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4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

**OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES**

MEMORANDUM

DATE: April 26, 2004

SUBJECT: Human Health Risk Assessment on the Tolerance Petition and Section 3 Registrations concerning the Domestic use of Folpet on Hops, and a New Use of Folpet on Avocados in Florida

DP Barcode: D285511, D286709, D286682
Decision #: 304728, 218140, 191804
MRID #: 45392700, 45392701, 45710401, 45784608
PC Code: 081601
Trade Name: FOLPAN
Class: Fungicide
Product Name (EPA Reg.#): FOLPAN 80 WDG (66222-UI), FOLPAN 50 W (66222-07)
40 CFR §180.191

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06/04

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INTRODUCTION

The Interregional Research Project Number 4 (IR-4), on behalf of the Washington State Hops Commission (which represents all hops growers in the United States [U.S.]), submitted a petition for the establishment of a 120 ppm tolerance for residues of the fungicidal active ingredient (*ai*) folpet in/on the raw agricultural commodity hops (dried). Currently, an import tolerance exists for residues of folpet in/on hop, dried cones at 120 ppm. Additionally, Makhteshim-Agan of North America, Inc. (MANA) has submitted proposed labels: one for a new use on hops for folpet formulation FOLPAN 50 W (a wettable powder, 50% ai), and another for a new folpet formulation FOLPAN 80 WDG (a water dispersible granule, 80% ai), for use on hops and avocados (the use on avocados is restricted to Florida only). The IR-4 tolerance petition and the MANA applications, as well as their associated data sets, complement each other, and are therefore addressed concurrently in the following human health risk assessment conducted by the Health Effects Division (HED).

The human health risks associated with the tolerance petition and registrations are characterized and estimated based on the proposed uses. Because the proposed labels for domestic use of folpet on hops and avocados do not alter the potential for exposure from the food pathway, this risk assessment incorporates dietary (food) risk estimates from the previous risk assessment conducted for the import tolerance for hops (D286670, W. Wassell, 02/20/03), and also relies on the 1999 Reregistration Eligibility Decision (RED). New assessments were required for residue chemistry, hazard characterization, and to estimate exposures from the water, residential and occupational exposure pathways. Amelia Acierto performed the residue chemistry review, Ayaad Assaad performed the toxicology review, Kelly O'Rourke performed the occupational and residential exposure assessment, Sarah Winfield performed the risk assessment, and the drinking water assessment was performed by the Environmental Fate and Effects Division (EFED).

Although this document focuses on folpet applied to hops, the new formulation, FOLPAN 80 WDG, includes a use for avocados (Florida only) on the proposed label. Exposure and risk from application of folpet formulated as FOLPAN 50 W to avocados (Florida only) was assessed in 1999 as part of the RED, and found to be acceptable. The RED assessment can be considered sufficient to support the use of FOLPAN 80 WDG on avocados in Florida for the following reasons:

- Water dispersible granule (WDG) formulations are sufficiently similar to wettable powder (W) formulations to allow translation of residue data between them; therefore, the residue data support the current tolerance.
- The use rates on the proposed FOLPAN 80 WDG label are less than or equal to those on the FOLPAN 50 W label; therefore the proposed use rates support the current tolerance and are supported by the occupational exposure and risk assessment of the RED.
- Occupational inhalation and dermal exposure from a WDG formulation is less than exposure from a W formulation; therefore, potential occupational inhalation and dermal exposure from the proposed formulation is supported by the occupational exposure and risk assessment of the RED.

Label Deficiencies
The proposed use directions for the FOLPAN 80 WDG formulation of folpet on avocados and hops are inadequate. For avocados the label should be amended to revise the preharvest interval (PHI) from 1 day to 7 days to be consistent with the FOLPAN 50 W formulation. For hops, the label should be amended to revise the maximum application rate to the equivalent of 2 lbs ai/A/application, and a maximum seasonal rate of 16 lb ai/A/season, to be consistent with the application rates used to generate the residue data.

Also, for the FOLPAN 80 WDG formulation, although the interim Restricted Entry Interval (REI) of 24 hours indicated on the proposed label is in compliance with the Worker Protection Standard (WPS), at the maximum application rate currently on the label (2.4 lb ai/A/application, which the HED is requiring be reduced to 2 lb ai/A/application) an REI of 48 hours is required to reach an acceptable MOE for postapplication activities. When the application rate on the label is amended, an REI of 24 hours will be adequate.

The proposed use directions on the FOLPAN 50 W formulation of folpet on hops are inadequate. For mixing/loading for aerial application, engineering controls in the form of water soluble bags are required. For mixing/loading for airblast application, personal protective equipment (PPE), including a double layer of clothing and chemical-resistant gloves, is required.

Recommendations for Tolerances and Registration
Provided revised Sections B and F (with the modifications specified in Section 8.0 of this risk assessment) are submitted, the residue chemistry and toxicological databases support the establishment of the FOLPAN 80 WDG registration, the FOLPAN 50 W new use on hops registration, and a permanent tolerance for residues of folpet in/on the following raw agricultural commodity (RAC):

Hop, dried cones ..... 100 ppm

Additionally, folpet formulated as a wettable powder is registered for domestic (*i.e.*, in the U.S.) use on avocados in Florida, and the established tolerance for residues of folpet in/on avocados is 25 ppm. There are tolerances established (40 CFR§180.191) for residues of folpet *per se* in/on a variety of other RACs, **but these are import tolerances only (which means there are no U.S. registrations for use on these RACs), and should be indicated as such in 40 CFR§180.191.** The following RACs are import tolerances: apples (25 ppm), cranberries (25 ppm), cucumbers (15 ppm), grapes (25 ppm), hops (120 ppm), lettuce (50 ppm), melons (15 ppm), dry bulb onions (15 ppm), strawberries (25 ppm), and tomatoes (25 ppm).

1.0 EXECUTIVE SUMMARY

Folpet, a dicarboximide fungicide (which is the same class that captan and captafol are in), acts by reacting with thiol groups, thereby denaturing fungal proteins. In the agricultural setting, folpet (formulated as a water dispersible granule [WDG] and wettable powder [W]) is used as a

post-emergent foliage protectant fungicide to control scab on avocados and downy mildew on hops. Folpet prevents spore germination and subsequent fungal penetration of plant tissues via multiple foliar applications, which cover new plant growth and replenish the fungicide that has deteriorated or has been washed off by rain. Applications are made up to a week to two weeks before harvest. In the residential setting, folpet is used to control wood rot fungi, mold/mildew, and spoilage fungi on wood and other surfaces.

Estimating risks from chemicals involves assessing both the hazard of the chemical by examining its toxicity, and exposure to the chemical by examining residues and various activities (eating, playing, working, etc.). The Health Effects Division (HED) has examined adequate toxicological and residue chemistry data submitted to support the proposed new uses, as well as the label amendments and the tolerance petition. In mammals, folpet is highly reactive with biological tissues. The N-trichloromethylthio (S-CCl_3) side chain reacts under neutral/alkaline conditions in the presence of tissue/blood thiols, forming the short-lived intermediate, thiophosgene. Thiophosgene is highly reactive and severely irritating to mucus membranes and tissues it comes in contact with; it is also a skin irritant and sensitizer. However, due to its transient nature, it is difficult to characterize its role in folpet's toxicity.

Folpet is highly irritating to the eyes and the respiratory system, and although it is not a skin irritant, it is a skin sensitizer. Subchronic and chronic studies in rats (both males and females) demonstrated that the critical systemic toxic effect was treatment related acanthosis and hyperkeratosis and/or ulceration/erosion of the stomach following high oral doses of folpet. Hydrocephaly was observed in one rabbit developmental study, but not in a second rabbit developmental study. Because no other signs of neurotoxicity were observed in other studies and species, there is low concern for folpet's potential for neurotoxicity. Folpet may have characteristics of an endocrine disrupting chemical, and may be subject to more definitive testing to better characterize its possible endocrine disrupting activity when appropriate screening and/or testing protocols have been developed and implemented. Folpet is a probable human carcinogen based on increased incidences of adenomas and carcinomas in the duodenum of male and female mice (two strains: CD-1 and B6C3F1) in two oral studies (the Q* used to predict cancer risk from lifetime exposure to folpet was based on these findings). In rats, there was an increase in the incidences of C-cell adenomas, carcinomas of the thyroid, interstitial cell tumors of the testes, and hyperkeratosis of the esophagus and stomach, but there was no evidence of duodenal tumors. Folpet is also considered mutagenic in a variety of *in vitro* short-term tests for gene mutation, DNA repair and chromosomal aberrations, which supports the weight of evidence for carcinogenicity.

From toxicological studies, the HED determines the dose at which there are no observed adverse effects (termed NOAEL, for No Observed Adverse Effects Level), and uses this as the basis for the hazard component of risk assessment. The NOAEL from the rabbit developmental study, based on the endpoint of hydrocephaly, was used to assess risk for the acute dietary (females 13-50 years), short- and intermediate-term adult dermal (with a 2.7% absorption rate), and short- and intermediate-term inhalation exposure routes (100% absorption assumed). The same

NOAEL and study were used for assessing risk from short- and intermediate-term incidental oral exposure routes and short- and intermediate-term child dermal exposure routes, but the NOAEL was based on the endpoint of maternal decrease in food consumption. The NOAEL from the combined chronic toxicity/carcinogenicity study in rats, based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females, was used to assess risk from chronic dietary exposure (all populations), and risk from long-term dermal and inhalation exposure as well.

The special safety factor for infants and children mandated by the Food Quality Protection Act (FQPA) of 1996 has been reduced to 1X. The reduction was made for the reasons stated above regarding the low concern for folpet's potential for neurotoxicity, in addition to no evidence of qualitative or quantitative susceptibility in two rat developmental toxicity studies, and no evidence of enhanced susceptibility to the pups in two different rat two-generation reproduction studies. However, in order to address the sensitivity of infants and children, the NOAEL from the rabbit developmental study where hydrocephaly was observed, as well as conservative exposure data, were employed in this risk assessment.

FOLPAN 80 WDG (80% ai) and FOLPAN 50 W (50% ai) were considered as sources for exposure to folpet via occupational handler and postapplication activities to hops and avocados in the agricultural setting. Also, Sherwin-Williams Semi-Transparent Wood Preservative Clear Base A14T5 (0.66% ai) was considered as the most conservative residential source of exposure via application to decks and playsets, and then exposure via contact with decks and playsets. To assess risk from these sources, as well as exposure to folpet through the diet, a residue chemistry review, a hazard characterization, an occupational and residential assessment, and an aggregate assessment were conducted; additionally, the previous dietary assessment and 1999 RED were used to support this document.

The exposure contribution from the dietary (food) pathway is minimal. Exposure to folpet via the food pathway could occur from domestic and imported commodities. Dietary exposure to folpet from consumption of avocados and hops, and also from the following import items, was considered (but at most, 1% of these crops are imported): apples, cranberries, cucumbers, grapes, lettuce, melons, onions, strawberries, and tomatoes. The risk contributions from the food pathway were also minimal. At the 99.9th percentile, **6.4% of the acute Population Adjusted Dose (PAD) was used for Females 13-50 years** (the only population subgroup identified as relevant for the acute dietary endpoint), and at the 99.9th percentile, **less than 1% of the chronic PAD was used for the General U.S. Population and all other population subgroups. EPA generally has no concern for exposures below 100% of the acute or chronic PAD. Dietary cancer risk from folpet is 7.2E-08, which also does not exceed the HED's level of concern.**

The exposure and risk contributions from the residential pathway are the most considerable in this risk assessment. The application scenario, an adult applying wood sealant to a deck or playset, includes both inhalation and dermal exposure. Exposure and risk estimates for residential handlers were assessed using the same dermal and inhalation endpoints. **The**

calculated non-occupational handler MOEs are greater than the target of 100, and therefore, not of concern to the HED. The handler cancer risks range from 7.6E-08 to 1.0E-07, which also do not exceed the HED's level of concern. The HED policy for assessing the postapplication scenario of an adult (dermal) or child (dermal and incidental oral) contacting treated decks/playsets has significantly changed since the last residential assessment of folpet (1999 Folpet RED). Currently, exposure to treated wood is considered similarly to exposure from treated turf, which results in a very conservative assessment. **Dermal postapplication exposure to adults results in an MOE of 550, which is above the target MOE of 100 and therefore, not of concern to the HED**. The postapplication scenario for children, is a toddler exposed through incidental oral ingestion and dermal exposure. **The combined postapplication (incidental oral and dermal) exposure to children results in an MOE of 160, also above the target MOE of 100, and not of concern to the HED**. The postapplication cancer risk is 2.1E-07, which also does not exceed the HED's level of concern. In addition, the **cancer risk from combined application and postapplication exposures is 3.1E-07, and does not exceed the HED's level of concern.**

Folpet does not persist in the environment, and therefore, the exposure and risk contributions from the water pathway are minimal. Furthermore, folpet use in the U.S. is geographically limited. Hops are primarily grown in the Pacific Northwest, and folpet use on avocados is restricted to Florida. These geographic limitations, as well as the effects of processing raw water, are not considered in the water assessment, and therefore, the exposure and risk contributions from the water pathway are most likely lower than estimated.

Since folpet may be applied to decks/playsets as well as to agricultural crops, there is potential for people to be exposed to this fungicide in the residential setting as well as through their diet. The HED has performed an aggregate assessment that includes exposure from the dietary, drinking water, and residential pathways. The HED has also performed an aggregate cancer assessment for combined exposure to folpet and captan through the oral route (based on their shared metabolite thiophosgene). **The HED is reasonably certain that no adverse human health effects will occur in the U.S. population or in any population subgroup, including those of infants and children, from the requested uses of folpet.**

There is also potential for occupational exposure to folpet during mixing/loading, application, and postapplication activities. Occupational handlers' total MOEs **are greater than the target MOE (100) and therefore, are not of concern** when **engineering controls**, in the form of water-soluble bags, are used to mitigate exposure from mixing/loading wettable powder for **aerial** application. **The cancer risks also do not exceed the HED's level of concern**, when **engineering controls** are used to mitigate exposure. Postapplication risks were assessed for workers entering hops yards to train, irrigate, and harvest the hops vines. The registrant submitted a chemical-specific dislodgeable foliar residue (DFR) study on hops (MRID#: 45710401). The study was found to be acceptable, and the results are considered useful for occupational postapplication risk assessment purposes. The MOEs resulting from postapplication exposure (based on the proposed WDG label rate of 2.4 lb ai/A) range from 82 to 1,600 on the day of application; **MOEs reach 100 on the second day after application for**

training and harvesting, and 420 by day 14 (i.e, the pre-harvest interval [PHI]) for harvesting. **These MOEs are greater than the target MOE (100) and do not exceed the HED's level of concern. The cancer risks range from 4.7E-07 to 5.0E-06, which also do not exceed the HED's level of concern.**

The proposed label for FOLPAN 80 WDG has an interim 24-hour Restricted Entry Interval (REI). While the technical material has a Toxicity Category IV for Acute Dermal toxicity and Skin Irritation, Primary Eye Irritation is considered to be in Toxicity Category II. Per the Worker Protection Standard (WPS), a 24-hour REI is required for chemicals classified under Toxicity Category II. While the interim REI of 24 hours indicated on the proposed label is in compliance with the WPS, at the application rate currently on the FOLPAN 80 WDG label (2.4 lb ai/A, which the HED is requiring be reduced to 2.0 lb ai/A), **48 hours is required to reach an MOE of 100 for training hops vines**, based on systemic effects. **Pending revision of the application rate, an REI of 24 hours will be adequate**.

The folpet database is considered complete for this risk assessment. However, revised Sections B and F are needed. A listing of the data gaps and label amendments associated with this risk assessment can be found in Section 8 of this document.

2.0 PHYSICAL/CHEMICAL PROPERTIES CHARACTERIZATION

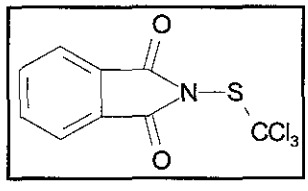
References:

Folpet. PP#1E06310. Petition for the Establishment of a Permanent Tolerance on Hop, Dried Cones and Section 3 Registration Application (ID#066222-UI) for FOLPAN 80 WDG End-use Fungicide on Hops. Summary of Analytical Chem and Residue Data. A. Acierto, D285651, D286707, 04/30/03 (attachment 1).

Folpet - Reregistration Eligibility Decision, EPA 738-R-99-011, 11/1999.

Folpet is the common name of the pesticide chemical (N-(trichloromethylthio)phthalimide). The chemical name and structure of folpet are presented in Table 1.

Table 1: Test Compound Chemical Identity and Structure

Compound	Chemical Structure of Folpet 
Common name	Folpet
Company experimental name	Folpet or Folpan
IUPAC name	*N*-(trichloromethylthio)phthalimide; *N*-(trichloromethanesulfenyl)phthalimide

CAS name	2-[(trichloromethyl)thio]-1*H*-isoindole-1,3(2*H*)-dione
CAS #	133-07-3
End-use product/EP	Folpet 50 W (EPA Reg. No. 66222-07) Folpet 80 WDG (EPA Reg. No. 66222-UI)

Pure folpet is a white crystalline solid with a melting point of 177°C. Technical folpet is an off-white to tan powder with a melting point of 169-177°C. Folpet has low solubility in water at room temperature (0.8 mg/L), has very low solubility in aliphatic hydrocarbon solvents, and has low solubility in aromatic, polar, oxygenated, and hydrocarbon solvents. Folpet is stable in dry conditions at ambient or elevated temperatures, but is not stable under alkaline conditions at high temperatures. Folpet's physicochemical properties are summarized in Table 2.

Table 2: Physicochemical Properties

Parameter	Value	Reference
Melting point/range	177°C (decomp)	*The Pesticide Manual*, 11th edition, British Crop Protection Council
pH	not applicable	
Density	1.72 (20°C)	*The Pesticide Manual*, 11th edition
Water solubility (room temperature)	0.8 mg/L	*The Pesticide Manual*, 11th edition,
Solvent solubility (g/L at 25°C)	6 in carbon tetrachloride 26 in toluene 3 in methanol	*The Pesticide Manual*, 11th edition
Vapor pressure at 25°C	2.1 x 10^{-2} m Pa	*The Pesticide Manual*, 11th edition
Dissociation constant (pK_a) in water	not applicable since the TGAI is not an acid or base	
Octanol/water partition coefficient Log(K_{ow})	logP=3.11	*The Pesticide Manual*, 11th edition
UV/visible absorption spectrum	Media / λmax (nm) / absorbance / molar coeff. (ϵ) dm³/mol/cm neutral 223 0.829 47100 236 0.139 7900 295 0.627 1780 300 0.607 1720 acid 223 0.925 52600 237 0.148 8410 296 0.624 1770 301 0.605 1720 base 225 1.397 19900 238 0.798 11300 247 0.521 7410 280 0.127 1810 289 0.116 1650 301 0.093 1320 [99.5% PAI; UV/visible spectrophotometer]	*MRID 45053701*, D264048

3.0 HAZARD CHARACTERIZATION

References:

Folpet - 3rd Report of the Hazard Identification Assessment Review Committee, A. Assaad, TXR No. 0052080, 08/19/2003 (attachment 2).

Folpet - Reregistration Eligibility Decision, EPA 738-R-99-011, 11/1999.

A more detailed hazard characterization and a discussion of the selected endpoints are provided in the 2003 HED Hazard Identification Assessment Review Committee (HIARC) report and the 1999 RED document, referenced above.

3.1 Hazard Profile

The physical and chemical characteristics of folpet are relevant to the evaluation of its toxicity. Folpet is highly reactive with biological tissues. The labile N-trichloromethylthio (S-CCl_3) side chain is the reactive portion of the molecule and degrades rapidly under neutral/alkaline conditions in the presence of tissue/blood thiols such as cysteine and glutathione to form a key short-lived intermediate, thiophosgene. Thiophosgene is highly reactive and severely irritating to mucus membranes and tissues it comes in contact with; it is also a skin irritant and sensitizer. The thiophosgene moiety is most likely responsible for folpet's activity as a surface fungicide and its toxicity in mammals.

Acute Toxicity

Folpet has low acute oral and dermal toxicity, but is irritating to the mucus membranes in the eyes, esophagus, lungs and stomach. In the acute inhalation study in rats, folpet was moderately toxic but clinical signs of survivors were consistent with upper and lower respiratory irritation (discharge from nose, gasping, labored breathing). Folpet is a dermal sensitizer. The acute toxicity of folpet is summarized in Table 3.

Table 3. Acute Toxicity Profile for Folpet.

Guideline No.	Study Type	MRID #(S).	Results	Toxicity Category
870.1100	Acute Oral - Rat	00144057	LD_{50} =43.8 g/kg (M); 19.5 g/kg (F)	IV
870.1200	Acute Dermal - Rabbit	00141728	LD_{50} = >5.0 g/kg	IV
870.1300	Acute Inhalation - Rat	40592301	LC_{50} = 0.34 mg/L (M); 1.00 mg/L (F); 0.48 mg/L (M+F)	II
870.2400	Primary Eye Irritation	00160444	Irritation	II
870.2500	Primary Skin Irritation	00160430	No Irritation	IV
870.2600	Dermal Sensitization	00160431	Sensitizer	N/A

Subchronic and Chronic Toxicity
Subchronic and chronic studies in rats (both males and females) demonstrated that the critical systemic toxic effect was treatment related acanthosis and hyperkeratosis (abnormal thickening of the skin) and/or ulceration/erosion of the stomach following high oral doses of folpet. In both oral and dermal studies, rats had a dose related decrease in body weight gains.

Developmental and Reproductive Toxicity
In rabbits, there was evidence of qualitative susceptibility following *in utero* exposure to folpet in a study where hydrocephaly and related skull malformations were seen in fetuses at the same dose that caused minimal maternal toxicity (decrease in food consumption). And in another rabbit study there was quantitative evidence of susceptibility following *in utero* exposure to folpet, where fetal effects (delayed ossification) were seen at a dose lower than that which produced maternal toxicity.

However, there was no qualitative or quantitative evidence of increased susceptibility in rats following *in utero* exposure to folpet. Developmental effects were seen at doses higher than or equal to doses at which maternal toxicity was observed. Furthermore, there was no quantitative or qualitative evidence of increased susceptibility in either of the two-generation reproduction studies in rats.

Neurotoxicity
The HIARC concluded there is not a concern for neurotoxicity resulting from exposure to folpet. There are no signs of neurotoxicity in any species and strain tested except in one rabbit developmental study where hydrocephaly was observed.

Carcinogenicity
Folpet has been classified as a B2 carcinogen (probable human carcinogen) based on the increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two oral studies conducted with two strains (CD-1 and B6C3F1). In rats, folpet was classified as a carcinogen in males only based on an increase in the incidences of C-cell adenomas and carcinomas of the thyroid as well as interstitial cell tumors of the testes. There was no evidence of duodenal tumors in rats, however there was a dose related increase in incidence and severity of hyperkeratosis of the esophagus and stomach.

Mutagenicity
The HIARC concluded that there is a concern for mutagenicity resulting from exposure to folpet. Folpet exhibited positive mutagenic activity in a variety of *in vitro* short term tests for gene mutation, DNA repair and chromosomal aberrations; all of which support the weight of evidence for carcinogenicity.

3.2 FQPA Considerations

The HED HIARC met on February 13, 2003 to evaluate the available hazard and exposure data for folpet (as required by the FQPA of August 3, 1996). The HIARC made a determination of susceptibility, as well as performed a degree of concern analysis regarding pre- and/or postnatal

toxicity resulting from exposure to folpet. The HIARC recommended that the FQPA Safety Factor be reduced to 1X based upon the following:

- There was no evidence of quantitative or qualitative evidence of increased susceptibility following *in utero* exposure in two developmental toxicity studies in the rat;
- There was no quantitative or qualitative evidence of enhanced susceptibility to the pups in two different two-generation reproduction studies in the rat;
- Although there was qualitative evidence of susceptibility in one developmental study in the rabbit (hydrocephaly [developmental LOAEL = 20 mg/kg/day; developmental NOAEL = 10 mg/kg/day]), and quantitative evidence of susceptibility in the other developmental study in the rabbit (delayed ossification [developmental LOAEL = 40 mg/kg/day; developmental NOAEL = 10 mg/kg/day]), the HIARC determined that there is low concern for the observed susceptibility because:
  - clear NOAELs/LOAELs were established in these studies;
  - there were inconsistencies in the results seen between these studies (hydrocephaly seen in one study of was not seen in the other study);
  - a conservative determination was made to use hydrocephaly as the endpoint for acute dietary, and short- and intermediate-term dermal and inhalation exposure scenarios, in spite of lack of replication of this effect;
  - the dose selected for overall risk assessment would address the concerns for developmental toxicity seen in this species;
  - the structure-activity relationship analysis showed that there was not evidence of increased susceptibility in rabbits following *in utero* exposure to captan, a structural analog of folpet.
  - and there are no other signs from the available toxicology database of a concern for neurotoxic effects.
- Therefore, the HIARC concluded that there is no residual uncertainty for pre-and or post-natal toxicity.

The HIARC also determined that a developmental neurotoxicity (DNT) study for folpet is not warranted based upon the following considerations:

- The hydrocephalus seen in one fetus/1 litter at 20 mg kg/day in the presence of maternal toxicity was not seen at higher doses (40 or 160 mg/kg/day) in another study in the same strain of rabbit.
- No alterations to the fetal nervous system were seen in the developmental rat study at the same doses that induced hydrocephaly in the rabbits.
- Although there are no acute or subchronic neurotoxicity studies, there is no evidence of neurotoxicity or neuropathology in adult animals in any of the studies.
- The available data indicate that the DNT study would have to be tested at dose levels higher than 150 mg/kg/day, because no developmental toxicity was observed in rats at 2,000 mg/kg/day. In addition, given the results in the two-generation reproduction study (NOAEL of 168 mg/kg/day), it is anticipated that in order to elicit any fetal nervous system abnormalities in the DNT study, the selected dose levels would have to be higher than 160 mg/kg/day.
- Since the dose level selections for the DNT study would be greater than 160 mg/kg/day, the resultant NOAEL would be either comparable to, or higher than, the doses currently used in

the risk assessment. The NOAEL of 10 mg/kg/day selected for the acute reference dose and the residential exposure assessment are seventeen times lower than the offspring NOAEL in the reproduction study. The NOAEL of 9 mg/kg/day selected for the chronic reference dose is nineteen times lower than the offspring NOAEL in the reproduction study. Therefore, it is unlikely that the DNT study would change the current doses used for overall risk assessments.

3.3 Dose Response Assessment

On February 13, 2003 and on May 27, 2003, the HED HIARC reviewed the recommendations of the toxicology reviewer for folpet with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to folpet was also re-evaluated as required by the FQPA of 1996 under the 2002 Office of Pesticide Programs (OPP) 10X Guidance document. The doses and toxicological endpoints selected by the HIARC for various exposure scenarios are summarized in Table 4.

Table 4. Summary of Toxicological Doses and Endpoints for Folpet

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = **10** mg/kg/day UF = **100** **Acute RfD** = **0.1** mg/kg/day	FQPA SF = **1X** **aPAD** = acute RfD / FQPA SF = **0.1** mg/kg/day	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations.
Acute Dietary (General population including infants and children)	An appropriate endpoint attributable to a single dose was not identified for the General Population including Infants and Children for this risk assessment in the toxicology database.		
Chronic Dietary (All populations)	NOAEL= **9** mg/kg/day UF = **100** **Chronic RfD** = **0.09** mg/kg/day	FQPA SF = **1X** **cPAD** = chronic RfD / FQPA SF = **0.09** mg/kg/day	Combined Chronic Toxicity/ Carcinogenicity Study in Rats LOAEL = **35** mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females.
Short-Term Incidental Oral (1-30 days)	NOAEL (maternal) = **10** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on a *decrease in food consumption*
Intermediate-Term Incidental Oral (1- 6 months)	NOAEL (maternal) = **10** mg/kg/day	**Residential** LOC for MOE = **100** **Occupational** = NA	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on a decrease in food consumption

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Short-Term Dermal (1 to 30 days)	NOAEL (developmental)= **10** mg/kg/day (dermal absorption rate = 2.7 %	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations.
Intermediate-Term Dermal (1 to 6 months)	NOAEL (developmental)= **10** mg/kg/day (dermal absorption rate = **2.7** %	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations.
Long-Term Dermal (>6 months)	NOAEL= 9 mg/kg/day (dermal absorption rate = **2.7** %when appropriate)	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Combined Chronic Toxicity/ Carcinogenicity Study in Rats LOAEL = **35** mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females.
Short-Term Inhalation (1 to 30 days)	NOAEL (developmental) = **10** mg/kg/day ‡	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations.
Intermediate-Term Inhalation (1 to 6 months)	NOAEL (developmental) = **10** mg/kg/day ‡	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Rabbit Developmental Toxicity LOAEL = **20** mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations.
Long-Term Inhalation (>6 months)	NOAEL= 9 mg/kg/day ‡	**Residential** LOC for MOE = **100** **Occupational** LOC for MOE = **100**	Combined Chronic Toxicity/ Carcinogenicity Study in Rats LOAEL = **35** mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females.
Cancer (oral, dermal, inhalation)	Folpet is a B2 carcinogen (probable human carcinogen) based on the increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two strains (CD-1 and B6C3F1). The **Q_1* is** 1.86 x 10^{-3} $(mg/kg/day)^{-1}$.		

UF = uncertainty factor, FQPA SF = Special FQPA safety factor, NOAEL = no observed adverse effect level, LOAEL = lowest observed adverse effect level, PAD = population adjusted dose (a = acute, c = chronic) RfD = reference dose, MOE = margin of exposure, LOC = level of concern, NA = Not Applicable
‡ = Assume inhalation absorption rate = 100% of the oral absorption.

NOTE: The Special FQPA Safety Factor recommended by the HIARC **assumes** that the exposure databases (dietary food, drinking water, and residential) are complete and that the risk assessment for each potential exposure scenario includes all metabolites and/or degradates of concern and does not underestimate the potential risk for infants and children.

3.4 Endocrine Disruption

The EPA is required under the Federal Food, Drug, and Cosmetic Act (FFDCA), as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific bases for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. The EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

The Environmental Fate and Effects Division (EFED) has found that folpet may have characteristics of an endocrine disrupting chemical in smaller mammals, birds, and freshwater and estuarine/marine fishes and invertebrates. EFED found that effects include possible thyroid and adrenal involvement. When the appropriate screening and/or testing protocols being considered under the EPA's EDSP have been developed, folpet may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

4.0 EXPOSURE ASSESSMENT AND CHARACTERIZATION

References:

Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Folpet on Hops, D285666, K. O'Rourke, 04/20/04 (attachment 3).

Folpet. PP#1E06310. Summary of Analytical Chem and Residue Data, D285651, D28670, A. Acierto, 04/30/03 (attachment 1).

PP#2E06512; HED Dietary Exposure Assessment: Human Dietary Exposure Assessment for Use of Folpet on Hops to be Imported, D286670, W. Wassell, 02/20/2003 (attachment 4).

Folpet Acute, Chronic, and Cancer Dietary Exposure Analyses. D287372, T. Morton, 12/19/2002.

Environmental Risk Assessment for Folpet Use On Hops (PC Code 081601, DP Barcode D285512), L.R. Brown, I.L. Maher, S. Abel, P. Jennings, 10/09/2003.

4.1 Summary of Proposed and Registered Uses

Folpet was first registered in the U.S. as a fungicide, insecticide and miticide on roses and other ornamental plants. Currently, folpet is registered as a fungicide, as well as a wood sealant/preservative, and an additive to coatings and sealants in paint, stain and caulk. There is a

tolerance for folpet residues in/on avocados, and a registration for folpet formulated as a wettable powder for use on avocados in Florida (also, there is a proposed registration for folpet formulated as a WDG for use on avocados in Florida). Folpet containing paints and stains are available for use both occupationally and by the homeowner. Additionally, tolerances are established for residues of folpet on apples, cranberries, cucumbers, grapes, hops, lettuce, melons, dry bulb onions, strawberries, and tomatoes to allow commodities treated with folpet to be imported. Domestic uses for folpet are not established for these crops. However, folpet formulated as a W and a WDG are being proposed for domestic use on hops. Most of the hops grown in the U.S. are located in the Pacific Northwest. Table 5 below lists the folpet products and their use profiles as they pertain to the registered and proposed uses addressed in this document.

Table 5: Use Profile and Summary of Directions for Registered and Proposed Uses of Folpet Formulations

Product Name/ Formulation	*agricultural*								
	Crops	**Diseases**	**Applic. Rate (lb ai/A)**	**Max No. of Applic. per Season**	**Max Seasonal Applic. Rate (lb ai/A)**	**Interval b/n applic.**	**PHI (days)**	**Application Method**	**Use Directions and Limitations**
FOLPAN 50 W (wettable powder) (50% ai)	hops	To control downy mildew	2.0	8	16	10-14	14	Labeled as foliar applicant by ground or aerial equipment: • aerial • airblast sprayer	Begin when spikes first appear on hop crowns in spring by foliar spray, ground or aerial application. Do not apply through any type of irrigation system. Do not graze cover crops that have been treated or harvest the forage for silage or hay. Do not use in combination with or closely following oil sprays. Do not apply directly to water, to areas where surface water is present, or to intertidal areas below the mean high water mark since the pesticide is highly toxic to fish.*
FOLPAN 80 WDG (water dispersible granule) (80% ai)	hops	To control downy mildew	2.4 (2.0)*	8	25.6 (16)*	10-14	14	Labeled as foliar applicant by ground equipment: • airblast sprayer	
	avocado	To control scab (*Sphaceloma*)	3.0	5	21 (15)*		1 (7)*	Labeled as foliar applicant	Apply to foliage when bloom buds begin to swell, or late bloom, depending on susceptibility.*
Product Name/ Formulation	*non-agricultural*								
	Use Sites	**Diseases**	**Applic. Rate (lb ai/gal)**	**Max No. Applic. per Season**	**Max Seasonal Applic. Rate**	**drying time (hrs)**		**Application Method**	**Use Directions and Limitations**
Sherwin-Williams Semi-Transparent Wood Preservative Clear Base A14T5 (0.66% ai)	decks and wood siding	protects wood from rot, deterioration, and mildew	0.045	two coats	NA	allow 24 hours to dry if 2nd coat is necessary or before walking on it.		apply uniformly with • brush • pad • spray	Use at 50°F and above. Stir thoroughly before and occasionally during use. Cover 100 to 200 sq. ft. per gallon on rough or porous surfaces. Up to 350 sq. ft. per gallon on smooth, non-porous wood surfaces. Do not stain in direct sun or on hot surface. Use two coats on badly weathered or unfinished wood and whenever prominent unsightly lap marks appear on first coat. Do not use on composition board or wood roofs. Be sure decks and floors are either bare or well worn before staining.Reapplication timing not specified.
Olympic (R) Clear Wood Preservative (0.50% ai)	exterior wood above ground surfaces	protects wood from rot, decay, mildew, ultra violet light, and moisture damage	0.033	one coat	NA	24-48		apply with: • natural bristle brush • dipping • spray	Use at 50°F and above, but avoid application to a hot surface in direct sunlight. Stir thoroughly before and occasionally during use. Cover 150 to 250 sq. ft. per gallon depending on texture, porosity, and dryness of wood. Reapplication is recommended every 2-4 years.

*NOTE See following page for label deficiencies.

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Label Deficiencies

Both the FOLPAN 50 W and 80 WDG labels, should explicitly state that if other formulations containing the ai are applied, do not apply more than a total of 16 lb ai/A/yr (for hops) and 21 lb ai/A/yr or 15 lb ai/A/yr (for avocados, for the 50 W and 80 WDG labels respectively).

FOLPAN 80 WDG:

- The maximum rate of application on hops should be revised to be consistent with the amounts used to generate the residue data (*i.e.*, the amounts of product should be equivalent to 2 lb ai/A/application, and a maximum seasonal rate of 16 lb ai/A/season).
- The PHI for avocados should be revised to be consistent with the FOLPAN 50 W label (*i.e.*, 7 days).
- The maximum seasonal application rate for avocados should be revised to reflect the maximum application rate multiplied by the maximum number of applications per season (*i.e.*, 3.0 lb ai/A X 5 applications = 15 lb ai/A/season).
- At the application rate currently on the FOLPAN 80 WDG label, a 48 hour REI is required to reach an acceptable MOE for training hop vines. Pending revision of the application rate (as indicated in the first bullet of this list) the REI of 24 hours, currently on the label, will be adequate.

FOLPAN 50 W:

- The proposed use directions on hops should be revised to include engineering controls in the form of water soluble bags for mixing/loading for aerial application; and, for mixing/loading for airblast application, personal protective equipment (PPE), including a double layer of clothing and chemical-resistant gloves, is required.

4.2 Dietary Exposure/Risk Pathway

4.2.1 Residue Profile

Metabolism

The nature of the residue in plants has been defined. The residue of concern in plants is folpet *per se*. There are two metabolites of folpet, phthalimide and phthalic acid, but they are not regulated as phthalimide is not of toxicological concern, and phthalic acid is not a carcinogen and is far less toxic than the parent. The nature of the residue in livestock has not been defined, and is not required at the present time as there are no livestock feed items associated with avocado (the only registered food use for folpet) or hops.

Residue Data

U.S. Data: The geographic representation of the submitted residue data in/on dried hops are adequate with respect to the number and location of the field trials. The petitioner conducted six field trials in three typical hops growing areas in the U.S., which satisfied the requirement of the EPA. The residues in the untreated control crops were below the limit of quantification

(LOQ). Residues of folpet in treated crops ranged from 2.43 to 91.8 ppm, following eight applications of 2 lb ai/A/application or a total of 16 lb ai/A/season for either formulation (50W or 80WDG). The highest residues were <100 ppm, which supports a tolerance of 100 ppm.

Table 6. Summary of Folpet Residue Levels on Hop, Dried Cones from U.S. crop field trials.

Commodity	Total Applic. Rate, lb ai/A	PHI (days)	Analyte	Residue Levels (ppm)				
				Min.	Max.	HAFT*	Mean	Std. Dev.
Hop, dried cones	16	9-15	folpet	2.43	91.8	80.22	40.11	33.37

* HAFT = Highest Average Field Trial.

German Data: In 2003, MANA requested an import tolerance for residues of folpet in/on hops. At that time, MANA submitted crop field trials and a processing study that were conducted in Germany (MRIDs 457847-01, 457847-02, and 457847-03). Eight applications of FOLPAN 80 WDG were made at increasing concentrations (from 0.81 lb ai/A to 3.82 lb ai/A). The average amount of folpet applied to a field (considering the five fields treated) was 19.64 lb ai/A/trial. The resulting residues in/on hop, dried cones ranged from 24.7 ppm to 65 ppm. The average amount of folpet residues in/on hop, dried cones (considering the five fields treated) was 40.18 ppm. The application rates and resulting residues of the crop field trials are summarized below in Table 7.

Table 7. Summary of German crop field trials and Folpet Residue Levels on Hop, Dried Cones.

MRID:	45784701	45784702				Data Combined/Averaged
# of fields treated with folpet	1	4				5
lowest appl. rate (lb ai/A)	**0.81***	0.87	0.90	0.88	0.96	0.88
highest appl. rate (lb ai/A)	3.59	3.69	3.80	3.62	**3.82***	3.70
avg appl. rate (lb ai/A)	2.34	2.45	2.46	2.46	**2.56***	2.45
# of appl.	8	8	8	8	8	8
days between appl	8 to 16	8 to 14	8 to 14	7 to 15	7 to 15	7 to 16 (range)
total applied (lb ai/A)	18.74	19.62	19.70	19.70	**20.46***	19.64
residues; hops, dried cones (ppm) (DALT 14)**	24.7	65	59.4	25.5	26.3	40.18

*bolded numbers are the highest/lowest values

**DALT = days after last treatment, all are 14 days, which is equivalent to the PHI

These data support a tolerance of 100 ppm for residues of folpet in/on hops, dried cones.

Tolerances

Tolerances are established for residues of folpet (N-(trichloromethylthio)phthalimide) in/on various imported raw agricultural commodities (RACs) at levels ranging from 15 - 50 ppm (40 CFR §180.191). Avocado is the only domestic food crop currently registered for folpet in the

U.S. (tolerance: 25 ppm). No tolerances have been established on livestock commodities. The submitted residue chemistry data support the establishment of a tolerance for residues of folpet at 100 ppm in/on hop, dried cones.

Enforcement Methods
An adequate GC enforcement method is available for enforcing tolerances of folpet in/on plant commodities and is listed as Method I, in PAM, Vol. II. In addition, two GC/ECD methods, for oily crops (Method 568W-1) and for non-oily crops (Method FP/15/91), have undergone successful validation by the EPA. The enforcement methods described as Methods IIa and IIb in PAM, Volume II (Section 180.191) are based on colorimetric detection of folpet residues and are no longer considered suitable for tolerance enforcement. Folpet is completely recovered using FDA Multiresidue Protocols D and E (non- fatty) PAM I Sections 232.4 and 211.1) and is partially recovered using FDA Multiresidue Protocol E (fatty) (PAM I, Section 212.1).

International Harmonization
There are currently no Codex, Canadian, or Mexican MRLs or tolerances for folpet on hops. Therefore, international harmonization is not a concern at this time.

4.2.2 Acute Dietary

The HIARC identified an acute Reference Dose (aRfD) for females 13 to 50 years. An aRfD was not identified for the general population. The aRfD (0.1 mg/kg/day) is based on an increased number of fetuses and litters with hydrocephaly and related skull malformations at the lowest observed adverse effect level (LOAEL) of 20 mg/kg/day in the developmental toxicity study in rabbits (NOAEL = 10 mg/kg/day, Uncertainty Factor [UF] = 100, FQPA SF = 1X). The acute Population Adjusted Dose (aPAD) is equal to the aRfD divided by the FQPA SF (*i.e.* 0.1/1 = 0.1 mg/kg/day = aPAD). The aPAD was used to assess acute dietary risk.

The HED conducted the dietary exposure assessment using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID™, Version 1.3), which incorporates consumption data from USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1994-1996 and 1998. DEEM™ is a dietary exposure analysis system developed by Novigen Sciences, Inc. that is used to estimate exposure to pesticide residues in foods comprising the diets of the U.S. population, including population subgroups.

A Tier III acute probabilistic dietary exposure analysis was performed. The assumptions for most commodities (apples and apple juice; cranberries; cucumbers; grapes, grape juice, wine, raisins; lettuce; melons; onions; strawberries; and tomatoes) were anticipated residue levels (incorporated into residue distribution files) and the percent crop-treated estimate for imported crops consumed in the U.S. (which is a maximum of 1%, based on information derived through an analysis of import and domestic production data available from the USDA [United States Department of Agriculture] for the years 1995 through 1999, adjusted for the countries in which folpet is registered). For avocados, the assumptions of the acute dietary exposure

analysis were anticipated residue levels and 11% crop treated (because Florida avocado acreage is 11% of the total U.S. avocado acreage as reported by USDA). For hops, the assumptions of the acute dietary exposure analysis were tolerance level residues (100 ppm) and 100% crop-treated. The acute dietary exposure (food only) to folpet for the population subgroup females 13 to 50 years is presented in Table 8. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective). Refinements such as use of anticipated residue and percent crop-treated estimates for hops may yield lower estimates of acute dietary exposure.

Table 8. Results of the Acute Dietary Exposure Analysis for Folpet.

Population Subgroup	aPAD (mg/kg/day)	95th Percentile		99th Percentile		99.9th Percentile	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
Females 13 to 50 years	0.1	0.000030	<1	0.000320	<1	0.006397	6.4

4.2.3 Chronic Dietary

The HIARC identified a chronic Reference Dose (cRfD = 0.09 mg/kg/day), based upon hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach epithelium in both sexes at the LOAEL of 35 mg/kg/day in the rat chronic toxicity study (NOAEL = 9 mg/kg/day, UF = 100, FQPA SF = 1X). The chronic PAD (cPAD) is equal to the cRfD divided by the FQPA SF (cPAD = 0.09/1 = 0.09 mg/kg/day). The cPAD was used to assess chronic risk.

The HED used DEEM-FCID™, Version 1.3, for conducting a chronic dietary (non-cancer) exposure analysis. A Tier III chronic DEEM-FCID™ analysis was performed. The assumptions for the commodities considered in this Tier III analysis were the same as outlined above for the acute dietary analysis. The chronic dietary exposure (food only) to folpet for representative population subgroups are presented in Table 9. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective). Refinements such as use of anticipated residue and percent crop-treated estimates for hops may yield lower estimates of chronic dietary exposure.

Table 9. Results of Chronic Dietary Exposure Analysis for Folpet.

Population Subgroup	cPAD (mg/kg/day)	Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.09	0.000039	<1
All Infants (< 1 year)	0.09	0.000045	<1
Children 1-2 years	0.09	0.000107	<1
Children 3-5 years	0.09	0.000090	<1
Children 6-12 years	0.09	0.000048	<1
Youth 13-19 years	0.09	0.000027	<1
Adults 20-49 years	0.09	0.000031	<1
Females 13 to 50 years	0.09	0.000032	<1
Adults 50+ years	0.09	0.000033	<1

4.2.4 Cancer Dietary

The HED Cancer Peer Review Committee (CPRC) classified folpet as a B2 carcinogen (probable human carcinogen) based upon increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two strains. The Q_1^* for folpet is 1.86×10^{-3} $(mg/kg/day)^{-1}$.

A Tier III chronic (cancer) dietary exposure analysis was performed using DEEM-FCID™, Version 1.3. The assumptions of this Tier III analysis were the same as outlined above for the acute exposure analysis. The chronic dietary exposure (food only) to folpet for the general U.S. population is presented in Table 10. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective). Refinements such as use of anticipated residue and percent crop-treated estimates for hops may yield lower estimates of chronic dietary exposure.

Table 10. Chronic (Cancer) Dietary Exposure Results for Folpet.

Population Subgroup	Exposure (mg/kg/day)	Estimated Cancer Risk
General U.S. Population	0.000039	7.2×10^{-8}

4.3 Water Exposure/Risk Pathway

The environmental fate data submitted for folpet are considered incomplete. However, laboratory studies suggest that folpet breaks down via abiotic hydrolysis and microbially-mediated degradation. Folpet appears to degrade rapidly, based on laboratory half-lives ranging from 2.6 hours to 2 days in aquatic and terrestrial environments. Folpet's degradates include

phthalimide (PI), phthalamic acid (PAM), and phthalic acid (PAI). Limited data on PI suggest some persistence based on a half-life of 17 days, and some mobility based on a K_F ranging from 1.2-5.0 for most soil types (sand, loam, and clay soil) and 15.6 for loamy sand, indicating potential movement into ground and surface waters. For these reasons, both folpet and PI residues in drinking water were estimated. However, the HED Metabolism Committee concluded that only folpet residues need to be included in the non-cancer and cancer risk assessments, and therefore residues of PI in drinking water are not considered in this assessment.

The EPA currently lacks sufficient water-related exposure data from monitoring to complete a quantitative drinking water exposure analysis for folpet. Therefore, the potential groundwater and surface water exposure to folpet was assessed based on screening models, which provide Tier I computer-generated Estimated Drinking Water Concentrations (EDWCs). EDWCs are calculated by EFED using the highest application rate of folpet (the registered domestic use of FOLPAN 50 W on avocados: 21 lb ai/A/yr, 3.0 lb ai/A applied 7 times per year).

The FQPA Index Reservoir Screening Tool (FIRST) was used to generate EDWCs for surface water and the Screening Concentration in Ground Water model or SCI-GROW was used to generate EDWCs for groundwater. These models take into account the use patterns and the environmental profile of a pesticide, but do not include consideration of the impact that processing raw water for distribution as drinking water would likely have on the removal of pesticides from the source water. The primary use of these models by the EPA at this stage is to provide a coarse screen for determining whether pesticide residues in water are not of concern.

For any given pesticide, the FIRST model generates two surface water derived EDWCs: one for acute exposure to the pesticide, and another for chronic exposure to the pesticide. The SCI-GROW model on the other hand, generates a single groundwater derived EDWC. That EDWC is used in assessments of both acute and chronic dietary risk. It is not unusual for the groundwater EDWC to be significantly lower than the surface water EDWCs.

Tier I FIRST surface water modeling for folpet residues predicts the peak (acute) EDWC is not likely to exceed 309 ppb (µg/L) and the annual daily average chronic EDWC is not likely to exceed 0.62 ppb. The SCI-GROW modeling estimates that folpet residues in groundwater are not likely to exceed 0.06 ppb, a concentration that may be considered as both acute and chronic upper bound values. These EDWCs are used in the aggregate risk assessment to determine whether exposure to folpet through drinking water is of concern to the HED (see Section 5.0 of this document).

4.4 Residential Exposure/Risk Pathway

Products containing folpet are registered as a fungicide/preservative in wood sealants for use on exterior wood surfaces including residential/recreational decks and playsets, as well as siding, shingles, and fences. Two registered labels available for residential use are Sherwin-Williams Semi-Transparent Wood Preservative Clear Base A14T5 with 0.66% ai (EPA Reg. No. 577-

539), and Olympic® Clear Wood Preservative with 0.5% ai (EPA Reg. No. 7313-6). This residential exposure and risk assessment was primarily conducted using the label for the Sherwin-Williams product, because it has the highest application rate (*i.e.*, 1 gal/100 ft^2) and the largest amount of ai.

4.4.1 Home Uses

Residential handlers may receive short-term dermal and inhalation exposure to folpet when applying the ready-to-use formulations. Adults and children may be exposed to folpet residues from dermal contact with treated wood during postapplication activities. In addition, toddlers may receive short- and intermediate-term oral exposure from incidental ingestion (*i.e.*, hand-to-mouth) during postapplication activities on treated decks or playsets.

Exposure and risk estimates of dermal and inhalation exposure for residential handlers were assessed using: an oral NOAEL of 10 mg/kg/day (LOAEL = 20 mg/kg/day based on the increase in number of fetuses and litters with hydrocephaly and related malformations). Because the endpoints are based on an oral study, the estimated dermal exposures were adjusted by applying a 2.7 percent dermal absorption rate, while absorption in the lung was assumed to be 100 percent. In addition, these endpoints are applicable to females 13+ years old; therefore, a 60-kg body weight was used in the calculations. The endpoints are the same for both dermal and inhalation exposure, therefore, the individual dermal and inhalation MOEs were combined into a total MOE. The dermal endpoint used in the adult postapplication exposure assessment is the same as that for residential handlers. To assess toddler incidental ingestion and dermal exposure, the maternal NOAEL (10 mg/kg/day) from the rabbit developmental toxicity study was used; which is based on a decrease in food consumption at the LOAEL of 20 mg/kg/day. Please note that while this is not the endpoint that the HIARC selected for dermal exposure, it occurs at the same dose level as the developmental NOAEL (*i.e.*, protective of developmental effects), is from the same study, and is more applicable to toddlers than hydrocephaly effects, which apply only to females of child-bearing age. In addition, using the maternal NOAEL for the toddler dermal assessment is more protective in that it allows for combination with the toddler incidental oral assessment, because they are compared to the same endpoint. The HIARC decided to remove the FQPA safety factor (*i.e.*, reduce to 1X) for the U.S. population and all population subgroups and for all exposure scenarios. Thus, the target MOE for risk assessment purposes is 100.

To quantify cancer risk, the Q_1^* of 1.86×10^{-3} $mg/kg/day^{-1}$ was multiplied by the estimated lifetime average daily doses from handler and postapplication exposure. As with the non-cancer assessment, dermal doses were first adjusted for dermal absorption (*i.e.*, 2.7%) because the Q_1^* is based on an oral study, while inhalation doses were assumed to be 100% absorbed. Cancer risks for residential handler and postapplication that exceed 10^{-6} are indicative of concern.

No chemical-specific exposure or residue dissipation data for handler or postapplication activities were submitted to the HED in support of the registered wood sealant uses. Handler exposures were previously assessed in the 1999 RED for Folpet. The assessment has been revised in this document, using unit exposure data from the Residential SOPs, to account for the likelihood of the residential handler wearing short sleeves and short pants, rather than the long sleeves/pants assumed for both occupational and residential handlers in the RED. The postapplication risk assessment is based on modifications to the generic assumptions for turf assessment specified by the Recommended Revisions to the Residential SOPs and approaches evaluated by the HED's Exposure Science Advisory Committee (ExpoSAC).

4.4.1.1 Handler

Dermal and inhalation daily doses for residential handlers were calculated for the wood sealant formulation using data for applying a paint or stain. The following handler scenarios were evaluated:

1. application of ready-to-use wood sealant with a paint brush, and
2. application of ready-to-use wood sealant using an airless sprayer

The following assumptions (which include HED standard values) were used to calculate exposures:

- The maximum application rate from the Sherwin-Williams wood preservative product (EPA Reg. No. 577-539) of 0.045 lb ai/gal (*i.e.* 0.66% ai * 6.8 lb/gal) was assumed.
- Handlers were assumed to be using a paint brush to apply 5 gal/day, or an airless sprayer to apply 15 gal/day.
- The unit exposure values were obtained from Appendix B of the 1997 Draft SOPs for Residential Exposure Assessments.
- Residential handler body weight is 60 kg for the non-cancer assessment, because the endpoint is based on a developmental effect; 70 kg was used for the cancer assessment.
- For the cancer assessment, it was assumed that the residential handlers worked 1 day/year, for 50 years of a 70-year lifetime.

The unit exposure values from PHED are considered to be central tendency. The application rates, treatment variables, etc. used in this assessment are upper percentile values. Therefore, the potential dose is characterized as mid- to high-end. As shown in Table 11, the calculated non-occupational handler MOEs are greater than the target of 100, and therefore, are not of concern to the HED. The handler cancer risks range from 7.6E-08 to 1.0E-07, which also do not exceed the HED's level of concern.

Table 11. Exposure and Risk Assessment for Residential Handlers

Scenarios for Residential Folpet Uses	PHED Unit Exposure[1] (mg/lb ai)	Maximum Application Rate	Amount Used	Daily Dose[2] (mg/kg/day) [60kg BW]	Short-/ Int-Term MOE[3]	Total MOE[4]	LADD (mg/kg/day)[5]	Cancer Risk[6]
(1) Apply Sealant with a Paint Brush	Dermal: 230	0.045 lb ai/gal	5 gal/day	0.023	430	410	4.1E-05	7.6E-08
	Inhalation: 0.284			0.0011	9,400			
(2) Apply Sealant with an Airless Sprayer	Dermal: 79		15 gal/day	0.024	420	300	5.6E-05	1.0E-07
	Inhalation: 0.83			0.0093	1,100			

[1] PHED Unit Exposure values are for residential baseline protection (*i.e.*, short-sleeved shirt and short pants).
Paint brush: dermal - 14 to 15 replicates, BC grade, low to medium confidence;
inhalation - 15 replicates, C grade, medium confidence
Airless Sprayer: dermal - 15 replicates, B grade, high confidence;
inhalation - 15 replicates, C grade, medium confidence

[2] Daily Dose = (Unit Exposure x Absorption Factor [dermal = 0.027, inhalation = 1] x Application Rate x Amount Used)/Body Weight. A 60-kg body weight was used for non-cancer assessment because endpoint is based on a developmental effect; 70 kg used for the cancer assessment (not shown).

[3] MOE = NOAEL/ Daily Dose. Short-/Intermediate-term Dermal NOAEL= 10 mg/kg/day; Inhalation NOAEL= 10 mg/kg/day.

[4] Total MOE = 1 / ((1/ Dermal MOE) + (1/ Inhalation MOE))

[5] LADD = [(Dermal Daily Dose + Inhalation Daily Dose)] * (1 day worked per year / 365 days) * (50 years worked / 70-yr lifetime).

[6] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = 1.86 x 10^{-3} (mg/kg/day)$^{-1}$.

4.4.1.2 Postapplication

The following postapplication exposure scenarios resulting from contact with treated wood (*i.e.*, decks and playsets) were assessed: (1) adult and toddler dermal exposure, and (2) toddlers' incidental ingestion of pesticide residues on treated wood from hand-to-mouth transfer.

No chemical-specific data were submitted regarding dissipation of the wood sealant/preservative after it has been applied; therefore, the following label information and assumptions were used to estimate potential transferrable residues and subsequent exposure:

- The Sherwin-Williams wood sealant/preservative product (EPA Reg. No. 577-539) contains 0.045 lb ai/gal (*i.e.* 0.66% ai * 6.8 lb/gal);
- One gallon of sealant/preservative can treat 100 ft^2 of rough or porous surfaces;
- Using conversions for mass and area, the resulting amount applied per unit area is 220 $\mu g/cm^2$ (*i.e.*, 0.045 lb ai/gal * 1 gal/100 ft^2 * 4.54 x 10^8 μg/lb * 1 ft^2/929 cm^2);
- Because the sealant may be applied every 2 to 4 years, it was assumed that the minimum amount of time the product is effective (*i.e.*, when folpet is present) is 1,095 days, or 3 years; at the end of which, it was assumed that 99.9% of the folpet is gone.
- Pseudo-first order kinetics were assumed in estimating the decay/release rate, rather than a constant daily value, resulting in a curve indicating that the amount of folpet potentially available is highest immediately after application, and decreases over time. Using the first order equation:

$C_{(day\ of\ interest)} = C_{(day\ 0)}\ e^{(k * day\ of\ interest)}$

where: $C_{(day\ 0)} = 220\ \mu g/cm^2$,

$C_{(day\ of\ interest)} = C_{(day\ 1,095)} = 0.22\ \mu g/cm^2$ (*i.e.*, 99.9% gone, 0.1% remaining), and

day of interest = 1,095, and rearranging, "k" is found to be -0.0063.

- Substituting k into the equation and solving for $C_{(day\ 1)}$ results in a value of 218.6 $\mu g/cm^2$ remaining in the sealant; indicating that 220 - 218.6 = **1.4 $\mu g/cm^2$** are no longer bound in the sealant, and are assumed to be potentially available for human exposure **on the day after application.**
- The exposure and risk algorithms are based on modifications to the generic assumptions for turf assessment, from the Recommended Revisions to the Residential SOPs, and approaches evaluated by the HED's ExpoSAC.

The exposure and risk estimates for the residential exposure scenarios are assessed for the day after application (day "1") because it is assumed that adults and toddlers could contact the treated wood immediately after the application has dried (which takes 24 hours). Both short- and intermediate-term exposure is expected. The equations used for the exposure calculations, and the results, are presented in Tables 12 and 13, for dermal and incidental oral ingestion, respectively.

Table 12. Postapplication Dermal Exposure and Risk From Treated Wood

Subgroup Exposed	Estimated Dislodgeable Residue (ug/cm^2)[1]	Transfer Coefficient (cm^2/hr)	Exposure Time (hrs)	Body Wt (kg)	Daily Dermal Dose (mg/kg/day)[2]	Dermal MOE[3]	LADD[4]	Cancer Risk[5]
Adults	1.4/ 0.201	14,500 / 7,300	2 / 1	60 / 70	0.018	550	1.1E-04	2.1E-07
Children	1.4	5,200	2	15	0.026	270		

[1] Estimated Dislodgeable Residue Postapplication day 1 = 1.4 (ug/cm^2), calculated as described in text previously. For cancer assessment, an average daily residue was used based on an application made every 3 years, which is an average of the 2- to 4-yr recommended application interval (i.e, 220 $\mu g/cm^2$ applied / 1,095 days = 0.201 $\mu g/cm^2$).

[2] Daily Dermal Dose = (Estimated Dislodgeable Residue x Transfer Coefficient x Dermal Absorption Factor [0.027] x Exposure Time) / ([CF: 1000 ug/mg] x Body weight). A 60-kg body weight was used for adults in the non-cancer assessment because endpoint is based on a developmental effect. For the cancer assessment, a 70-kg body weight was used, as well as long-term average values for the Estimated Dislodgeable Residue (0.201 $\mu g/cm^2$), Transfer Coefficient (7,300 cm^2/hr), and Exposure Time (1 hr).

[3] MOE = Dermal NOAEL / Dermal Daily Dose. Short-/Intermediate-term Dermal NOAEL= 10 mg/kg/day.

[4] LADD = (Daily Dose) * (No. days exposed per year / 365 days) * (50 years exposed / 70-yr lifetime). Days exposed per year (100 days) estimated based on best judgement, assuming an average of 1 to 3 days per week, depending on time of year.

[5] Cancer Risk = LADD (mg/kg/day) * (Q_1*),where Q_1* = 1.86 x 10^{-3} $(mg/kg/day)^{-1}$; A separate cancer risk for children was not estimated, per the EPA's policy.

Table 13. Toddlers' Hand-to-Mouth Exposure and Risk from Treated Wood

Subgroup Exposed	Estimated Dislodgeable Residue (ug/cm^2)[1]	Saliva Extraction Factor	Hand Surface Area (cm^2/event)	Frequency (events/ hr)	Body Weight (kg)	Daily Dose[2] (mg/kg/day)	Oral MOE[3]
Toddlers	1.4	50%	20	20	15	0.037	270

[1] Estimated Dislodgeable Residue Postapplication day 1=1.4 (ug/cm^2), calculated as described in text previously.
[2]Daily Dose = [(Estimated Dislodgeable Residue (ug/cm^2) x Saliva Extraction Factor x Hand Surface Area (cm^2/event) x Frequency (events/hr) x cf (0.001 mg/µg) x Exposure Time (2 hrs/day)] / [Body Weight (kg)]
[3]Oral MOE = Oral NOAEL / Oral Daily Dose. Short-/Intermediate-term Oral NOAEL= 10 mg/kg/day.

All calculated non-occupational postapplication MOEs are greater than the target of 100, and therefore, not of concern to the HED. The cancer risk for the general population is 2.1E-07, which also does not exceed the HED's level of concern. A separate cancer risk for children was not estimated, per Agency policy.

The exposure estimates presented above are based on some upper-percentile (*i.e.*, maximum application rate, amount of dislodgeable residue, and duration of exposure) and some central tendency (*i.e.*, time interval between sealant applications, surface area, hand-to-mouth activity, and body weight) assumptions and are considered to be representative of high-end exposures. The uncertainties associated with this assessment stem from the use of an assumed amount of pesticide available from treated wood, and assumptions regarding transfer of chemical residues from a bound/solid matrix and hand-to mouth activity. The estimated exposures are believed to be reasonable high-end estimates.

Combined Exposure
It should be noted that, per the FQPA, residential exposures that could reasonably be expected to occur on the same day should be combined and compared to the appropriate toxicity endpoint. For children, the dermal and incidental oral (*i.e.*, hand-to-mouth) scenarios would reasonably be expected to occur on the same day. When these exposures are combined, the **resulting total MOE is 160**, which is above the target MOE of 100, and therefore, is not of concern. For adult handlers, dermal and inhalation exposures co-occur, and because a common toxicological endpoint (developmental malformations) was selected, these exposures were combined, as shown previously in Table 11. Handler and postapplication dermal exposures were not combined, because they are not expected to occur on the same day; the label indicates that 24 hours should be allowed for the sealant to dry before walking on the wood.

For the cancer assessment, the lifetime average daily doses from both handling (application with an airless sprayer) and dermal postapplication contact with treated wood, when combined, total 0.00017 mg/kg/day. **Cancer risk resulting from these combined exposures is 3.1E-7, and does not exceed the HED's level of concern.**

4.4.2 Recreational

Recreational exposures to treated wood on playsets are expected to be similar to those evaluated in section 4.4.1.2 Postapplication, therefore, a separate recreational exposure assessment was not included. Also, the HED does not believe it is reasonable to combine the conservative residential exposure estimates for children's exposure from treated wood to exposures from recreational activities. Rather, the residential exposure estimates should represent a conservative assessment for all such activities occurring on the same day.

4.4.3 Non-Occupational Off-Target Exposure

Spray drift is always a potential source of non-occupational off-target exposure to residents nearby to spraying operations. This is particularly the case with aerial application, but, to a lesser extent, could also be a potential source of exposure from the ground application method employed for folpet. The EPA has been working with the Spray Drift Task Force, EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices. The EPA is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. The EPA has completed its evaluation of the new database submitted by the Spray Drift Task Force, a membership of U.S. pesticide registrants, and is developing a policy on how to appropriately apply the data and the AgDRIFT computer model to its risk assessments for pesticides applied by air, orchard airblast and ground hydraulic methods. After the policy is in place, the EPA may impose further refinements in spray drift management practices to reduce off-target drift and risks associated with aerial as well as other application types where appropriate.

5.0 AGGREGATE RISK ASSESSMENTS AND RISK CHARACTERIZATIONS

References:

> *PP#2E06512; HED Dietary Exposure Assessment: Human Dietary Exposure Assessment for Use of Folpet on Hops to be Imported*, D286670, W. Wassell, 02/20/2003 (attachment 4).

Acute and chronic aggregate risk estimates are made up of the combined dietary exposures from food and water sources. The short- and intermediate-term aggregate risk estimate is made up of combined residential exposures (from dermal, inhalation, and incidental oral sources), as well as background/average dietary exposures (from food and water sources). The cancer aggregate risk estimate is made up of the combined risk from chronic dietary exposure (from food and water sources), as well as the estimated lifetime average daily doses from residential exposure (from adult handler and postapplication activities). An aggregate cancer assessment from combined dietary exposure to folpet and captan was also performed, based on their common metabolite, thiophosgene.

In the absence of drinking water monitoring data for a pesticide, a drinking water level of comparison (DWLOC) is calculated. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light of total aggregate exposure to

that pesticide from food, water, and residential uses (if applicable). The HED uses DWLOCs internally in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. The DWLOC is used as a point of comparison against the conservative EDWCs provided by computer modeling.

The HED back-calculates DWLOCs by a two-step process: exposure [food + residential (if applicable)] is subtracted from the PAD (or from the [NOAEL/Target MOE])to obtain the maximum acceptable exposure allowed in drinking water. DWLOCs are then calculated using that value and default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EDWCs. When EDWCs are less than DWLOCs, the HED considers the aggregate risk (from food + water + residential exposures [if applicable]) to be acceptable.

5.1 Acute Risk

5.1.1 Aggregate Acute Risk Assessment

The HIARC identified an aPAD for folpet for females 13 to 50 years based on an increase in number of fetuses and litters with hydrocephaly and related malformations in the rabbit developmental toxicity study at a LOAEL of 20 mg/kg/day (NOAEL = 10 mg/kg/day, UF = 100X, FQPA SF = 1X). An aPAD was not identified for the general population. The aPAD (0.10 mg/kg/day) was used to assess acute dietary risk.

No drinking water monitoring data are available for folpet. SCI-GROW and FIRST models were used to calculate EDWCs for this fungicide. Tier I (SCI-GROW) modeling estimates that folpet residues in groundwater are not likely to exceed 0.06 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for folpet residues predicts the peak (acute) EDWC is not likely to exceed 309 ppb.

5.1.2 Acute DWLOC Calculations

The DWLOC for acute exposure to folpet by females 13 to 50 years is summarized in Table 14.

Table 14. Summary of Acute Drinking Water Levels of Comparison for Folpet.

Population Subgroup[1]	aPAD mg/kg/day	Food Exposure mg/kg/day (99.9th percentile)	Maximum Water Exposure (mg/kg/day)[2]	Acute Ground-water EDWC[3] (µg/L)	Acute Surface Water EDWC[3] (µg/L)	DWLOC (µg/L)[4]
Females 13 to 50 years	0.10	0.0064	0.094	0.06	309	2800

[1] The HIARC identified an acute dietary endpoint for Females 13 to 50 years old, for this subpopulation body weight was assumed to be 60 kg (because the endpoint is based on a developmental effect [increase in fetuses with hydrocephaly and related malformations]) and water consumption was assumed to be 2 L/day. An appropriate endpoint attributable to a single dose was not identified for the General Population, including Infants and Children.

[2] Maximum acute water exposure (mg/kg/day) = [(aPAD (mg/kg/day) - acute food exposure (mg/kg/day)]

[3] Based on modeling results from SCI-GROW and FIRST using the crop producing the highest level, *i.e.* avocado: 21 lb ai/A/yr.

[4] Acute DWLOC(µg/L) = $\frac{\text{[maximum acute water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

As shown in Table 8 previously, the resulting dietary (food only) exposure for females 13 to 50 years occupies 6.4% of the aPAD at the 99.9th percentile. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective).

As shown in Table 14, the back-calculated DWLOC for assessing acute aggregate dietary risk is 2800 µg/L. The SCI-GROW and FIRST acute EDWCs are less than this DWLOC value. The HED thus concludes with reasonable certainty that residues of folpet in drinking water will not contribute significantly to the acute aggregate human health risk and that the acute aggregate exposure from folpet residues in food and drinking water will not exceed the EPA's level of concern (100% of the aPAD) for acute dietary aggregate exposure by females 13 to 50 years.

5.2 Short- and Intermediate-Term Risk

5.2.1 Aggregate Short- and Intermediate-Term Risk Assessment

The HIARC identified numerically equivalent short- and intermediate-term inhalation, dermal and incidental oral NOAELs to employ in evaluating the risk associated with folpet use. The endpoints are based on effects identified in the developmental toxicity study in rabbits. The inhalation and dermal NOAELs are based on a developmental effect (an increased number of fetuses and litters with hydrocephaly and related skull malformations), and the incidental oral NOAEL is based on a maternal effect (a decrease in food consumption). These effects were observed at the LOAEL of 20 mg/kg/day (NOAEL = 10 mg/kg/day, UF = 100, FQPA SF = 1X). However, as pointed out previously in section 4.4.1.2 Postapplication, to assess toddler incidental ingestion and dermal exposure, the NOAEL based on the maternal decrease in food consumption was used. Although this is not the endpoint that the HIARC selected for dermal exposure, it occurs at the same dose level as the developmental NOAEL, is from the same

study, and is more applicable to toddlers than hydrocephaly effects (which apply only to females of child-bearing age).

In the residential assessment, the highest adult exposure scenario (inhalation and dermal) was a residential handler applying Sherwin-Williams Semi-Transparent Wood Preservative Clear Base A14T5 with 0.66% ai (EPA Reg. No. 577-539) to a deck or playset. The highest child exposure scenario (dermal and incidental oral) is a toddler being exposed while mulling around on the deck/playset after the Sherwin-Williams formulation has dried (24 hours after application). Exposure from these scenarios, in addition to background exposure from food and water, were used to estimate the short- and intermediate-term aggregate risk to adults and children from folpet. For adults and children, all exposure routes were combined.

An average food exposure was also used to estimate the short- and intermediate-term aggregate risk to adults and children from folpet. The highest average food exposures from the respective subpopulation groups were used, *i.e.* 0.000107 mg/kg/day for children (children 1-2 years), and 0.000039 mg/kg/day for adults (General U.S. Population). The average food exposure for females 13 to 50 years (0.000032 mg/kg/day) was also considered, because the short- and intermediate-term dermal and inhalation developmental endpoint is particularly relevant to this subpopulation.

No drinking water monitoring data are available for folpet. SCI-GROW and FIRST models were used to calculate EDWCs for this fungicide. Tier I (SCI-GROW) modeling estimates that folpet residues in groundwater are not likely to exceed 0.06 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for folpet residues predicts the annual average EDWC is not likely to exceed 0.62 ppb.

5.2.2 Short- and Intermediate-Term DWLOC Calculations

The DWLOCs for short- and intermediate-term exposure to folpet for adults and children are summarized in Table 15.

Table 15. Short-Term and Intermediate-Term DWLOC Calculations

Population	Short- and Intermediate-Term Scenario													
	NOAEL (mg/kg/day)	Target MOE[1]	Max Exposure[2] (mg/kg/day)	Average Food Exposure[3] (mg/kg/day)	Incidental Oral Exposure[4] (mg/kg/day)	Inhalation Exposure[5] (handler) (mg/kg/day)	Dermal Exposure[6] (handler) (mg/kg/day)	Dermal Exposure[6] (postapp) (mg/kg/day)	Total Residential Exposure[7] (mg/kg/day)	Agg. MOE (food and res.)[8]	Max Water Exposure[9] (mg/kg/day)	Ground-water EDWC[10] (µg/L)	Surface Water EDWC[10] (µg/L)	DWLOC[11] (µg/L)
General U.S. Population	10	100	0.1	0.000039	NA	0.0093	0.024	NA	0.033	300	0.067	0.06	0.62	2300
Females 13 to 50 years	10	100	0.1	0.000032	NA	0.0093	0.024	NA	0.033	300	0.067	0.06	0.62	2000
Children 1-2 years	10	100	0.1	0.000107	0.037	NA	NA	0.026	0.063	160	0.037	0.06	0.62	370

[1] *The target MOEs are based on the conventional uncertainty factor of 100X (10X for intraspecies extrapolation and 10X for interspecies variation); the FQPA SF is considered,* however, because it is 1X, it does not alter the target MOE.
[2] Maximum Exposure (mg/kg/day) = NOAEL/Target MOE
[3] Average Food Exposure = chronic dietary exposure
[4] Incidental Oral Exposure = hand-to-mouth residential exposure
[5] Inhalation Exposure = high-end residential handler inhalation exposure
[6] Dermal Exposure (handler or postapplication exposure depending on which is highest) = residential handler (highest for adult) and postapplication dermal (child)
[7] Total Residential Exposure = Incidental Oral Exposure (if applicable) +Inhalation Exposure (if applicable) + Dermal Exposure (handler or postapplication, whichever is highest)]
[8] Aggregate MOE = [NOAEL ÷ (Avg Food Exposure + Total Residential Exposure)]
[9] Maximum Water Exposure (mg/kg/day) = Target Maximum Exposure - (Food Exposure + Residential Exposure)
[10] The crop producing the highest level was used, *i.e.* avocado: 21 lb ai/A/yr.
[11] DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$ General U.S. Popn: body weight 70 kg, 2L water
Females 13 to 50: body weight 60 kg, 2L water,
Child: body weight 10 kg, 1L water

NA = not applicable

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As shown in Tables 11, 12 and 13 previously, the resulting handler and postapplication (residential only) exposures for adults and children result in MOEs greater than the target MOE of 100, and are therefore not of concern to the HED. And as shown in Table 15, the resulting aggregated short- and intermediate-term MOEs (residential exposure + background food exposure) are also greater than the target MOE of 100, and thus, not of concern to the HED.

Additionally (as done for acute aggregate risk), short- and intermediate-term aggregate risk can be considered by back-calculating DWLOCs and comparing them to EFED's EDWCs. The back-calculated DWLOCs (Table 15) for assessing short- and intermediate-term aggregate risks are 2300 µg/L, 2000 µg/L, 370 µg/L, for the General U.S. Population, Females 13 to 50 years, and children 1-2 years, respectively. The SCI-GROW and FIRST background EDWCs are less than the EPA's levels of comparisons (the DWLOC values) for folpet residues in drinking water as a contribution to short- and intermediate-term aggregate exposure. The HED thus concludes with reasonable certainty that residues of folpet in drinking water will not contribute significantly to the short- and intermediate-term aggregate human health risk; and therefore, that short- and intermediate-term aggregate risk from exposure to folpet is not of concern.

5.3 Chronic Risk

5.3.1 Aggregate Chronic Risk Assessment

The HIARC identified a cPAD (0.09 mg/kg/day) for folpet based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females in the Combined Chronic Toxicity/ Carcinogenicity Study in rats at a LOAEL of 35 mg/kg/day (NOAEL = 9 mg/kg/day, UF = 100X, FQPA SF = 1X). The cPAD was used to assess chronic risk from exposure to folpet.

No drinking water monitoring data are available for folpet. SCI-GROW and FIRST models were used to calculate EDWCs for folpet in water. Tier I (SCI-GROW) modeling estimates that folpet residues in ground water, from the registered use on avocados, are not likely to exceed 0.06 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for folpet residues predicts the average annual (chronic-term) EDWC is not likely to exceed 0.62 ppb.

5.3.2 Chronic DWLOC Calculations

Table 16. Chronic DWLOC Calculations

Population Subgroup[1]	Chronic Scenario					
	cPAD (mg/kg/day)	Chronic Food Exp (mg/kg/day)	Max Chronic Water Exp[2] (mg/kg/day)	Groundwater EDWC[3] (µg/L)	Surface Water EDWC[3] (µg/L)	Chronic DWLOC (µg/L)
U.S. Population	0.09	0.000039	0.089961	0.06	0.62	3100
All Infants (<1year)	0.09	0.000045	0.089955	0.06	0.62	900
Children 1-2 years	0.09	0.000107	0.089893	0.06	0.62	900
Children 3-5 years	0.09	0.00009	0.089910	0.06	0.62	900
Children 6-12 years	0.09	0.000048	0.089952	0.06	0.62	900
Youth 13-19 years	0.09	0.000027	0.089973	0.06	0.62	2700
Adults 20-49 years	0.09	0.000031	0.089969	0.06	0.62	3100
Females 13+ years	0.09	0.000032	0.089968	0.06	0.62	2700
Adults 50+ years	0.09	0.000033	0.089967	0.06	0.62	3100

[1] The HIARC identified a chronic dietary endpoint for the General Population, including all subpopulations. The appropriate body weight was used when calculating each population subgroup's DWLOC value: a value of 70 kg was used for the general population and adults, a value of 60 kg was used for youth 13-19 years and Females 13+ years, and a value of 10 kg was used for children.

[2]Maximum Chronic Water Exposure (mg/kg/day) = [cPAD (mg/kg/day) - Chronic Dietary Exposure (mg/kg/day)]

[3]The crop producing the highest level was used, *i.e.* avocado: 21 lb ai/A/yr.

[4] Chronic DWLOC(µg/L) = $\frac{\text{[maximum chronic water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

As shown in Table 9 previously, the resulting dietary food exposures occupy <1% of the cPAD for all population subgroups included in the analysis. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective).

As shown in Table 16, the back-calculated DWLOCs for assessing chronic aggregate dietary risk range from 900 µg/L for the population subgroups All Infants and Children (1 to 2 years old) to 3100 µg/L for the U.S. Population and Adults (50+ years). The SCI-GROW and FIRST chronic EDWCs are less than the DWLOC value (EPA's level of comparison) for each population subgroup. The HED thus concludes with reasonable certainty that residues of folpet in drinking water will not contribute significantly to the aggregate chronic human health risk and that the chronic aggregate exposure from folpet residues in food and drinking water will not

exceed the EPA's level of concern (100% of the cPAD) for chronic dietary aggregate exposure by *any* population subgroup. EPA generally has no concern for exposures below 100% of the cPAD, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of *any* population subgroup.

5.4 Cancer Risk

5.4.1 Aggregate Cancer Risk Assessment

The HED CPRC classified folpet as a B2 carcinogen (probable human carcinogen) based upon increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two strains. The Q_1^* for folpet was determined to be 1.86×10^{-3} $(mg/kg/day)^{-1}$.

Chronic dietary and residential exposure are included in the aggregate cancer risk estimate. The residential exposure value used, the LADD, was determined by averaging expected residential exposure over a lifetime (both handler [dermal and inhalation] and postapplication [dermal] activities were included, see p. 26 and 27, Tables 11 and 12).

No drinking water monitoring data are available for folpet. SCI-GROW and FIRST models were used to calculate EDWCs for folpet in water. Tier I (SCI-GROW) modeling estimates that folpet residues in groundwater, from the registered use on avocados, are not likely to exceed 0.06 ppb (µg/L). Additionally, Tier I (FIRST) surface water modeling for folpet residues predicts the average annual (chronic-term) EDWC is not likely to exceed 0.62 ppb (µg/L).

5.4.2 Chronic (Cancer) DWLOC Calculations

Table 17. Cancer DWLOC Calculations (using the Q*Approach) for Folpet

Population	Q*	Negligible Risk Level[1]	Target Max Exposure[2] (mg/kg/day)	Chronic Food Exposure (mg/kg/day)	Residential Exposure LADD (mg/kg/day)	Total cancer exposure[3] (mg/kg/day)	Max Water Exposure[4] (mg/kg/day)	Groundwater EDWC[5] (µg/L)	Surface Water EDWC[5] (µg/L)	Cancer DWLOC[6] (µg/L)
U.S. Pop	1.86e-03	0.000001	0.00054	0.000039	0.00017	0.00021	0.00033	0.06	0.62	12

[1] As per EPA policy, a cancer risk of 1 x 10^{-6} or lower is considered acceptable.

[2] Target Maximum Exposure (mg/kg/day) = [negligible risk/Q*]

[3] Total Cancer Exposure(mg/kg/day) = Chronic Food Exposure (mg/kg/day) + Residential Exposure LADD (mg/kg/day)

[4] Maximum Water Exposure (mg/kg/day) = [Target Maximum Exposure - (Chronic Food Exposure + Residential Exposure (Lifetime Average Daily Dose))]

[5] The crop producing the highest level was used, *i.e.* avocado: 21 lb ai/A/yr.

[6] Cancer DWLOC(µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L) x } 10^{-3} \text{ mg/µg]}}$

For the U.S. population, the default body weight is 70 kg and the default water consumption is 2 L/day.

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As summarized previously in Table 10, the dietary cancer risk estimate (food only) for the U.S. population is 7.2×10^{-8}. This risk estimate is based upon a food only exposure of 0.000039 mg/kg/day. The results of this dietary exposure analysis should be viewed as partially refined and somewhat conservative (health protective). As summarized in section 4.4.1 Home Uses, the cancer risk resulting from residential exposure is 3.1×10^{-7} (LADD = 0.00017 mg/kg/day). The EPA generally has no concern for exposures which result in a cancer risk estimate less than 1×10^{-6}, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of any population subgroup.

As shown in Table 17, the back-calculated DWLOC for assessing chronic (cancer) aggregate dietary risk is 12 µg/L. The SCI-GROW and FIRST chronic (cancer) EDWCs are less than the cancer DWLOC for folpet. The HED thus concludes with reasonable certainty that residues of folpet in drinking water will not contribute significantly to the aggregate chronic (cancer) human health risk, and thus, that the aggregate cancer risk from exposure to folpet is not of concern.

5.5 Cancer Risk from Folpet and Captan

References:

> *PP#2E06512; HED Dietary Exposure Assessment: Human Dietary Exposure Assessment for Use of Folpet on Hops to be Imported*, D286670, W. Wassell, 02/20/2003 (attachment 4)
>
> *Captan (081301); Tier 3 Chronic Cancer and Non-Cancer Dietary Exposure Estimates for Captan*, D.E. Hrdy, 9/23/1999, D259452.

Folpet and captan share a common metabolite, thiophosgene. Thiophosgene is highly reactive and severely irritating to mucus membranes and tissues it comes in contact with. Thiophosgene is believed to be responsible for the carcinogenic effects of these compounds. The carcinogenic effect of concern is GI tract tumors from oral exposure to both folpet and captan. Therefore, the EPA believes it is reasonable to add the estimated cancer risks from the individual aggregate oral risks from both folpet and captan to obtain a worst-case scenario. The relevance of dermal and inhalation exposure to a GI tract tumor is unknown at this time. Oral (dietary) risks from both folpet and captan have not changed since the last risk assessment, and therefore the aggregate cancer assessment performed in the previous risk assessment has not changed (although the folpet EDWCs to which the aggregate cancer assessment is compared have changed, they do not impact the calculation, nor the conclusion).

The cancer risk estimate (food only) for the U.S. population (total) is 7.2×10^{-8} for folpet (food exposure = 0.000039 mg/kg/day) and 1.3×10^{-7} for captan (food exposure = 0.000053 mg/kg/day). The results of the dietary exposure analysis for folpet and captan should be viewed as partially refined and somewhat conservative (health protective). The EDWCs provided by EFED for assessing chronic (cancer) aggregate dietary risk for folpet are 0.06 µg/L (for groundwater) and 0.62 µg/L (for surface water). The EDWCs for assessing chronic (cancer) aggregate dietary risk for captan are 1 µg/L (for groundwater) and 4 µg/L (for surface water).

Table 18. Cancer DWLOC Calculations (using the Q*Approach) for Aggregate Exposure to Folpet and Captan

Population	Q*	Negligible Risk Level[1]	Target Max Exposure[2] (mg/kg/day)	Chronic Food Exposure[3] (mg/kg/day)	Aggregate Cancer Risk[4]	Max Water Exposure[5] (mg/kg/day)	Groundwater EDWC[6] (µg/L)	Surface Water EDWC[6] (µg/L)	Cancer DWLOC[7] (µg/L)
U.S. Population	2.40e-03	0.000001	0.00042	0.000092	2.0×10^{-7}	0.00032	0.06 (folpet) 1 (captan)	0.62 (folpet) 4 (captan)	11

[1] As per EPA policy, a cancer risk of 1×10^{-6} or lower is considered acceptable.

[2] Target Maximum Exposure (mg/kg/day) = [negligible risk/Q*]

[3] Chronic Food Exposure (mg/kg/day) = folpet chronic food exposure (0.000039 mg/kg/day) +captan chronic (cancer) food exposure (0.000053 mg/kg/day)

[4] Aggregate Cancer Risk = folpet cancer risk estimate from exposure to food (7.18×10^{-8}) + captan cancer risk estimate from exposure to food (1.26×10^{-7})

[5] Maximum Water Exposure (mg/kg/day) = [Target Maximum Exposure - (Chronic Food Exposure)]

[6] The crop producing the highest level was used, *i.e.* avocado: 21 lb ai/A/yr.

[7] Cancer DWLOC (µg/L) = $\frac{\text{[maximum water exposure (mg/kg/day) x body weight (kg)]}}{\text{[water consumption (L)} \times 10^{-3} \text{ mg/µg]}}$, a 70 kg body weight and 2L water consumption were assumed.

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As shown in Table 18, the back-calculated DWLOC (calculated using the Q_1^* for captan [2.4 x 10^{-3}] as this value is higher than that for folpet and should result in a worst-case estimate of risk) for assessing chronic (cancer) aggregate dietary risk is 11 µg/L. The chronic (cancer) EDWCs are less than the EPA's level of comparison for folpet and captan residues in drinking water as a contribution to chronic (cancer) aggregate exposure. The HED thus concludes with reasonable certainty that residues of folpet and captan in drinking water will not contribute significantly to the aggregate cancer human health risk from exposure to folpet and captan; and, that the aggregate exposure from folpet and captan residues in food and drinking water will not exceed the EPA's level of concern for cancer risk for the U.S. population. The EPA generally has no concern for exposures which result in a cancer risk estimate less than 1 x 10^{-6}, because it is a level at or below which daily aggregate dietary exposure over a lifetime will not pose appreciable risks to the health and safety of any population subgroup.

6.0 CUMULATIVE

Unlike other pesticides for which the EPA has followed a cumulative risk approach based on a common mechanism of toxicity, the EPA has not made a common mechanism of toxicity finding as to folpet and any other substances. Although, as outlined in Section 5.5 previously, folpet and captan share the common metabolite thiophosgene, because thiophosgene is transient and not easily measurable, its role in folpet's and captan's toxicity has not been determined. Therefore, for the purposes of this tolerance action and Section 3 registration, the EPA has not assumed that folpet has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's OPP concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

7.0 OCCUPATIONAL EXPOSURE

References:

> *Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Folpet on Hops*, D285666, K. O'Rourke, 04/20/04 (attachment 3).

7.1 Handler

There is a potential for exposure to folpet during mixing, loading, and application activities. An exposure/risk assessment using applicable endpoints selected by the HED HIARC and CPRC was performed. Handler's exposure and risk were estimated for mixing/loading wettable powder for aerial and airblast application; mixing/loading dry flowable formulation for airblast application; application via fixed-wing aircraft and airblast sprayer; and flagging for aerial sprays.

No chemical-specific handler exposure data were submitted in support of this Section 3 registration. In accordance with the HED's ExpoSAC policy, exposure data from the Pesticide Handlers Exposure Database (PHED) Version 1.1, as presented in PHED Surrogate Exposure Guide (8/98), were used with other HED default values for acres treated per day, body weight, and the level of personal protective equipment to assess handler exposures. The water-dispersible granular formulation is also known as a dry flowable formulation, which is the term used in the exposure assessment. The unit exposure values from PHED are considered to be central tendency. The application rates, treatment variables, etc. used in this assessment are upper percentile values. Therefore, the potential dose is characterized as high-end.

The minimum level of PPE for handlers is based on acute toxicity for the end-use product. The Registration Division (RD) is responsible for ensuring that PPE listed on the label is in compliance with the WPS.

Exposure assumptions and estimates for occupational handlers are summarized in Table 19, as well as the resulting MOEs and cancer risks. The total MOEs are greater than the target MOE (100) and, therefore, are not of concern when **engineering controls**, in the form of water-soluble bags, are used to mitigate exposure (from mixing/loading wettable powder for **aerial application**) or **PPE** is used to mitigate exposure (from mixing/loading wettable powder for airblast application). **The cancer risks also do not exceed the HED's level of concern**, when ***engineering controls*** are used to mitigate exposure.

Table 19. Exposure and Risk Assessment for Occupational Handlers

PHED Scenarios for Folpet Uses	PHED Unit Exposure[1] (mg/lb ai)	Maximum Application Rate (lb ai/A)	Area/ Amount Treated (Acres)	Daily Dose[2] (mg/kg/day) [60-kg BW]	Short-/ Int-Term MOE[3]	Total MOE[4]	LADD (mg/kg/day)[5]	Cancer Risk[6]
(1a) Mix/load : wettable powder for aerial spray **Baseline**	Dermal: 3.7	2.0	350	1.2	8.6	6	0.16	2.9E-04
	Inhalation: 0.043			0.50	20			
(1b) Mix/load : wettable powder for aerial spray **PPE**	Dermal: 0.13			0.041	240	71	0.051	9.5E-05
	Inhalation: 0.0086			0.10	100			
(1c) Mix/load : wettable powder for aerial spray **Engineering Control**	Dermal: 0.0098			0.0031	3,200	1,700	0.00055	1.0E-06
	Inhalation: 0.00024			0.0028	3,600			
(2a) Mix/load : wettable powder for airblast **Baseline**	Dermal: 3.7	2.0	40	0.13	75	52	0.027	5.0E-05
	Inhalation: 0.043			0.057	170			
(2b) Mix/load : wettable powder for airblast **PPE**	Dermal: 0.13			0.0047	2,100	160	0.0087	1.6E-05
	Inhalation: See baseline			See baseline	See baseline			
(3) Mix/load : water dispersible granules for airblast	Dermal: 0.066	2.4		0.0029	3,500	2,400	0.00058	1.1E-06
	Inhalation: 0.00077			0.0012	8,100			
(4) Apply: fixed-wing aircraft (enclosed cockpit)	Dermal: 0.005	2.0	350	0.0016	6,300	4,200	0.00022	4.1E-07
	Inhalation: 0.000068			0.00079	13,000			
(5) Apply: airblast sprayer	Dermal: 0.36	2.4	40	0.016	640	440	0.0032	6.0E-06
	Inhalation: 0.0045			0.0072	1,400			
(6) Flagging (Sprays) for Aerial Operations	Dermal: 0.011	2.0	350	0.0035	2,900	1,300	0.00068	1.3E-06
	Inhalation: 0.00035			0.0041	2,400			

[1] PHED Unit Exposure values are for baseline protection (long-sleeved shirt, long pants, shoes plus socks) unless otherwise indicted in the scenario column. Personal protective equipment (PPE) includes double layer of clothing, gloves, and a dust/mist respirator (respirator not needed for scenario #2). The engineering control for wettable powder is a water-soluble bag.

[2] Daily Dose = (Unit Exposure x Absorption Factor [dermal = 0.027, inhalation = 1] x Application Rate x Area Treated)/Body Weight. A 60-kg body weight was used for non-cancer assessment because endpoint is based on a developmental effect; 70 kg used for the cancer assessment (not shown).

[3] MOE = NOAEL/ Daily Dose. Short-/Intermediate-term Dermal NOAEL= 10 mg/kg/day; Inhalation NOAEL= 10 mg/kg/day.

[4] Total MOE = 1 / ((1/ Dermal MOE) + (1/ Inhalation MOE))

[5] LADD = [(Dermal Daily Dose + Inhalation Daily Dose)] * (No. days worked per year / 365 days) * (35 years worked / 70-yr lifetime). Days worked per year estimated by dividing the average hop farm size (i.e., 300 acres) for the county with the largest farms (i.e., Yakima County) in the state that produces the largest quantity of hops (i.e., Washington), according to U.S. Dept. of Commerce 1992 Census of Agriculture, by the area treated per day, and multiplying by the maximum number of applications per season (i.e., 8) and the number of farms on which a handler is expected to work (i.e., 2 farms for airblast and 10 farms for aerial application). Thus, activities were estimated to occur 120 days/yr for airblast and 80 days/yr for aerial application.

[6] Cancer Risk = LADD (mg/kg/day) * (Q_1*), where Q_1* = 1.86×10^{-3} $(mg/kg/day)^{-1}$.

7.2 Postapplication

This Section 3 action for folpet involves foliar applications. Therefore, postapplication exposure is possible for workers entering treated hops yards to tend (*e.g.*, irrigate and train) or harvest the hops vines. The registrant submitted a chemical-specific dislodgeable foliar residue (DFR) study conducted on hops (MRID#: 45710401). These data have been reviewed, and the results are considered useful for risk assessment purposes.

Predicted DFR values, based on measurements obtained from the Washington state site, were used for the postapplication assessment. The residues from the Washington site were chosen because they had the best field recoveries, highest predicted initial residue (*i.e.*, 63% application rate, with 11% dissipation per day), and best r^2 value. It is also notable that, according to the USDA Crop Profiles, Washington state accounts for 77% of the U.S. hops production.

In addition to these DFR data, transfer coefficients (Tc), which relate the leaf residue values to activity patterns (*e.g.*, harvesting), were used to estimate postapplication exposures. The transfer coefficients used in this assessment are from an interim transfer coefficient guidance developed by the HED's ExpoSAC using proprietary data from the Agricultural Re-entry Task Force (ARTF) database (SOP # 3.1). This SOP is periodically updated to incorporate additional information about agricultural practices in crops and new data on transfer coefficients. Much of this information originates from exposure studies currently being conducted by the ARTF, from further analysis of studies already submitted to the Agency, and from studies in the published scientific literature. The application rate, transfer coefficients, and dislodgeable residue data used in this assessment are central tendency to upper-percentile values. Therefore, the daily dose is characterized as mid- to high-end.

Inputs and calculated postapplication risk estimates can be seen in Table 20. Risk calculations for postapplication workers result in MOEs ranging from 82 to 1,600 on the day of application; **MOEs reach 100 on the second day after application for training and harvesting**, and 420 by day 14 (*i.e*, the pre-harvest interval [PHI]) for harvesting. Cancer risks range from 4.7E-07 to 5.0E-06. Because the postapplication MOEs exceed the target MOE of 100, and the cancer risks are less than, or within, the range of 10^{-6} to 10^{-4}, these risks do not trigger the HED's concern for postapplication workers in hops yards treated with folpet.

The proposed label for Folpan 80WDG has an interim 24-hour REI. While the technical material has a Toxicity Category IV for Acute Dermal toxicity and Skin Irritation, Primary Eye Irritation is considered to be in Toxicity Category II. Per the WPS, a 24-hour REI is required for chemicals classified under Toxicity Category II. While the interim REI of 24 hours indicated on the proposed label is in compliance with the WPS, 48 hours is required to reach an MOE of 100 for training hop vines, based on systemic effects. Pending revision of the application rate from 2.4 lb ai/A on the proposed label, to 2.0 lb ai/A, an REI of 24 hours will be adequate.

Table 20. Occupational Exposure and Risk Estimates for Postapplication Activities on Hops

Activity	Post-application Day (t)	Dislodgeable Foliar Residue (µg/cm²)[1]		Dermal Transfer Coefficient (cm²/hr)	Daily Dose[2] (mg/kg/day)	Short-/Int.-Term Dermal MOE[3]	Days Worked/ Year[4]	LADD[5] (mg/kg/day)	Cancer Risk[6]
Irrigation	0	16.9	10.6 (10-day)	100	0.0061	1,600	90	4.0E-04	7.5E-07
Train	0	16.9		2,000	0.12	82	30	2.7E-03	5.0E-06
	1	15.1			0.11	92			
	2	13.4			0.097	100			
Harvest	0	16.9	0.75 (40-day)	2,000	0.12	82	40	2.5E-04	4.7E-07
	1	15.1			0.11	92			
	2	13.4			0.097	100			
	14 (PHI)	3.32			0.024	420			

[1] Predicted values based on the DFR study on hops; the values were adjusted up to account for the difference in the proposed label application rate of 2.4 lb ai/A compared to the rate fo 2.0 lb ai/A used in the study. Values are from the Washington site which had the best field recoveries, highest predicted initial residue (i.e., 63% application rate, with 11% dissipation per day), and best r^2 value. To calculate the LADD and cancer risk, the values shown in the second column were used: 10-day average (i.e., the shortest application interval) for irrigation and training and 40-day average (i.e., day 14, which is the PHI, through day 53) for harvesting.

[2] Daily Dose = (Dislodgeable Foliar Residue x Transfer Coefficient x Dermal Absorption Factor [0.027] x Exposure Time) / ((CF: 1000 ug/mg) x Body weight). Exposure time is assumed to be 8 hr/day. A 60-kg body weight was used for non-cancer assessment because endpoint is based on a developmental effect; 70 kg used for the cancer assessment (not shown).

[3] MOE = NOAEL / Daily Dose. Short-/Intermediate-term Dermal NOAEL= 10 mg/kg/day

[4] Days worked per year estimated from information in "USDA Crop Profile for Hops in Washington" regarding timing and duration of activity and used in LADD calculation.

[5] LADD = (Daily Dose) * (No. days worked per year / 365 days) * (35 years worked / 70-yr lifetime).

[6] Cancer Risk = LADD (mg/kg/day) * (Q_1*),where Q_1* = 1.86 x 10^{-3} (mg/kg/day)$^{-1}$.

8.0 DATA NEEDS/LABEL REQUIREMENTS

Both the FOLPAN 50 W and 80 WDG labels, should explicitly state that if other formulations containing the ai are applied, do not apply more than a total of 16 lb ai/A/yr (for hops) and 21 lb ai/A/yr or 15 lb ai/A/yr (for avocados, for the 50 W and 80 WDG labels respectively).

The following changes should be made to the FOLPAN 80 WDG label:

- The maximum rate of application on hops should be revised to be consistent with the amounts used to generate the residue data (*i.e.*, the amounts of product should be equivalent to 2 lb ai/A/application, and a maximum seasonal rate of 16 lb ai/A/season).
- The PHI for avocados should be revised to be consistent with the FOLPAN 50 W label (*i.e.*, 7 days).

- The maximum seasonal application rate for avocados should be revised to reflect the maximum application rate multiplied by the maximum number of applications per season (*i.e.*, 3.0 lb ai/A X 5 applications = 15 lb ai/A/season).
- While the interim REI of 24 hours indicated on the proposed label is in compliance with the WPS, at the application rate currently on the FOLPAN 80 WDG label, 48 hours is required to reach an MOE of 100 for training hop vines, based on systemic effects. Pending revision of the application rate, an REI of 24 hours will be adequate

The following changes should be made to the FOLPAN 50 W label:

- The proposed use directions for hops are inadequate: for mixing/loading for aerial application, engineering controls in the form of water soluble bags are required; for mixing/loading for airblast application, personal protective equipment (PPE), including a double layer of clothing and chemical-resistant gloves are required.

Attachments:

Attachment 1. Folpet. PP#1E06310. Petition for the Establishment of a Permanent Tolerance on Hop, Dried Cones and Section 3 Registration Application (ID#066222-UI) for FOLPAN 80 WDG End-use Fungicide on Hops. Summary of Analytical Chemistry and Residue Data. A. Acierto, 04/30/03 D285651, D286707

Attachment 2. Folpet - 3rd Report of the Hazard Identification Assessment Review Committee, 08/19/2003, A. Assaad, TXR No. 0052080

Attachment 3. Occupational and Residential Risk Assessment to Support Request for a Section 3 Registration of Folpet on Hops, D285666, K. O'Rourke, 4/20/04

Attachment 4.PP#2E06512; HED Dietary Exposure Assessment: Human Dietary Exposure Assessment for Use of Folpet on Hops to be Imported, D286670, W. Wassell, 02/20/2003

cc without attachments: S. Winfield, A. Acierto, A. Assaad, K. O'Rourke, RAB3 Reading File.

RDI: P. Deschamp, S. Dapson

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Chemical:	**Folpet**
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