estimated residue at the time of reentry interval (REI). See Table 17 in EAD by Dong (2012) for specific hourly dermal transfer rates and DFRs assumed for each scenario.

c SADD = Seasonal Absorbed Daily Dosage. The estimation of SADD is same as ADD except the DFR is set at the REI + 3 days.

d AADD = Annual Average Daily Dosage which is the SADD x (number of months for annualization) / 12 months. The number of months for annualization range from 3 to 7. See Table 10 in EAD by Dong (2007) for specific values for each scenario.

e LADD = Lifetime Average Daily Dosage which is the AADD x (40 years of work in a lifetime) / (75 years in a lifetime).

f The value parentheses is for cotton scouts. Their AADDs and LADDs are lower due to a fewer number of months used per year (4 vs. 7 months).

As with handlers, the dermal concentration for fieldworkers was estimated; however, the dermal exposure was initially calculated for the whole body. The estimated acute and seasonal dermal concentrations on the hands and the rest of the body are summarized in Table 23. Hand (699 cm^2) exposure which included forearm (1,032 cm^2) exposure was assumed to be approximately 85% of the whole body exposure, except for corn/cotton scouts and grape cane turners/girdlers for which all body parts were assumed to have equal exposure. The dermal concentration was estimated by multiplying the external dermal dose in mg/day (= ADD divided by the dermal absorption and multiplied by the body weight) by the percentage deposited in that body region (85% for hand, 15% for rest of body) and dividing by the body region surface area (1731 cm^2 for hand, 16269 cm^2 for the rest of the body). Unlike handlers, the female body surface area (18,000 cm^2) was assumed for fieldworkers since they are more likely to be involved in these types of activities. The net effect of this assumption was to increase the dermal concentration since the dermal exposure was divided by a smaller number. As with the ADDs, rose harvesters/cutters and corn detasselers consistently had the highest dermal concentrations for both the body (acute: 1.0-1.3 $\mu g/cm^2$; seasonal: 0.8 $\mu g/cm^2$) and hand (acute: 54.7-68.7 $\mu g/cm^2$; seasonal: 40.0-44.2 $\mu g/cm^2$) while Christmas tree/conifer transplanters consistently had the lowest dermal concentrations on their body (acute: 0.02 $\mu g/cm^2$; seasonal: 0.02 $\mu g/cm^2$) and hands (acute: 1.1 $\mu g/cm^2$; seasonal: 0.9 $\mu g/cm^2$).

II.B.2. Bystander and Ambient Air Exposure

III.B.2.a. Bystander Air Exposure

Individuals might be exposed to propargite if they are working or standing adjacent to fields that are being treated or have recently been treated (i.e., bystanders). Air monitoring for propargite was conducted following an application to a grape vineyard in Fresno County in the summer of 1996 (ARB, 1998). The highest propargite air level, 0.44 $\mu g/m^3$, was found at the east sampling site during the 25th hour post-application. In another study, application site air was monitored following an application to grapes in July of 1999 (ARB, 2000). The highest 24-hr air concentration was 3.5 $\mu g/m^3$ that was observed during the first 1.5 hours post application. The highest 24-hour time-weighted average (TWA) air concentration was 0.93 $\mu g/m^3$ which occurred on day 1 post application. The application rate in this study was1.92 lb AI/acre where the maximum allowable application rate is 4.8 lb AI/acre. Adjusting for the maximum allowable application rate, the highest air concentrations at 90 minutes and for 24-hour TWA would be 8.75 and 2.31 $\mu g/m^3$, respectively. Assuming a breathing rate of 0.025 m^3/kg/hr and 0.59 m^3/kg/day for infants, the 1-hr and 24-hr infant bystander ADDs would be 0.219 and 1.361 μg/kg/day, respectively (Table 24). Assuming a breathing rate of 0.012 m^3/kg/hr and 0.28 m^3/kg/day for adults, the 1-hr and 24-hr adult bystander ADDs would be 0.105 and 0.646 μg/kg/day, respectively. An average air level of 1.0 $\mu g/m^3$ from all the sampling sites around the application site during the 3 days of monitoring were used for estimating seasonal exposure. Based on this average air concentration, the bystander SADDs were 0.590 μg/kg/day for infants and 0.280 μg/kg/day for adults. The chronic exposure estimates were calculated for application site air assuming the number of months used per year to be 4 months. Based on this assumption, the bystander AADDs were 0.197 and 0.093 μg/kg/day for infants and adults, respectively.

Table 23. Estimated Dermal Concentrations of Propargite for Fieldworkers[a]

Scenario	Acute DC[b]		Seasonal DC	
	Body[c] µg/cm²	Hand µg/cm²	Body µg/cm²	Hand µg/cm²
Corn harvesters	0.2	13.0	0.2	11.8
Corn detasselers	1.0	54.7	0.8	40.0
Corn/cotton scouts	0.6	0.6	0.4	0.4
Grape cane turners/girdlers	0.8	0.8	0.7	0.7
Grape harvesters/cultivators	0.1	3.7	0.1	3.0
Nectarine harvesters	0.2	7.9	0.1	6.5
Nectarine pruners/leaf thinners	0.3	15.8	0.2	12.9
Citrus pruners/leaf thinners	0.3	14.7	0.3	13.7
Rose harvesters/cutters	1.3	68.7	0.8	44.2
Jojoba harvesters	0.2	11.6	0.2	10.2
Christmas tree/conifer transplanters	0.02	1.1	0.02	0.9
Strawberry transplanters	0.1	2.7	0.04	2.1
Dry bean harvesters	0.1	3.7	0.05	2.6
Almond sweepers/mech. harvesters	0.1	4.1	0.06	3.4
Walnut sweepers/mech. harvesters	0.1	6.4	0.1	5.3
Potato/peanut mech. harvesters	0.1	6.4	0.1	5.3
Alfalfa/clover seed mech. harvesters	0.1	6.4	0.1	5.3
Grain sorghum mech. harvesters	0.1	6.4	0.1	5.3
Irrigator and other cultivators	0.1	6.4	0.1	5.3

a Dermal concentration estimates from Table 19 and 20 in the EAD by Dong (2012)

b DC = Dermal concentration

c Body = Dermal concentration for the whole body, except the hands.

Table 24. Estimated Inhalation Exposure for Bystanders Near Application Sites Treated with Propargite[a]

Exposure Dosages	Infants	Adults
ADD[b] - 1 hr (μg/kg)	0.22	0.11
ADD - 24 hr (μg/kg)	1.36	0.65
SADD[c] (μg/kg/day)	0.59	0.28
AADD[d] (μg/kg/day)	0.20	0.09

a Application site monitoring study for propargite conducted in grape vineyards in Fresno County during summer of 1996 and 1999. Inhalation exposure estimates from Table 23 of the EAD by Dong (2012).

b ADD = Absorbed Daily Dosage. The 1-hr exposure is based on 90-minute air concentration of 8.75 $\mu g/m^3$ at the south site after adjusting for the maximum application rate. The 24-hr exposure was based on the 24-hr weighted air concentration of 2.31 $\mu g/m^3$ at the east collocated (duplicated) site during the first three sampling periods and adjusted for the maximum application rate. A default inhalation absorption of 100% was used. For more explanation of the calculations, see the exposure assessment document for propargite (Dong, 2012).

c SADD = Seasonal Average Daily Dosage using on the mean air concentration of 1.0 $\mu g/m^3$ from all monitoring sites around the application site during the monitoring period. No adjustment was made for the maximum application rate.

d AADD = Annual Average Daily Dosage = SADD x annual use months/12 months. Annual use months were assumed to be 4 months per year for application site air.

III.B.2.b. Ambient Air Exposure

Ambient air monitoring was conducted in the summer of 1996 in Fresno County to coincide with the use of propargite on grapes (ARB, 1998). One hundred samples were collected, but none of them were found above the limit of quantitation (0.28 $\mu g/m^3$).

Ambient air monitoring of propargite was also conducted in the summer of 1999 in Fresno Counties to coincide with its use on cotton and grapes (ARB, 2000). Samplers were set up at 7 school sites (Alvina Elementary School, Helm Elementary School, Huron Elementary School, Kerman High School, Stratford Elementary School, San Joaquin Elementary School, Kingsbury School District Bus Barn) about 8 to 39 feet above the ground. Urban samples were collected at the ARB monitoring station in Fresno as a background. During a 6-week period between June 24 and August 3 of 1999, 176 samples collected. The minimum detection limit was 16.7 ng/sample while the limit of quantitation was 83.5 ng/sample. The Alvina Elementary School was the site with the highest maximum air concentration of 1.3 $\mu g/m^3$, and the highest average air concentration of 0.17 $\mu g/m^3$. No exposure estimates were calculated for ambient air since the maximum and average air concentrations at all sites were lower than those around the applications site.

III.B.3. Aggregate Exposure

III.B.3.a. Agricultural Workers

The exposure to propargite through the diet, drinking water and residential (ambient) air was also considered in the potential exposure for agricultural workers. The application site air

exposure estimates for adults were used to estimate aggregate exposure assuming workers lived adjacent to treated fields. The application site air exposure estimates were adjusted to 0.27, 0.056 and 0.019 µg/kg/day for acute, seasonal and chronic exposure, respectively, assuming a maximum exposure of 16 hours per day to residential air for agricultural workers. In the previous RCD for propargite in which dietary and drinking water exposure were evaluated, the acute exposure to propargite for workers (males and females 16 years and older) was estimated to be 2.73 µg/kg/day based on the 95th percentile of user-day exposure (Lewis, 2004). The chronic dietary and drinking water exposure for workers was estimated to be 0.18 µg/kg/day based on the average exposure for the U.S. population (custom subpopulations could not be calculated for chronic exposure). When the dietary and drinking water exposure were evaluated previously, the exposure was not adjusted for absorption because the oral NOEL had not been adjusted for absorption. To calculate the aggregate exposure, the dietary and drinking water exposure were converted to absorbed dosages since the occupational exposure and ambient air exposure were expressed as absorbed dosages. The absorbed dosages for acute and chronic dietary and drinking water exposure were estimated to be 1.09 and 0.072 µg/kg/day, respectively. The occupational exposure represented 80 to 99.9% of the aggregate exposure for agricultural workers while the oral exposure from dietary and drinking water exposure was usually less than 10%. The scenarios in which dietary and drinking water exposure represented more than 5% were those in which the occupational exposure was relatively low. Residential air exposure represented even less of the total exposure, usually less than 5%. Therefore, no additional analysis of the aggregate exposure for agricultural workers was performed. Since route-specific NOELs were used to analyze the exposure from various routes, a single combined aggregate exposure dose was not used except for evaluating carcinogenicity. Instead the aggregate exposure was taken into consideration in the calculation of the combined MOE which is defined in the Risk Characterization section of this document.

III.B.3.b. General Public

The aggregate exposure to propargite through the diet, drinking water and residential (application site) air was considered in the potential exposure for the general public. The application site air exposure from Table 24 was used for the residential air exposure for infants and adults. Based on the previous assessment of the dietary and drinking water exposure to propargite, the estimated acute exposure was assumed to be 6.22 and 4.36 µg/kg/day for infants (non-nursing, less than 1 year old) and adults (U.S. population), respectively, (Lewis, 2004). As with the occupational aggregate exposure, the dietary and drinking water exposure were converted to absorbed dosages. The absorbed acute oral exposure from diet and drinking water were estimated to be 2.49 and 1.74 µg/kg/day for infants and adults, respectively, assuming an oral absorption of 40%. For the 1-hr exposure estimates the acute oral dose was divided by 3 since it was not reasonable to assume people consumed a whole day's worth of food in one hour. Since no seasonal exposure was estimated for dietary and drinking water exposure, the chronic dietary and drinking water exposures were used for seasonal aggregate exposure. From the previous assessment, the estimated chronic dietary and drinking water exposure was 0.29 µg/kg/day for infants (non-nursing, less than 1 year old) and 0.18 µg/kg/day for adults (U.S. population), respectively. After adjusting for oral absorption, the chronic dietary and drinking water exposure was assumed to be 0.12 and 0.07 µg/kg/day, respectively. The aggregate exposure dosages for the general public are summarized in Table 25. Unlike workers, dietary

exposure represented a significant portion of the aggregate exposure to propargite for the general public, ranging from 16% (seasonal) to 79% (1-hr acute) of the total exposure for infants and from 20% (seasonal) to 89% (1-hr acute) of the total exposure for adults.

Table 25. Estimated Aggregate Exposure for the General Public to Propargite in the Diet, Drinking Water and Residential Air[a]

Exposure Dosages	Infants	Adults
ADD[b] - 1 hr (µg/kg)	1.05	0.69
ADD - 24 hr (µg/kg)	3.85	2.39
SADD[d] (µg/kg/day)	0.71	0.35
AADD[e] (µg/kg/day)	0.31	0.21

a The aggregate exposure estimates are the sum of the combined dietary and drinking water exposure (Lewis, 2004) and the ambient air exposure (Table 24). After adjusting for oral absorption (40%), the combined acute dietary and drinking water exposure was assumed to be 2.49 µg/kg/day for infants based on non-nursing infants less than 1 years old and 1.74 µg/kg/day for adults based on the U.S. population. The acute oral exposure was divided by 3 for the 1-hr aggregate exposure estimates. The absorbed chronic dietary and drinking water exposure was assumed to be 0.12 µg/kg/day for infants (non-nursing infants less than 1 year old) and 0.07 µg/kg/day for adults (U.S. population).

b ADD = Absorbed Daily Dosage. The 1-hr exposure is based on 90-minute air concentration of 8.75 µg/m^3 at the south site after adjusting for the maximum application rate. The 24-hr exposure was based on the 24-hr weighted air concentration of 2.31 µg/m^3 at the east collocated (duplicated) site during the first three sampling periods and adjusted for the maximum application rate. A default inhalation absorption of 100% was used. For more explanation of the calculations, see the EAD for propargite (Dong, 2012).

c SADD = Seasonal Average Daily Dosage using on the mean air concentration of 0.3 µg/m^3 from all monitoring sites around the application site during the monitoring period. No adjustment was made for the maximum application rate.

d AADD = Annual Average Daily Dosage = SADD x annual use months/12 months. Annual use months were assumed to be 4 months per year for application site air.

III.C. RISK CHARACTERIZATION

The risk for non-oncogenic human health effects is expressed as a margin of exposure (MOE). The MOE is the ratio of the NOEL from experimental animal studies to the human exposure dosage.

$$MOE = \frac{NOEL}{Exposure\ Dosage}$$

When route-specific NOELs are used, then a combined MOE is calculated.

$$MOE_{combined} = \frac{1}{(1/MOE_{route1}) + (1/MOE_{route2}) + (1/MOE_{route3})}$$

Using a linear approach, the risk for oncogenic effects was calculated by multiplying the oncogenic potency by the exposure dosage.

Oncogenic Risk = Oncogenic Potency x Exposure Dosage

III.C.1. Occupational Exposure

The estimated margins of exposure (MOEs) for systemic effects from dermal and inhalation exposure to propargite in applicators is summarized in Table 26. In most cases, the MOEs were lowest for aerial application of WP/WSB formulations and highest for groundboom application of EC formulations. Although the dermal route was the main route of exposure for applicators, the acute MOEs for dermal exposure were generally higher than those for inhalation exposure because the acute dermal NOEL (17 mg/kg after adjusting for dermal absorption) was also higher than acute 8-hr oral NOEL used to evaluate inhalation exposure (0.8 mg/kg after adjusting for oral absorption). The acute dermal MOEs ranged from 3 to 1100 while the acute inhalation MOEs were between 7 and 48. With seasonal and chronic exposure, the MOEs for the dermal route were generally lower than those for the inhalation route not only because the dermal exposure was greater, but also because the subchronic/chronic dermal NOEL (0.17 mg/kg/day) was lower than the subchronic and chronic inhalation NOEL (0.8 and 1.5 mg/kg/day, respectively). The seasonal dermal MOEs for applicators were all less than 100, ranging from less than 1 to 44 while the seasonal inhalation MOEs were between 18 and 190. The chronic

Table 26. Estimated Margins of Exposure for Systemic Effects in Applicators Exposed to Propargite[a]

Exposure Scenarios	Acute		Seasonal		Chronic	
	Derm.[b]	Inhal.[b]	Derm.	Inhal.	Derm.	Inhal.
EC[c]						
Aerial	29	7	<1	18	3	100
Airblast	47	11	2	46	6	260
Groundboom	1,100	48	44	190	130	1,100
WSB[c]						
Aerial	3	8	<1	21	<1	110
Airblast	4	11	<1	43	<1	240
Groundboom	91	40	4	160	11	900

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. After adjusting for dermal absorption, the acute, seasonal and chronic dermal NOELs were 17 mg/kg (rabbits - no clinical signs or body weight reductions after 1 week of exposure), 0.17 mg/kg/day (rabbits - reduced body weights, changes in clinical chemistry and hematology and increased kidney and liver weights), and 0.17 mg/kg/day (same as subchronic), respectively. Inhalation exposure was evaluated using the following acute, seasonal and chronic oral NOELs: 0.8 mg/kg (pregnant rabbit - maternal: anorexia, adipsia; fetal: delayed ossification), 0.8 mg/kg/day (pregnant rabbit - maternal; anorexia, adipsia, reduced body weight gain and reduced survival), and 1.5 mg/kg/day (rats: reduced body weights and food consumption), after adjusting for oral absorption (40%). The exposure dosages are from Table 16. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

dermal MOEs were slightly higher although the same NOEL was used because the seasonal exposure was amortized over the year. The chronic inhalation MOEs were even larger because a slightly larger oral NOEL (1.5 mg/kg/day absorbed) was used for evaluating the chronic inhalation exposure. Consequently, the chronic dermal MOEs ranged from less than 1 to 130 while the chronic inhalation MOEs were between 100 and 1,100.

Table 27 contains the estimated MOEs for mixer/loaders exposed to propargite. Compared to applicators, the MOEs were slightly higher as a whole. Like applicators, the lowest MOEs for mixer/loaders was seen with aerial and airblast application of WSB formulations and the highest MOEs with groundboom application of EC. The acute dermal MOEs for mixer/loaders were also higher than the acute inhalation MOEs despite the higher dermal exposures since the acute dermal NOEL was higher. The acute dermal MOEs ranged from 32 to 970 while the acute inhalation MOEs were between 17 and 250. As with applicators, the seasonal dermal MOEs were generally lower than the inhalation MOEs for the same scenario since the dermal exposures were higher and the oral NOEL used to evaluated inhalation exposure was higher. The seasonal dermal MOEs for mixer/loaders were ranged from less than 1 to 39 while the seasonal inhalation MOEs were between 42 to 1,000. The same pattern was true for the chronic MOEs although the chronic MOEs were larger. The chronic dermal MOEs ranged from 2 to 120 while the chronic inhalation MOEs were between 230 and 3,000.

Table 27. Estimated Margins of Exposure for Systemic Effects in Mixer/Loaders Exposed to Propargite[a]

Exposure Scenarios	Acute		Seasonal		Chronic	
	Derm.[b]	Inhal.[b]	Derm.	Inhal.	Derm.	Inhal.
EC[c]						
Aerial	180	43	7	170	21	980
Airblast	530	120	21	500	64	2,800
Groundboom	970	250	39	1,000	120	3,000
WSB[c]						
Aerial	32	17	<1	42	2	230
Airblast	79	42	2	100	6	590
Groundboom	130	67	3	170	10	940

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. After adjusting for dermal absorption, the acute, seasonal and chronic dermal NOELs were 17 mg/kg (rabbits - no clinical signs or body weight reductions after 1 week of exposure), 0.17 mg/kg/day (rabbits - reduced body weights, changes in clinical chemistry and hematology and increased kidney and liver weights), and 0.17 mg/kg/day (same as subchronic), respectively. Inhalation exposures were evaluated using the following acute, seasonal and chronic oral NOELs: 0.8 mg/kg (pregnant rabbit - maternal: anorexia, adipsia; fetal: delayed ossification), 0.8 mg/kg/day (pregnant rabbit - maternal; anorexia, adipsia, reduced body weight gain and reduced survival), and 1.5 mg/kg/day (rats: reduced body weights and food consumption), after adjusting for oral absorption (40%). The exposure dosages are from Table 17. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

The estimated MOEs for mixer/loader/applicators (M/L/As) and human flaggers exposed to propargite are summarized in Table 28. The lowest dermal MOEs were generally seen in flaggers for WSB formulations and highest in flaggers for EC formulations and in M/L/As using WSB formulations with low pressure equipment. The lowest inhalation MOEs were also seen in flaggers for WSB formulations, but the highest inhalation MOEs were usually in M/L/As using backpack sprayers which had very low inhalation exposure. As with applicators and mixer/loaders, the acute dermal MOEs for M/L/As and flaggers were usually higher than the acute inhalation MOEs for the same scenario, except for backpack M/L/As whose inhalation exposure was relatively low compared to dermal exposure. The acute dermal MOEs ranged from 17 to 210 while the acute inhalation MOEs were between 24 and 1,300. Like applicators and mixer/loaders, the dermal MOEs for seasonal and chronic exposure were always lower than their respective inhalation MOEs. The seasonal dermal MOEs ranged from less than l to 10 while the seasonal inhalation MOEs were between 82 and 4,000. The chronic dermal MOEs were between 2 and 31 while the chronic inhalation MOEs ranged from 460 to 22,000.

Table 28. Estimated Margins of Exposure for Systemic Effects in Mixer/Loader/Applicators and Human Flaggers Exposed to Propargite[a]

Exposure Scenarios	Acute		Seasonal		Chronic	
	Derm.[b]	Inhal.[b]	Derm.	Inhal.	Derm.	Inhal.
Flagger						
EC[c]	150	26	6	100	18	580
WSB[c]	17	29	<1	120	2	650
Mixer/Loader/Applicator						
Low Pressure	210	24	10	120	31	670
High Pressure	90	33	2	82	7	460
Backpack	120	1,300	4	4,000	10	22,000

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. After adjusting for dermal absorption, the acute, seasonal and chronic dermal NOELs were 17 mg/kg (rabbits - no clinical signs or body weight reductions after 1 week of exposure), 0.17 mg/kg/day (rabbits - reduced body weights, changes in clinical chemistry and hematology and increased kidney and liver weights), and 0.17 mg/kg/day (same as subchronic), respectively. Inhalation exposure was evaluated using the following acute, seasonal and chronic oral NOELs: 0.8 mg/kg (pregnant rabbit - maternal: anorexia, adipsia; fetal: delayed ossification), 0.8 mg/kg/day (pregnant rabbit - maternal; anorexia, adipsia, reduced body weight gain and reduced survival), and 1.5 mg/kg/day (rats: reduced body weights and food consumption), after adjusting for oral absorption (40%). The exposure dosages are from Table 18. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Derm. = Total dermal exposure including hand exposure; Inhal. = Inhalation exposure.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

MOEs for dermal irritation were calculated for agricultural workers using the estimated dermal concentration of propargite on the body (minus hands) and hands separately and the NOELs for dermal irritation expressed in $\mu g/cm^2$ (acute: 700 $\mu g/cm^2$, subchronic: 210 $\mu g/cm^2$). The MOEs for dermal irritation for applicators are summarized in Table 29. Since the dermal concentration on the hands was always higher than the rest of the body, the MOEs for the hands was always lower, usually by an order of magnitude. Aerial and airblast applicators usually had the lowest MOEs on their hands which were often less than 10, especially with WSB

Table 29. Estimated Margins of Exposure for Dermal Irritation in Applicators Exposure to Propargite[a]

Exposure Scenarios	Acute		Seasonal	
	Body[b]	Hand	Body	Hand
EC[c]				
Aerial	170	4	150	3
Airblast	160	10	190	12
Groundboom	7,000	130	10,000	150
WSB[c]				
Aerial	19	<1	17	<1
Airblast	15	1	18	1
Groundboom	580	11	700	13

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. The acute and subchronic NOELs for dermal irritation were 700 μg/cm^2 (rabbits) and 210 μg/cm^2 (rabbits), respectively. The estimated dermal concentration for the body and hands are from Table 19. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Body = MOE for dermal irritation on the body, except the hands.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

formulations. The MOEs for the body were generally greater than 100 except for aerial and airblast applicators with WSB formulations. The MOEs were not that different between acute and seasonal exposure with the body MOEs ranging from 15 to 7,000 for acute and from 17 to 10,000 for seasonal. The hand MOEs ranged from less than 1 to 130 for acute and from less than 1 to 150 for seasonal.

The MOEs for dermal irritation in mixer/loaders is summarized in Table 30. In general, the MOEs were higher in mixer/loaders than applicators with most being greater than 100, except for aerial application with the WSB formulations. Unlike applicators, the MOEs for the hands in mixer/loaders using WSB formulations were often higher than the rest of the body. The MOEs were usually the lowest on the hands of mixer/loaders for aerial application of the EC formulations regardless of duration of exposure and highest on the body of mixer/loaders for groundboom application of EC formulations. As with the applicators, the acute and seasonal MOEs were similar for the same scenario. The acute MOEs for the body ranged from 65 to 12,000 while the seasonal MOEs for the body ranged from 49 to 10,000. For the hands, the acute MOEs were between 18 and 1,800 and the seasonal MOEs were between 22 and 2,600.

The MOEs for dermal irritation in M/L/As and human flaggers were generally not as high as mixer/loaders (Table 31). Like applicators, the MOEs for the hand were usually lower than the rest of the body with the one exception being the M/L/As using backpack sprayers whose acute MOEs for the hands were nearly 2 orders of magnitude higher. The MOEs were usually lowest on the hands of flaggers with WSB formulations and highest on the hands of M/L/As using backpack sprayers regardless of exposure duration. As with applicators and mixer/loaders, the MOEs for acute and seasonal exposure were similar for the same scenarios. The acute MOEs for the body ranged from 40 to 540 while the seasonal MOEs for the body ranged from 48 to 700.

Table 30. Estimated Margins of Exposure for Dermal Irritation in Mixer/Loaders Exposed to Propargite[a]

Exposure Scenarios	Acute		Seasonal	
	Body[b]	Hand	Body	Hand
EC[c]				
Aerial	1,800	18	2,100	22
Airblast	7,000	55	7,000	66
Groundboom	12,000	99	10,000	120
WSB[c]				
Aerial	65	470	49	520
Airblast	160	1,200	120	1,000
Groundboom	270	1,800	210	2,600

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. The acute and subchronic NOELs for dermal irritation were 700 μg/cm^2 (rabbits) and 210 μg/cm^2 (rabbits), respectively. The estimated dermal concentration for the body and hands are from Table 20. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Body = MOE for dermal irritation on the body, except the hands.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

Table 31. Estimated Margins of Exposure for Dermal Irritation in Mixer/Loader/Applicators and Human Flaggers Exposed to Propargite[a]

Exposure Scenarios	Acute		Seasonal	
	Body[b]	Hand	Body	Hand
Flagger				
EC[c]	350	89	420	100
WSB[c]	40	10	48	12
Mixer/Loader/Applicator				
Low Pressure	540	75	700	110
High Pressure	190	150	140	110
Backpack	230	23,000	210	21,000

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. The acute and subchronic NOELs for dermal irritation were 700 μg/cm^2 (rabbits) and 210 μg/cm^2 (rabbits), respectively. The estimated dermal concentration for the body and hands are from Table 21. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Body = MOE for dermal irritation on the body, except the hands.

c EC = Emulsifiable Concentrate; WSB = Water Soluble Bag.

The acute MOEs for the hands were between 10 and 23,000 while the seasonal MOEs for the hands were between 12 and 21,000.

The dermal MOEs for systemic effects in fieldworkers are summarized in Table 32. Most of the acute dermal MOEs for systemic effects were greater than 100 for fieldworkers, ranging from 50 to 3,000. In contrast, the seasonal and chronic MOEs for systemic effects were almost all less than 100 due to the significantly lower seasonal and chronic dermal NOEL (170

Table 32. Estimated Margins of Exposure for Systemic Effects with Dermal Exposure to Propargite in Fieldworkers[a]

Scenario	Acute	Seasonal	Chronic
Corn harvesters	260	3	6
Corn detasselers	63	<1	2
Corn (cotton) scouts[b]	710	10	19 (29)
Grape cane turners/girdlers	470	6	18
Grape harvesters/other cultivators	930	12	35
Nectarine harvesters	440	5	16
Nectarine pruners/leaf thinners	220	3	8
Citrus pruners/leaf thinners	230	3	15
Rose harvesters/cutters	50	<1	2
Jojoba harvesters	290	3	14
Christmas tree/conifer transplanters	3,000	38	90
Strawberry transplanters	1,300	16	39
Dry bean harvesters	940	13	40
Almond sweepers/mech. harvesters	830	10	24
Walnut sweepers/mech. harvesters	530	7	16
Potato/peanut mech. harvesters	530	7	16
Alfalfa/clover seed mech. harvesters	530	7	16
Grain sorghum mech. harvesters	530	7	16
Irrigator and other cultivators	530	7	16

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. After adjusting for dermal absorption, the acute, seasonal and chronic dermal NOELs were 17 mg/kg (rabbits - no clinical signs or body weight reductions after 1 week of exposure), 170 µg/kg/day (rabbits - reduced body weights, changes in clinical chemistry and hematology and increased kidney and liver weights), and 170 µg/kg/day (same as subchronic), respectively. The estimated exposure dosages are from Table 22. Values were rounded to two significant figures or the nearest whole number if less than 10.

b The values in the table are for corn scouts. The MOEs for cotton scouts are the same except for the chronic MOE which is 29.

µg/kg/day) for systemic effects compared to the acute dermal NOEL (17 mg/kg/day). The seasonal MOEs for systemic effects ranged from less than one to 38. The chronic MOEs were between 2 and 90. The lowest MOEs for systemic effects were seen in rose harvesters/cutters and corn detasselers while the highest were seen in Christmas tree/conifer transplanters.

Table 33 summarizes the MOEs for dermal irritation in fieldworkers. The acute MOEs for dermal irritation on the body of fieldworkers were all greater than 100. On the other hand, the acute MOEs for dermal irritation on the hands were less than 100 for some scenarios, including corn harvesters and detasselers, nectarine harvesters, nectarine and citrus pruners/leaf thinners, rose harvesters/cutters, and jojoba harvesters. The seasonal MOEs for dermal irritation on the body were all greater than 100. In contrast, the seasonal MOEs for dermal irritation on the hands of fieldworkers were usually less than 100 and a couple were less than 10, including rose harvesters/cutters and corn detasselers.

Table 33. Estimated Margins of Exposure for Dermal Irritation in Fieldworkers Exposed to Propargite

Scenario	Acute		Seasonal	
	Body[b]	Hand	Body	Hand
Corn harvesters	3,500	54	1,000	19
Corn detasselers	700	13	260	5
Cotton/corn scouts	1,200	1,200	520	520
Grape cane turners/girdlers	870	870	300	300
Grape harvesters/other cultivators	7,000	190	2,100	70
Nectarine harvesters	7,000	89	2,100	32
Nectarine pruners/leaf thinners	3,500	44	1,000	16
Citrus pruners/leaf thinners	2,300	48	700	15
Rose harvesters/ cutters	540	10	260	5
Jojoba harvesters	3,500	60	1,000	21
Christmas tree/conifer transplanters	35,000	640	10,000	230
Strawberry transplanters	12,000	260	5,200	100
Dry bean harvesters	7,000	190	4,200	81
Almond sweepers/mech. harvesters	7,000	170	3,500	62
Walnut sweepers/mech. harvesters	7,000	110	2,100	40
Potato/peanut mech. harvesters	7,000	110	2,100	40
Alfalfa/clover mech. harvesters	7,000	110	2,100	40
Grain sorghum mech. harvesters	7,000	110	2,100	40
Irrigator and other cultivators	7,000	110	2,100	40

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. The acute and subchronic NOELs for dermal irritation were 700 µg/cm^2 (rabbits) and 210 µg/cm^2 (rabbits), respectively. The estimated dermal concentration for the body and hands are from Table 23. Values were rounded to two significant figures or the nearest whole number if less than 10.

b Body = Dermal concentration for the whole body, except the hands.

The cancer risk estimates for handlers are summarized in Table 34. The cancer risk was calculated using the LADDs in Tables 15-17 and the cancer potency estimates based on jejunal sarcomas in male rats (5.9×10^{-2} $(mg/kg/day)^{-1}$ for MLE or 8.4×10^{-2} $(mg/kg/day)^{-1}$ for 95% UB) after adjusting for the oral absorption (40%). The estimated carcinogenic risk for handlers using the MLE for carcinogenic potency ranged 5.9×10^{-5} to 1.9×10^{-2}. When the 95% UB for carcinogenic potency was used, the estimated carcinogenic risk for workers ranged from 8.4×10^{-5} to 2.6×10^{-2}. The cancer risk estimates were highest for aerial applicators with WSB formulations. The lowest cancer risk estimates were for mixer/loaders for groundboom application of EC formulations.

Table 34. Estimated Carcinogenic Risk for Handlers Based on Potential Lifetime Exposure to Propargite[a]

Exposure Scenarios	Maximum Likelihood Estimate	95% Upper Bound Estimate
Applicators		
EC[c]		
Aerial	2.5×10^{-3}	3.6×10^{-3}
Airblast	1.1×10^{-3}	1.6×10^{-3}
Groundboom	8.3×10^{-5}	1.2×10^{-4}
WSB		
Aerial	1.9×10^{-2}	2.6×10^{-2}
Airblast	1.0×10^{-2}	1.5×10^{-2}
Groundboom	5.4×10^{-4}	7.7×10^{-4}
Mixer/Loaders		
EC		
Aerial	3.0×10^{-4}	4.2×10^{-4}
Airblast	9.4×10^{-5}	1.3×10^{-4}
Groundboom	5.9×10^{-5}	8.4×10^{-5}
WSB		
Aerial	2.4×10^{-3}	3.5×10^{-3}
Airblast	9.8×10^{-4}	1.4×10^{-3}
Groundboom	5.9×10^{-4}	8.4×10^{-4}
M/L/As[d] and Flaggers		
Flagger		
EC	3.8×10^{-4}	5.4×10^{-4}
WSB	2.7×10^{-3}	3.9×10^{-3}
Mixer/Loader/Applicator		
Low Pressure	2.4×10^{-4}	3.4×10^{-4}
High Pressure	9.0×10^{-4}	1.3×10^{-3}
Backpack	5.1×10^{-4}	7.3×10^{-4}

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosages were the LADD in Tables 16-18. After adjusting for oral absorption, the maximum likelihood estimate for carcinogenic potency is 5.9×10^{-2} $(mg/kg/day)^{-1}$ for propargite. The 95% upper bound estimate for carcinogenic potency is 8.4×10^{-2} $(mg/kg/day)^{-1}$.

Table 35 summarizes the cancer risk estimates for fieldworkers. The cancer risk estimates were calculated using the LADDs in Table 22 and the cancer potency estimates at the MLE and 95% UB. The cancer risk estimates at the MLE ranged from 5.9×10^{-5} to 3.1×10^{-3}. At the 95% UB, the cancer risk estimates were between 8.4×10^{-5} to 4.4×10^{-3}. The highest risk estimates were seen in corn detasselers while the lowest risk estimates were found in Christmas tree/conifer transplanters.

Table 35. Estimated Carcinogenic Risk for Fieldworkers Based on Potential Lifetime Exposure to Propargite[a]

Exposure Scenarios	Maximum Likelihood Estimate	95% Upper Bound Estimate
Corn harvesters	8.6×10^{-4}	1.2×10^{-3}
Corn detasselers	3.1×10^{-3}	4.4×10^{-3}
Corn scouts	2.8×10^{-4}	3.9×10^{-4}
Cotton scouts	1.8×10^{-4}	2.6×10^{-4}
Grape cane turners/girdlers	3.1×10^{-4}	4.4×10^{-4}
Grape harvesters/other cultivators	1.5×10^{-4}	2.2×10^{-4}
Nectarine harvesters	3.4×10^{-4}	4.8×10^{-4}
Nectarine pruners/leaf thinners	6.7×10^{-4}	9.6×10^{-4}
Citrus pruners/leaf thinners	3.5×10^{-4}	5.0×10^{-4}
Rose harvesters/cutters	2.9×10^{-3}	4.1×10^{-3}
Jojoba harvesters	4.0×10^{-4}	5.6×10^{-4}
Christmas tree/conifer transplanters	5.9×10^{-5}	8.4×10^{-5}
Strawberry transplanters	1.4×10^{-4}	1.9×10^{-4}
Dry bean harvesters	1.4×10^{-4}	1.9×10^{-4}
Almond sweepers/mech. harvesters	2.2×10^{-4}	3.1×10^{-4}
Walnut sweepers/mech. harvesters	3.4×10^{-4}	4.9×10^{-4}
Potato/peanut mech. harvesters	3.4×10^{-4}	4.9×10^{-4}
Alfalfa/clover mech. harvesters	3.4×10^{-4}	4.9×10^{-4}
Grain sorghum mech. harvesters	3.4×10^{-4}	4.9×10^{-4}
Irrigator and other cultivators	3.4×10^{-4}	4.9×10^{-4}

a Carcinogenic Risk = Carcinogenic Potency x Exposure Dosage. The exposure dosage was the LADD in Table 22. After adjusting for oral absorption, the maximum likelihood estimate for carcinogenic potency is 5.9×10^{-2} $(mg/kg/day)^{-1}$ for propargite. The 95% upper bound estimate for carcinogenic potency is 8.4×10^{-2} $(mg/kg/day)^{-1}$.

III.C.2. Application Site Bystander Exposure

The MOEs for acute inhalation exposure for bystanders near fields treated with propargite were calculated using an acute oral NOEL of 0.8 mg/kg based on anorexia and adipsia in pregnant rabbits and delayed ossification in their fetuses after adjusting for oral absorption (40%) and the ADDs in Table 24. The 1-hr acute MOEs for bystanders were 3,700 for infants and 7,600 for adults (Table 36). The 24-hr acute MOEs were calculated using the same acute adjusted oral NOEL. The 24-hr acute MOEs for bystanders ranged from 590 for infants to 1,200 for adults. The MOEs for seasonal bystander exposure to propargite were calculated using the lowest subchronic oral NOEL of 0.8 mg/kg/day which came the same developmental toxicity in rabbits and the SADDs from Table 24. The seasonal MOEs for bystanders were 1,400 for infants and 2,900 for adults. The MOEs for chronic bystander exposure to propargite were calculated using an oral NOEL from a 2 year chronic study in rats of 1.5 mg/kg/day after adjusting for oral absorption (40%) and the AADDs from Table 24. The chronic MOEs for bystanders were 7,600 for infants and 16,000 for adults. The carcinogenic risk was calculated using the AADDs for adults (Table 24) and the estimated carcinogenic potency based on the jejunal sarcomas in male rats (5.9×10^{-2} $(mg/kg/day)^{-1}$ for MLE or 8.4×10^{-2} $(mg/kg/day)^{-1}$ for 95% UB) after adjusting for the oral absorption (40%). For the application site, the carcinogenic risk estimates were between 5.5×10^{-6} (MLE) and 7.8×10^{-6} (95% UB).

Table 36. Estimated Margins of Exposure for Bystanders Near Application Sites Treated with Propargite[a]

Exposure Dosages	Infants	Adults
Acute - 1 hr	3,700	7,600
Acute - 24 hr	590	1,200
Seasonal	1,400	2,900
Chronic	7,600	16,000

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. Inhalation exposures were evaluated using the following acute, seasonal and chronic oral NOELs: 0.8 mg/kg (pregnant rabbit - maternal: anorexia, adipsia; fetal: delayed ossification), 0.8 mg/kg/day (pregnant rabbit - maternal: anorexia, adipsia, reduced body weight gain and reduced survival), and 1.5 mg/kg/day (rats - reduced body weights and food consumption), after adjusting for oral absorption (40%). The exposure dosages are from Table 24. Values were rounded to two significant figures or the nearest whole number if less than 10.

III.C.3. Aggregate Exposure

The aggregate MOEs for the general public were calculated using the aggregate exposure estimates in Table 25 and the acute, seasonal and chronic oral NOELs were 0.8, 0.8 and 1.5 mg/kg/day, respectively, after adjusting for oral absorption (40%) (Lewis, 2004). The 1-hr acute aggregate MOEs at the application site for infants and adults were 760 and 1,200, respectively (Table 37). The 24-hr acute aggregate MOEs were 210 for infants and 330 for adults. The seasonal aggregate MOEs at the application site were 1,100 for infants and 2,300 for adults. The chronic aggregate MOEs at the application site were 4,800 and 7,200 for infants and adults, respectively. The aggregate carcinogenic risk for the general public was calculated using the chronic aggregate exposure estimate for adults and the estimated carcinogenic potency based

on the jejunal sarcomas in male rats (5.9×10^{-2} $(mg/kg/day)^{-1}$ for MLE or 8.4×10^{-2} $(mg/kg/day)^{-1}$ for 95% UB) after adjusting for oral absorption (40%). The estimated cancer risk for the general public based on potential aggregate lifetime exposure to propargite in the diet, drinking water and application site air ranged from 1.2 10^{-5} (MLE) to 1.8×10^{-5} (95% UB).

Table 37. Estimated Aggregate Margins of Exposure for the General Public Exposed to Propargite in the Diet, Drinking Water and Application Site Air

Exposure Dosages	Infants	Adults
Acute - 1 hr	760	1,200
Acute - 24 hr	210	330
Seasonal	1,100	2,300
Chronic	4,800	7,200

a Margin of Exposure (MOE) = NOEL / Exposure Dosage. Aggregate exposures were evaluated using the following acute, seasonal and chronic oral NOELs: 0.8 mg/kg (pregnant rabbit - maternal: anorexia, adipsia; fetal: delayed ossification), 0.8 mg/kg/day (pregnant rabbit - maternal: anorexia, adipsia, reduced body weight gain and reduced survival), and 1.5 mg/kg/day (rats - reduced body weights and food consumption), after adjusting for oral absorption (40%). The exposure dosages are from Table 25. Values were rounded to two significant figures or the nearest whole number if less than 10.

IV. RISK APPRAISAL

Risk assessment is the process used to evaluate the potential for human exposure and the likelihood that the adverse effects observed in toxicity studies with laboratory animals will occur in humans under the specific exposure conditions. Every risk assessment has inherent limitations on the application of existing data to estimate the potential risk to human health. Therefore, certain assumptions and extrapolations are incorporated into the hazard identification, dose-response assessment, and exposure assessment processes. These, in turn, result in uncertainty in the risk characterization which integrates all the information from the previous three processes. Qualitatively, risk assessments for all chemicals have similar uncertainties. However, the degree or magnitude of the uncertainty can vary depending on the availability and quality of the data, and the types of exposure scenarios being assessed. Specific areas of uncertainty associated with this risk assessment for propargite are delineated in the following discussion.

IV.A. HAZARD IDENTIFICATION

Oral studies were selected to evaluate inhalation exposure to propargite using route-to-route extrapolation since there was only the inhalation LC_{50} study conducted by Hoffman (1992a) available. In this study, a NOEL was not established and one death was observed at the LOEL. It was concluded there was more uncertainty associated with estimating a NOEL from a LOEL at which death was observed than with route-to-route extrapolation from an observed oral NOEL where effects at the LOEL were milder. However, if the LC_{50} study had been used, the NOEL would be 31 µg/L or 5.00 mg/kg if estimated by dividing the LOEL (0.31 mg/L or 50 mg/kg, assuming a rat breathes 960 L/kg/day x 4 hrs/24 hrs) by a default uncertainty factor of 10. The 8-hr and 24-hr NOELs would then be 2.5 mg/kg and 0.83 mg/kg, respectively, by applying Haber's Law. Using these NOELs to evaluate the 1-hr, 8-hr and 24-hr exposure, the MOEs would be approximately 6-fold higher, 3-fold higher and the same for the respective exposures compared to those calculated using the oral NOEL for all three acute exposure durations. The inhalation LC_{50} study could have also been used to derive subchronic and chronic inhalation NOELs by dividing the LOEL by additional default uncertainty factors of 10 and 100, resulting in a estimated subchronic and chronic inhalation NOELs of 83 and 8.3 µg/kg/day, respectively. If these estimated NOELs had been used for evaluating inhalation exposure rather than the lowest observed subchronic and chronic oral NOELs, the subchronic and chronic inhalation MOEs would be approximately 10- and 180-fold lower, respectively. Due to greater uncertainty with the additional factors used, route-to-route extrapolation was considered preferable for evaluating all duration of inhalation exposure.

The dermal LD_{50} study conducted by Kiplinger (1993b) was considered in the evaluation of risks for systemic effects from acute dermal exposure to propargite in agricultural workers. Only one dose level was tested in this study, so it was not possible to do a BMD analysis. A NOEL was estimated by dividing the only dose tested by an default uncertainty factor of 10. Without any other dose levels tested, the shape of the dose response curve is unknown. Consequently, the estimated NOEL of 400 mg/kg could easily be over or underestimated. However, in the two 21-day dermal toxicity studies in rabbits no clinical signs or reddened lungs

(the acute effects seen at the limit dose tested in the dermal LD_{50} study) were seen at 100 mg/kg/day after 21 days of exposure. Therefore, this dose level from the 21-day dermal study was selected as the critical NOEL for evaluating acute dermal exposure. This NOEL may overestimate the risk for systemic effects with acute dermal exposure since this was the highest dose level tested in this study. However, even adjusting for dermal absorption, the adjusted acute dermal NOEL (17 mg/kg) is higher than the acute oral NOEL (2 mg/kg) observed in the developmental toxicity study in rabbits conducted by Serota *et al.* (1983) based on anorexia in the does and delayed ossification in the fetuses even without the adjustment for oral absorption. This should not be surprising since the rabbits in the developmental toxicity study were getting daily bolus doses whereas the absorption through the skin in the 21-day dermal toxicity study should be more gradual resulting in lower peak blood levels. However, if the acute oral NOEL from the developmental toxicity study conducted by Serota *et al.* (2 mg/kg/day) had been used to evaluate the acute dermal exposure to propargite, the MOEs would be about 20 fold lower than estimated. On the other hand, it's possible that the severe dermal irritation that occurred with repeated dosing resulted in significant deterioration of the skin so that total absorption of propargite was greater than would be expected with a single exposure. If the acute dermal NOEL had been estimated by dividing the LOEL from the dermal LD_{50} study by 10, the MOEs would be 4 times higher than estimated.

In evaluating the risk for dermal irritation from propargite, the intraspecies uncertainty factor was dropped in estimating the RfC based on evidence that rabbits were more sensitive than humans to dermal irritation (Campbell and Bruce, 1981; Phillips et al., 1972; Marzulli and Maibach, 1975; Brown, 1971; Nixon et al., 1975; Monteiro-Riviere et al., 1990). This greater sensitivity of rabbits compared to humans appears to be due to greater hair density and less skin thickness (for more details see the discussion under IV.C. Risk Characterization section under the IV Risk Appraisal section). After one outbreak among nectarine harvesters, the investigators estimated the dislodgeable foliar residue (DFR) NOEL for dermal irritation with repeated exposure was 0.2 $\mu g/cm^2$. Theoretically, this would be equivalent to a dermal concentration of 1.2 $\mu g/cm^2$ on the hands and forearms using the same assumptions in estimating exposure for nectarine harvesters from this risk assessment. This is about 6-fold lower than the seasonal RfC for dermal irritation of 7 $\mu g/cm^2$, suggesting humans may be more sensitive than rabbits. However, the assumptions used to estimate the theoretical dermal concentration for nectarine harvesters include a transfer rate and the percentage of the dose that ends up on the hands and forearms. Since the actual dermal concentration was not measured in this study using dosimetry patches, it is uncertain how accurate these assumptions are. If the actual dermal concentration could have been measured in this outbreak, then it could have been used as a human NOEL for dermal irritation from propargite. Since this was not possible and there is not other evidence to suggest humans are more sensitive than rabbits to propargite and the assumption that rabbits are more sensitive was retained.

The study selected for evaluating the risk for systemic effects with seasonal dermal exposure was the 21-day study conducted by Bailey (1987). This study was preferred over the study conducted by Goldenthal (1989) which applied propargite neat because the latter study did not examine the kidneys and livers of the low and mid-dose animals despite seeing chronic nephritis and inflammation of the liver in the high-dose animals. However, the study conducted by Bailey used acetone as the vehicle which could have exacerbated the effects seen by

increasing the absorption and/or from its own toxicity. Consequently, the subchronic NOEL for systemic effects with dermal exposure to propargite could have been higher than estimated. Assuming that the NOEL for systemic effects in the Goldenthal study was the mid-dose level, 10 mg/kg/day, the subchronic dermal MOEs for systemic effects could be 10-fold higher than estimated.

There were no chronic dermal toxicity studies for propargite. It appears from a comparison of NOELs from the subchronic and chronic oral toxicity studies for propargite that a steady state is reached within the first few months and the toxicity does not increase significantly afterwards. The NOELs from the 2-generation reproductive toxicity study in rats conducted by Schardein (1989) are essentially the same as the NOEL from the 2-year chronic toxicity/ oncogenicity study in rats conducted by Goldenthal (1993). Based on this observation, it was assumed that the NOELs for chronic dermal toxicity were the same as the subchronic NOELs for this route. However, if the lowest oral NOEL from the chronic oral toxicity study in rats had been used to evaluate chronic dermal exposure to propargite, the MOEs would be higher. The chronic dermal MOEs would be almost 9-fold higher than estimated. A chronic MOE for dermal irritation was not calculated because it did not seem reasonable to amortize dermal exposure over the year for this endpoint since it was assumed that the dermal irritation was a concentration dependent effect. Therefore, the greatest risk for dermal irritation should be with seasonal exposure to peak use.

There was an increase in undifferentiated sarcomas of the jejunum in rats in the study conducted by Trutter (1991). The incidence showed a dose-related trend and was statistically significant from controls by pairwise comparison. This increase was considered toxicologically significant in the weight of evidence for the following reasons: 1) this tumor type is relatively rare in rats; 2) there was a shortening of time to tumor in males; 3) the tumor was determined to be the cause of death in the majority of male rats with it; 4) it was demonstrated in another study with the same strain without the propylene oxide stabilizer and 5) similar tumors were observed in a study with Wistar rats. Because the tumor was associated with ulceration and ectatic mucosal glands, there was some question if the tumors might be due to an increase in cell proliferation. In addition, all of the genotoxicity studies were negative except one marginally acceptable HPRT gene mutation assay with CHO cells. In this study, the propargite in the dosing solution appeared to have either broken down or reacted with the vehicle, DMSO. Other well-conducted HPRT gene mutation assays using either acetone and DMSO as the vehicle at similar concentrations to the positive study were negative. A few cell proliferation studies were conducted which showed a transient increase in cell proliferation at 800 ppm. However, it is unclear if a transient increase in cell proliferation is sufficient to cause tumors. Therefore, a health protective assumption was made that a genotoxic mechanism was responsible for the increase in tumors and a linearized multistage model was used to evaluate the carcinogenicity of propargite.

If there had been sufficient evidence to support a threshold mechanism, a non-linear approach could have been used. In this case, the U.S. EPA guidelines recommend dividing the LED_{10} by the exposure dosage to calculate a margin of exposure for carcinogenicity (U.S. EPA, 2005). The LED_{10} was 1.10 mg/kg/day after adjusting for oral absorption (40%). The LED_{10} is

only slightly lower than the NOEL of 1.5 mg/kg/day observed for the same study. Consequently, the MOEs for carcinogenicity would be similar to the MOEs for chronic toxicity. One problem with using the nonlinear approach for threshold mechanisms, as suggested by U.S. EPA's cancer guidelines, is that they have not suggested how large the MOE for carcinogenicity should be to be considered adequate. However, Gaylor et al. (1999) have proposed that the LED_{10}/10,000 or an MOE of 10,000 would be adequate for irreversible adverse health effects, including nongenotoxic carcinogenic effects. This proposal assumes the LED_{10} is equivalent to a LOAEL, so that an uncertainty factor of 10 is needed to extrapolate to a NOAEL. An additional uncertainty factor of 1,000 is recommended for interspecies extrapolation, intraspecies variation in susceptibility, and increased susceptibility for children. Dividing the LED_{10} by the LADD, the MOEs for carcinogenicity for agricultural workers would all be less than 1,000. The MOEs for carcinogenicity for the general public exposure to propargite in the application site air would be approximately 39,000.

IV.B. EXPOSURE ASSESSMENT

The uncertainties associated with the exposure assessment are discussed in detail in the Exposure Appraisal section of the Exposure Assessment Document for propargite (Dong, 2012). The uncertainties discussed include the uncertainty inherent in the PHED database used for handler exposure estimates, the uncertainties associated with default usage values for handlers, the uncertainties associated with the transfer factors and dislodgeable foliar residues used to estimate fieldworkers exposure, the uncertainties associated with estimating an upper end exposure for acute exposure using PHED data, the uncertainties associated with using the DPR's Pesticide Use Report to estimate high-use months or months included for amortizing chronic exposure, the uncertainties associated with the dermal absorption estimate, and the uncertainties associated with the transfer factor for cotton scouts due to limited data.

IV.C. RISK CHARACTERIZATION

Generally, an MOE of at least 100 is considered sufficiently protective of human health when the NOEL for an adverse systemic effect is derived from an animal study. The MOE of 100 allows for humans being 10 times more sensitive than animals and for a 10-fold variation in sensitivity between the lower range of the normal distribution in the overall population and the sensitive subgroup (Dourson *et al.*, 2002). For dermal irritation, a MOE of 10 is considered adequate when the NOEL is based on dermal irritation in rabbits. The assumption is that there is a 10-fold difference in inter-individual differences in response, but no inter-species difference in sensitivity between laboratory animals and human. The latter assumption was supported by comparative studies on species sensitivity to potential skin irritants (Campbell and Bruce, 1981; Phillips et al., 1972; Marzulli and Maibach, 1975; Brown, 1971; Nixon et al., 1975). These studies showed that the rabbit is the most sensitive species, when compared to the guinea pig and human. Possible factors responsible for the greater sensitivity in rabbits than humans is greater hair density and less skin thickness. Phillips *et al*. (1972) suggested that the greater hair density in rabbits resulted in increased permeability by providing direct entryways to the inner epidermal layer and the dermis through the pores and shaft. Monteiro-Riviere et al. (1990) compared the skin thickness among 9 species (cat, cow, dog, horse, monkey, mouse, pig, rabbit, rat) and found

that rabbits had the thinnest epidermis of the species tested. Humans also had the thickest stratum corneum.

Some have proposed doing a quantitative assessment of risk for dermal sensitization using the EC3 values from mouse local lymph node assays (Griem, 2008). Although it was noted that EC3 values were comparable to human NOELs for dermal sensitization, an interspecies uncertainty factor of 3 was suggested. Other uncertainty factors recommended were 10 for an intraspecies factor, 1-10 for a matrix factor, and 1-10 for a use factor. Since these uncertainty factors have not been fully vetted, the risks for dermal sensitization are uncertain. Furthermore, no mouse local lymph node assays were available for propargite, so estimating the risk for dermal sensitization using the EC3 value was not possible. Instead, it is recommended that an additional uncertainty factor of at least 3 be added to the intraspecies uncertainty factor for dermal irritation to protect against dermal sensitization. Therefore, to protect against both dermal irritation and dermal sensitization the target MOE is 30.

The potential for acute systemic effects from occupational exposure appears to be high for many handler exposure scenarios based on their MOEs being less than the target MOE of 100. The acute dermal and inhalation MOEs for systemic effects were less than 100 for aerial and airblast applicators with both formulations and for groundboom applicators with WSB formulations. Among mixer/loaders, both acute dermal and inhalation MOEs for systemic effects were less than 100 for aerial and airblast application of WSB formulations. Flaggers with WSB formulations also had both acute dermal and inhalation MOEs for systemic effects less than 100 as well as M/L/As using WSB formulations with high pressure equipment. For some scenarios, only the acute inhalation MOEs were less than 100. These scenarios included groundboom applicators of EC formulations, mixer/loaders for aerial application of EC formulations and for groundboom application of WSB, flaggers with EC formulations, and M/L/As using low pressure sprayers with WSB formulations. By contrast, the potential for systemic effects from occupational exposure in fieldworkers appears to be low with most of the acute dermal MOEs being greater than 100 except for rose harvesters/cutters and corn detasselers. Acute inhalation MOEs were not calculated for fieldworkers since their inhalation exposure was considered negligible.

The potential risk for systemic effects with seasonal exposure in handlers was greater since the seasonal MOEs for dermal exposure for all handlers were less than 100. Although seasonal exposure estimates for handlers were less than their corresponding acute estimates, the subchronic dermal NOEL was significantly lower resulting in lower dermal MOEs for seasonal exposure. The seasonal MOEs for inhalation exposure were also less than 100 for some handler scenarios, including aerial and airblast applicators using EC and WSB formulations, mixer/loaders for aerial application of WSB formulations, and M/L/As using high pressure sprayers with WSB formulations. As with handlers, the seasonal dermal MOEs for fieldworkers were all less than 100.

The potential risk for systemic effects with chronic occupational exposure still remained high for handlers with most scenarios. The MOEs were slightly higher with chronic exposure due to the amortization of seasonal exposure over the year to estimate chronic exposure. The

few handler scenarios with chronic dermal MOEs greater than 100 included groundboom applicators and mixer/loaders with the EC formulations. However, none of the chronic inhalation MOEs for handlers were less than 100. For fieldworkers, the chronic dermal MOEs were all less than 100.

The risks for local dermal effects on the body was low in handlers with acute and seasonal exposure, except for aerial and airblast applicators using WSB formulations. However, the risks for dermal irritation on the hands of handlers was much greater. The acute and seasonal dermal irritation MOEs for the hands were less than 30 for all applicators except for groundboom applicators with EC formulations, mixer/loaders for aerial application of EC formulations, and flaggers with WSB formulations. The risk for local dermal effects on the hands of fieldworkers was slightly higher. The field worker scenarios with acute or seasonal local dermal MOEs for the hand less than 30 were corn detasselers, nectarine and citrus pruners/leaf thinners, rose harvesters/cutters and jojoba harvesters.

An oncogenic risk level less than 10^{-6} is generally considered negligible. The oncogenic risk estimates for handlers and fieldworkers were all greater than 1×10^{-6}, and most were greater than 1×10^{-4}. As discussed earlier under the Hazard Identification, the oncogenic risk may also have been overestimated if a threshold mechanism was responsible for the tumors in rats. In this case the NOEL for these tumors would be the same as the NOEL used for chronic effects and, therefore, the MOEs would be the same as the chronic MOEs. Since many of the chronic MOEs for occupational exposure scenarios were less than 100, the risk for tumors is still a concern.

The acute, seasonal and chronic inhalation MOEs for bystanders near application sites treated with propargite were all greater than the conventional target of 100. However, the 24-hr MOE for children was less than 1,000, meeting the criteria for consideration as a possible toxic air contaminant, since the MOE is not 10-fold greater than the benchmark that is considered adequately protective of human health (California Code of Regulations, Title 3, Division 6, Section 6890). The carcinogenic risk estimates for the application site air (5.5×10^{-6} to 7.8×10^{-6}) were slightly above the default negligible risk level (1×10^{-6}) suggesting that mitigation should be considered. The cancer risk level was also high enough to meet the criteria for consideration as a possible toxic air contaminant (greater than 10^{-7} risk level).

The MOEs for aggregate exposure for agricultural workers were not calculated since the MOEs were less than 100 from occupational exposure alone, consequently, their aggregate MOEs were not significantly lower with the addition of dietary, drinking water and residential air exposure. On the other hand, nearly all of the MOEs for the general public exposed to application site air were greater than 100, so aggregate MOEs were calculated to see if the combined exposure from the diet, drinking water and application site air exceeded targets. The aggregate MOEs for the general public were still greater than 100, but the MOEs for 24-hour exposures were less than 1,000. With acute exposure, dietary and drinking water exposure represented 64-89% of the exposure while it only represented 16-43% of the exposure with seasonal and chronic exposure.

IV.D. U.S. EPA'S REREGISTRATION ELIGIBILITY DOCUMENT FOR PROPARGITE

U.S. EPA completed a Reregistration Eligibility Decision (RED) for propargite in September 2001 (U.S. EPA, 2001a). U.S. EPA evaluated dietary, drinking water and occupational exposure to propargite using route-specific NOELs whenever possible. The discussion here will be limited to the occupational exposure estimates derived by U.S. EPA. A discussion of U.S. EPA's dietary and drinking water risk estimates were discussed in DPR's RCD for addressing dietary and drinking water exposure to propargite (Lewis, 2004). To evaluate short-term dermal exposure in workers, U.S. EPA selected the maternal NOEL of 6 mg/kg/day from the developmental toxicity study in rabbits conducted by Schardein (1989). This oral NOEL was adjusted to a dermal NOEL of 43 mg/kg/day by dividing by a dermal absorption factor of 14%. In this risk assessment, a NOEL of 100 mg/kg/day was selected for evaluating systemic effects from a 21-day dermal toxicity study conducted by Bailey (1987) based on the lack of clinical signs and body weight reductions during the first week of exposure. Unlike U.S. EPA's risk assessment, in this risk assessment occupational exposure dosages were calculated as internal dosages even when the NOELs are route specific. Therefore, this external dermal NOEL was converted to an absorbed NOEL of 17 mg/kg/day by adjusting for dermal absorption, which was assumed to be 17%. Due to the severity of the dermal irritation observed with propargite, a NOEL for this endpoint was identified in this risk assessment; however, it was expressed in terms of concentration on skin rather than a body weight basis. A NOEL for this endpoint was estimated at 0.7 mg/cm^2 from another 21-day dermal toxicity study conducted by Goldenthal (1989) where erythema was observed after the first exposure at the lowest dose tested. U.S. EPA did not identify any NOELs for dermal irritation, short or intermediate-term.

For intermediate-term dermal exposure, U.S. EPA selected the parental NOEL of 4 mg/kg/day from the 2-generation reproductive toxicity study conducted by Kehoe (1990). U.S. EPA divided this NOEL by a dermal absorption factor of 14% to calculate their intermediate dermal MOEs for propargite. In this risk assessment, subchronic dermal exposure to propargite was evaluated using the 21-day dermal toxicity study conducted by Bailey (1987) where a NOEL was observed at 1 mg/kg/day based on reduced body weights, changes in clinical chemistry and hematological values and increased liver and kidney weights. After adjusting for dermal absorption, the absorbed NOEL was 0.17 mg/kg/day. In this risk assessment, a different 21-day dermal toxicity study conducted by Goldenthal (1989) was selected to evaluate subchronic dermal irritation with an estimated NOEL of 0.21 mg/cm^2. The NOEL was estimated by dividing by a default uncertainty factor of 10 for this endpoint.

U.S. EPA evaluated short and intermediate term inhalation exposure to propargite using the LOEL of 0.31 mg/L from the inhalation LC_{50} study conducted by Hoffman (1992a). An uncertainty factor of 10 was used for extrapolating from the LOEL to the NOEL. U.S. EPA assumed the inhalation absorption was 100%. In this risk assessment, an oral NOEL of 2 mg/kg/day from a developmental toxicity study in rabbits (Serota *et al.*, 1983) was used to evaluate acute inhalation exposure based on maternal anorexia seen in the first few days of exposure and fetal delayed ossification which could be from a single exposure. It was adjusted to an absorbed NOEL of 0.8 mg/kg/day assuming 40% oral absorption. This same NOEL was

also used for evaluating seasonal inhalation exposure since it was also the lowest oral NOEL with subchronic exposure. Although the NOEL did not change with longer exposure more maternal effects were seen at the LOEL including adipsia, reduced body weight gain and reduced survival.

U.S. EPA did not calculate chronic MOEs for occupational exposure to propargite, presumably because they did not believe that the exposures occurred frequently enough throughout the year to be considered chronic exposure. In this risk assessment, it was assumed that exposure to propargite occurred over 4 months of the year for most workers and, therefore, it was frequent enough to consider it chronic. Therefore, chronic NOELs for evaluating dermal and occupational exposure were selected. Since there were no chronic dermal studies for propargite and the NOELs for subchronic and chronic oral studies were comparable, the subchronic dermal NOEL was used for evaluating chronic dermal exposure. Chronic inhalation exposure was evaluated using an oral NOEL of 3.8 mg/kg/day from a 2-year feeding study in rats based on reduced food consumption (Trutter, 1991). Assuming 40% oral absorption, the absorbed NOEL was 1.5 mg/kg/day.

U.S. EPA classified propargite as a group B_2 carcinogen (probable human carcinogen) based on the jejunal tumors in rats (Trutter, 1991) and calculated a Q_1* value of 3.3×10^{-2} $(mg/kg/day)^{-1}$ using a multistage quantal model. The same study and tumors were used in this risk assessment to calculate the oncogenic potency of propargite using the multistage-cancer model in the U.S. EPA BMDS software (version 2.2) to calculate potency. The oncogenic potency estimates derived ranged from 2.4×10^{-3} $(mg/kg/day)^{-1}$ for the MLE to 3.4×10^{-2} $(mg/kg/day)^{-1}$ for the 95% UB. The difference in the upper bound potency estimates appears to be due to a different estimate of the number of animals at risk (U.S. EPA, 1992). To evaluate dermal and inhalation exposures, the potency estimates were adjusted in this risk assessment by an estimated oral absorption of 40%. The adjusted potencies were 5.9×10^{-2} $(mg/kg/day)^{-1}$ for the MLE and 8.4×10^{-2} $(mg/kg/day)^{-1}$ for the 95% UB.

As part of the Food Quality Protection Act (FQPA), U.S. EPA evaluated the developmental and reproductive toxicity studies for propargite and recommended the 10X uncertainty factor be reduced to 1X for several reasons: 1) developmental effects were only observed at maternally toxic doses; 2) exposure assessments did not underestimate potential dietary exposure for infants and children; 3) there is no residential use of propargite. This risk assessment also concluded there was no evidence of increased pre- or post-natal sensitivity to propargite from the developmental and reproductive toxicity studies in rats and rabbits.

U.S. EPA amended their RED several times since the 2001 draft (U.S. EPA, 2008). In 2005, the exposure estimates were revised based on changes to the REIs for walnuts, citrus and mint, changes in spray intervals for potatoes and mint, and changes in application rate for potatoes. Also, there were format changes to some of the appendices for clarity. The RED was amended in 2007 to modify the spray drift label language, the airblast spray application maximum use rate and required personal protective equipment. Another addendum was issued in 2008 to clarify the propargite plant back intervals. There were no changes to the toxicity in any of these amendments.

IV.E. ISSUES RELATED TO THE FOOD QUALITY PROTECTION ACT

The Food Quality Protection Act of 1996 mandated U.S. EPA to "upgrade its risk assessment process as part of the tolerance setting procedures" (U.S. EPA, 1997a and b). The improvements to risk assessment were based on the recommendations from the 1993 National Academy of Sciences report, "Pesticides in the Diets of Infants and Children" (NAS, 1993). The Act required an explicit finding that tolerances are safe for children. U.S. EPA was required to use an extra 10-fold safety factor to take into account potential pre- and post-natal developmental toxicity and the completeness of the data unless U.S. EPA determined, based on reliable data, that a different margin would be safe. In addition, U.S. EPA must consider available information on: 1) aggregate exposure from all non-occupational sources; 2) effects of cumulative exposure to the pesticide and other substances with common mechanisms of toxicity; 3) the effects of *in utero* exposure; and 4) the potential for endocrine disrupting effects.

IV.E.1. Prenatal and Postnatal Sensitivity

Four developmental toxicity studies (2 with rats and 2 with rabbits) were available for propargite. All four studies were acceptable based on FIFRA guidelines. Fetal effects included increased abortions, increased resorptions, reduced fetal viability, delayed ossification, malaligned or fused sternebrae, hydrocephaly and reduced body weights. The lowest developmental NOEL in an acceptable study was equal to or greater than 2.0 mg/kg/day based on delayed ossification of the skull in rabbits. There was only one study in which there was evidence of increased prenatal sensitivity to propargite in rats (Knickerboker, 1979). In this developmental toxicity study in rats, the developmental NOEL was 6 mg/kg/day based on various skeletal variations related to delayed ossification while the maternal NOEL was 25 mg/kg/day based on clinical signs (bloody nasal discharge, diarrhea, soft stools, urinary incontinence, vaginal discharge, abnormal respiration and alopecia). Two reproductive toxicity studies in rats were available for propargite, the main study and an ancillary cross-fostering study. The main study was found acceptable to DPR toxicologists based on FIFRA guidelines. The primary effect observed in pups was reduced body weights. The pup NOEL was the same as parental NOEL, 80 ppm (4 mg/kg/day), suggesting there is no increased postnatal sensitivity to propargite. This risk assessment concluded there may be increased prenatal susceptibility to propargite based on the one developmental toxicity study in rats. However, an additional uncertainty is not recommended based on potential increased prenatal sensitivity since the acute and subchronic NOELs are from a developmental toxicity study. Although there is no indication of increased postnatal sensitivity to propargite with oral exposure in the reproductive toxicity studies for propargite, it is possible that infants and young children may have increased postnatal sensitivity with inhalation exposure. Humans form 80% of their alveoli postnatally, with the alveoli continuing to develop until age eight (Plopper and Fanucchi, 2004; Boyden, 1971). Since propargite is a respiratory irritant based on the LC_{50} study by Hoffman (1992) and there is a lack of long-term inhalation studies for propargite, an additional uncertainty factor is recommended for infants and children.

IV.E.2. Endocrine Effects

The Food Quality Protection Act (FQPA) of 1996 required U.S. EPA to develop a screening program to determine the endocrine disruption potential of pesticides. In 1997, the Risk Assessment Forum of the U.S. EPA published a report that reviewed the current state of science relative to environmental endocrine disruption (U.S. EPA, 1997c). U.S. EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) to develop a strategy for screening and testing of pesticides for their potential to produce endocrine disruption. The EDSTAC members include various stakeholders and scientific experts. This screening and testing process was expected to be implemented by August of 1999 as required by FQPA.

Environmental chemicals can interact with the endocrine system, resulting in cancer, reproductive and/or developmental anomalies (EDSTAC, 1998). It may produce these effects by affecting hormonal production and synthesis, binding directly to hormone receptors or interfering with the breakdown of hormones (U.S. EPA, 1997c). The interim science policy stated in U.S. EPA's 1997 report is that "*the Agency does not consider endocrine disruption to be an adverse endpoint per se, but rather to be a mode or mechanism of action leading to other outcomes*. There were no adverse effects in laboratory animals exposed to propargite that appear to be related to endocrine disruption.

IV.E.3. Cumulative Toxicity

Cumulative toxicity is not anticipated with propargite since it is the only organosulfur pesticide used on food and it is not expected to share any common mechanism of toxicity with any other pesticides.

IV.E.4. Aggregate Exposure

The combined dietary, drinking water and occupational exposure in workers has been addressed in this document. The dietary, drinking water and residential air exposure was less than 10% of the aggregate exposure for most workers. Consequently, its addition did not significantly impact the aggregate exposure. Only for work activities where the occupational exposure was low (e.g., nursery transplanters), did the dietary, drinking water and residential air represent a significant contribution. Even for these activities, the dietary, drinking water and residential air exposure represented only 16% of the aggregate exposure.

The combined exposure in the general population to propargite in the diet, drinking water and residential air was also addressed in this document. A worse case scenario was assumed using the application site air for residential air. The aggregate MOEs for the general public were all greater than 100 and some MOEs (infants - seasonal and chronic, adult - 1-hr, seasonal and chronic) were greater than 1,000. The aggregate carcinogenic risk estimate for the general public was greater than the negligible risk level using the application site air (9.4×10^{-6} to 1.3×10^{-5}). The dietary and drinking water exposure appears to be the primary contributor to

the acute and chronic aggregate exposures for the general public ranging from 76-96% of the total exposure. With seasonal exposure, the application site air exposure represented more than 50% of the total exposure to propargite.

V. CONCLUSIONS

The risks for potential non-oncogenic adverse human health effects with occupational and residential air exposure to propargite were evaluated using margin of exposure (MOE) estimates. The MOE is the ratio of the no-observed-effect level (NOEL) from an animal study to the human exposure dosage. Generally, an MOE of at least 100 is desirable for systemic effects assuming that humans are 10 times more sensitive than animals and that there is a 10-fold variation in the sensitivity between the lower range of the normal distribution of the overall population and the sensitive subgroup. For local irritation with dermal exposure, a MOE of 10 is generally considered adequate when the NOEL is based on dermal irritation in rabbits since rabbits appear to be more sensitive than humans to dermal irritation. However, an uncertainty factor of 30 is recommended with propargite for local dermal effects to protect against dermal sensitization in addition to dermal irritation. The negligible carcinogenic risk level is generally considered one excess cancer case in a million people.

Occupational exposure for propargite handlers is of concern since many of the MOEs for systemic effects with acute, seasonal and chronic exposure were less than the target of 100. The acute dermal MOEs for systemic effects were less than 100 for most applicators, for mixer/loaders with aerial and airblast application of both formulations, for flaggers with WSB formulations and for mixer/loader/applicators (M/L/As) with high pressure equipment. Due to the significantly lower subchronic NOEL, the subchronic dermal MOEs were less than 10 for most handlers. The chronic dermal MOEs for handlers were higher due to the amortization of seasonal exposure over the year, but they were still less than 100 for most scenarios. The acute inhalation MOEs were less than 100 for all applicators regardless of formulation, for mixer/loaders with aerial application of EC formulations and with application methods of the WSB formulations, for all flaggers and for M/L/As with low and high pressure sprayers. The subchronic inhalation MOEs were higher with most greater than 100 except for applicators with aerial or airblast application of both formulations, for mixer/loaders with aerial application of WSB formulations and for M/L/As with high pressure sprayers. The chronic inhalation MOEs were all greater than 100. The acute and subchronic MOEs for local dermal effects were greater than the target of 30 on the body of most handlers, but were less than 30 on the hands of many handlers (most applicators, mixer/loaders for aerial application with EC formulations and flaggers with WSB formulations). The cancer risk estimates for handlers all exceeded the negligible risk level, ranging from 5.9 excess cancer cases in 100,000 to 2.6 excess cancer cases in 100. Aerial applicators using WSB formulations had the highest estimated cancer risk for handlers.

There is less concern about the occupational exposure for fieldworkers since the acute dermal MOEs for systemic effects for fieldworkers were all greater than the target of 100 except for corn detasslers and rose harvesters/cutters. As with handlers, the seasonal dermal exposures for fieldworkers were a concern since all subchronic MOEs were less than 100. The chronic dermal MOEs were higher, but still less than 100 for all scenarios. The acute and seasonal MOEs for local dermal effects were all greater than the target of 30 for the body, but less than 30 for the hands for some scenarios including corn harvesters and detasslers, nectarine and citrus pruners/ leaf thinners, rose harvesters/cutters and jojoba harvesters. The cancer risk estimates

for fieldworkers were between 5.9 in 10,000 and 4.4 in 1,000. Corn detasslers had the highest cancer risk estimates.

The acute, seasonal and chronic inhalation MOEs for bystanders near application sites treated with propargite were all greater than the conventional target of 100. However, the 24-hr MOE for children was less than 1,000 which would meet the criteria for consideration as a possible toxic air contaminant. The carcinogenic risk estimates for bystanders (5.5×10^{-6} to 7.8×10^{-6}) were slightly above the level indicative of negligible risk, suggesting that mitigation should be considered. The cancer risk levels are also high enough to meet the criteria for consideration as a possible toxic air contaminant.

The MOEs for most agricultural workers were already significantly less than 100 from occupational exposure alone, consequently, their aggregate MOEs were not significantly lower with the addition of dietary, drinking water and residential air exposure. In contrast, the aggregate MOEs for the general public were significantly lower with the addition of dietary and drinking water exposure due to their large contribution to the total exposure. Residential air exposure was the major contributor to the aggregate exposure for the general population with seasonal and chronic exposure. Even with dietary and drinking water exposure making a major contribution, the aggregate MOEs for the general public were all greater than 100.

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APPENDIX A

BMDS Multistage Cancer Model Printout

```
================================================================
        Multistage Cancer Model. (Version: 1.9;  Date: 05/26/2010)
        Input Data File: C:/BMDS/BMDS220/Data/Propargite/msc_sarcomas males at risk_Opt.(d)
        Gnuplot Plotting File:  C:/BMDS/BMDS220/Data/Propargite/msc_sarcomas males at risk_Opt.plt
                                                Tue Apr 24 10:06:49 2012
================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

  The form of the probability function is:

  P[response] = background + (1-background)*[1-EXP(
            -beta1*dose^1-beta2*dose^2)]

  The parameter betas are restricted to be positive


  Dependent variable = Sarcomas
  Independent variable = Dose

Total number of observations = 5
Total number of records with missing values = 0
Total number of parameters in model = 3
Total number of specified parameters = 0
Degree of polynomial = 2


Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008


            Default Initial Parameter Values
              Background =           0
                 Beta(1) =    0.0340967
                 Beta(2) =   0.00257144


        Asymptotic Correlation Matrix of Parameter Estimates
```

(*** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

Beta(2)

Beta(2) 1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
Background	0	*	*	*
Beta(1)	0	*	*	*
Beta(2)	0.00588103	*	*	*

* - Indicates that this value is not calculated.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-57.1448	5			
Fitted model	-58.2966	1	2.30373	4	0.6801
Reduced model	-97.5874	1	80.8852	4	<.0001

AIC: 118.593

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
0.0000	0.0000	0.000	0.000	44	0.000
0.7000	0.0029	0.135	0.000	47	-0.368
1.2000	0.0084	0.371	0.000	44	-0.612
5.8000	0.1795	8.257	11.000	46	1.054
11.8000	0.5591	25.717	24.000	46	-0.510

Chi^2 = 1.88 d.f. = 4 P-value = 0.7577

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 4.23265
BMDL = 2.96796
BMDU = 4.90899

Taken together, (2.96796, 4.90899) is a 90 % two-sided confidence interval for the BMD

Multistage Cancer Slope Factor = 0.0336932