**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**WASHINGTON, D.C. 20460**

**OFFICE OF CHEMICAL SAFETY**
**AND POLLUTION PREVENTION**

**MEMORANDUM**

DATE: November 28, 2012

**SUBJECT:** **Folpet:** Human Health Risk Scoping Document in Support of Registration Review.

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## EXECUTIVE SUMMARY

Attached is the Health Effects Division's (HED) and Antimicrobial Division's (AD) human health risk assessment scoping document for folpet conducted as part of the Registration Review process.

The HED and AD Folpet Registration Review Teams have evaluated the most recent human health risk assessments and databases for folpet to determine the scope of the work necessary to support Registration Review. The most recent human health risk assessment for folpet was conducted in 2004 to support a petition for domestic use of folpet on hops and registration of a new formulation for folpet on avocados in Florida (D285511, D286709, D286682). The 1999 Reregistration Eligibility Decision (RED) document for folpet was also considered (EPA738-R-99-011).

Folpet (Folpan®) is a dicarboximide fungicide. Folpet is formulated as water dispersible granules or wettable powder for use as a foliar treatment on avocados in Florida to manage scab and on hops to manage downy mildew. It is also registered for a number of foreign food uses for which the Agency has established tolerances with no U.S. registrations. There are seven end use antimicrobial products that contain folpet. One product is a wood preservative and six products are materials preservatives. The wood preservative product is formulated as a ready to use liquid that is applied using brush, roller or airless spray. The material preservative products are formulated as liquid concentrates, wettable powders and water dispersible granules that are added during material manufacture. The wood preservative product contains another active ingredient, 3-iodo-2-propynl butyl carbamate (IPBC). The material preservative products do not contain any other active ingredients.

Folpet has low acute oral and dermal toxicity (Toxicity Category IV for both) but is irritating to mucus membranes such as the eyes (Toxicity Category II), esophagus, lungs and stomach. Although it is not a skin irritant (Toxicity Category IV), it is a skin sensitizer. In the acute inhalation study in rats (Toxicity Category II), folpet was moderately toxic but clinical signs of survivors were consistent with upper and lower respiratory irritation (discharge from nose, gasping, labored breathing at 0.48mg/L). Folpet has low dermal penetration (2.7 % absorption).

Subchronic and chronic toxicity studies in rats demonstrated that the systemic effect was treatment related acanthosis and hyperkeratosis and/or ulceration/erosion of the stomach following high oral doses of folpet. In a 21-day dermal toxicity study, rats treated with folpet at dose levels as low as 1 mg/kg developed treatment-related skin damage which consisted of acanthosis and exudate and higher doses (10 and 30 mg/kg) produced skin ulcers. In both the oral and dermal studies, rats had dose related decreases in body weight gains. The local irritating effect to mucus membranes may be responsible, in part, for secondary toxicity such as decreased body weight gain in adult mammals.

Qualitative and quantitative susceptibility was observed following *in utero* exposure to folpet in rabbits. No susceptibility was seen in either the developmental or the 2-generation reproduction toxicity study in rats.

The previously assessed highly refined dietary exposures and risks (food only) were below the Agency's level of concern (6.4% for aPAD, <1% for cPAD). Estimated dietary cancer risk (food only) from folpet was $7.2 \times 10^{-8}$- based on the $Q_1^*$ for folpet of $1.86 \times 10^{-3}$ $(mg/kg/day)^{-1}$. Risks from potential exposure to folpet in drinking water from all sources were evaluated by comparing modeled estimated drinking water concentrations (EDWCs) against calculated drinking water levels of comparison (DWLOCs). The most recent risk assessment for folpet was conducted in 2004. At the request of the folpet registrant, EPA's Cancer Assessment Review Committee (CARC) re-evaluated Folpet in 2010 and changed the cancer classification to "Not likely to be carcinogenic to

humans at doses that do not cause an irritation response in the mucosal epithelium." Quantification of cancer risk will be through a non-linear (RfD) approach since there are sufficient data to ascertain the mode of action for the tumor response. As previously noted, the last risk assessment for folpet used the $Q_1$*approach.

Residential handler exposure scenarios that were previously assessed were below the Agency's level of concern with margins of exposure (MOEs) ranging from 1,100 to 9,400 for inhalation exposure, and 420 to 430 for dermal exposure. The MOE estimates of dermal post application exposure to treated wood ranged from 270 (for children) to 550 (for adults), and for children's hand-to-mouth exposure to treated wood was 270 on the day of application. The residential handler cancer risk estimates ranged from 7.6E-08 to 1.0E-07, while the post-application cancer risk estimate was 2.1E-07, using the old $Q_1$* methodology. These cancer risk estimates were not of concern. The aggregate MOE estimates for food and residential use ranged from 160 to 300, and the drinking water estimates did not contribute significantly to the aggregate risk estimate.

The previously assessed occupational exposures and risks for agricultural uses were below the Agency's level of concern with baseline attire, or when personal protective equipment (PPE) was added for certain scenarios. For handlers, inhalation MOEs ranged from 100 to 13,000 and dermal MOEs ranged from 240 to 6,300. Post application MOEs ranged from 82 to 1,600 on the day of application, and reached 100 on the second day after application. Note that the restricted entry interval (REI) on the current label is 24 hours. Although folpet cancer risk should now be evaluated based on a non-linear risk assessment, previously assessed cancer risks using the old $Q_1$* methodology ranged from 4.1E-07 to 2.9E-04 for occupational handlers, while those for post-application exposure ranged from 4.7E-07 to 5.0E-06.

For the antimicrobial uses, occupational exposures were last evaluated in the 1999 RED as total MOEs. This evaluation indicated that the handler risks of mixing/loading wettable powder during paint preservation had total MOEs of 12 at baseline and 130 with PPE. Because the total MOE of 12 was less than the required MOE of 100 for baseline PPE, the risks were considered to be of concern and the requirement for gloves and respiratory protection was added to the labels.

## Introduction

HED and AD have evaluated the most recent human health risk assessments for folpet to determine whether sufficient data are available and to determine the scope of the work necessary to support Registration Review. HED and AD have also considered updates to folpet's toxicity, exposure and usage databases, and current Agency science policies and risk assessment methods.

## Use Profile

a. **Agricultural Uses:** Folpet (N-(trichloromethylthio) phthalimide) belongs to the dicarboximides class of fungicides. Captan and captafol are also dicarboximide fungicides. Folpet is a broad spectrum contact protectant, which reacts with thiol groups in proteins causing denaturing of the fungal proteins. In agricultural settings, 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. Folpet is used to control the following: scab on avocados; downy mildew on hops; and wood rot fungi; mold/mildew; and spoilage fungi on wood and other surfaces. Folpet is formulated as a water dispersible granule [WDG] and wettable powder [W or WP]. Applications are made up to a day to two weeks prior to harvest. In the residential setting, folpet is used to control wood rot fungi, mold/mildew, and spoilage fungi on wood and other surfaces.

b. **Non-Agricultural (Antimicrobial) Uses:** Folpet is registered for use on the following non-agricultural (antimicrobial) sites (7 active labels currently); domestic dwellings (outdoor), wood and wood structure protection, materials preservatives (adhesives, caulks, coatings, paints, plastics, stains, wood plastic composites), surface treatments (outdoor furniture, tile, finished wood, plaster, wood surface), and polymer compounds. Polymer compound uses are limited to non-food and non-drinking water articles. Materials preserved with folpet are not to be used in toys, personal care items, or clothing.

**Table 1: Folpet Antimicrobial Uses**

| Use | Application Rate (in terms of a.i.) | Representative Label |
|---|---|---|
| **Materials Preservative** | | |
| Adhesives, caulks, cement based products, plastics, paper and wood composite material | 0.2 to 1.4 percent | 66222-126 |
| Paints, stains and coatings | 0.4 to 1.4 percent | 66222-125 |
| PVC membranes, roof shingles, carpet yarns and fiber, cordage, gaskets, vinyl upholstery, pond liners | 0.25 to 1.5 percent | 66222-112 |

| Table 1: Folpet Antimicrobial Uses | | |
|---|---|---|
| **Use** | **Application Rate (in terms of a.i.)** | **Representative Label** |
| **Wood Preservative** | | |
| Clearwood Preservative | 0.5 percent (150 to 250 $ft^2$/gallon) | 7313-25 |

**Hazard Identification/Toxicology**

The physical and chemical characteristics of folpet are relevant to the evaluation of its toxicity. In mammals, 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 intermediate, thiophosgene. Thiophosgene is highly reactive and severely irritating to tissues as it comes in contact with, such as mucus membranes. Thiophosgene is also a skin irritant and sensitizer. The thiophosgene moiety is most likely responsible for the predominant toxicity in mammals. However, due to thiophosgene's transient nature, it is difficult to characterize its role in folpet's toxicity.

Folpet has low acute oral and dermal toxicity (Toxicity Category IV for both) but is irritating to mucus membranes such as the eyes (Toxicity Category II), esophagus, lungs and stomach. Although it is not a skin irritant (Toxicity Category IV), it is a skin sensitizer. In the acute inhalation study in rats (Toxicity Category II), folpet was moderately toxic but clinical signs of survivors were consistent with upper and lower respiratory irritation (discharge form nose, gasping, labored breathing at 0.48mg/L). Folpet has low dermal penetration (2.7 % absorption).

Subchronic studies in rats demonstrated that the systemic effect was treatment related acanthosis and hyperkeratosis and/or ulceration/erosion of the stomach following high oral doses of folpet. Folpet administered in the diet of rats at 614/718 mg/kg/day (males/females) for 13 weeks produced acanthosis, hyperkeratosis, focal erosion and focal ulceration in stomachs of both sexes. In a 21-day dermal toxicity study, rats treated with folpet at dose levels as low as 1 mg/kg developed treatment-related skin damage which consisted of acanthosis and exudate and higher doses (10 and 30 mg/kg) produced skin ulcers. In both the oral and dermal studies, rats had a dose related decrease in body weight gains. The local irritating effect to mucus membranes may be responsible, in part, for secondary toxicity such as decreased body weight gain in adult mammals.

There was no qualitative or quantitative evidence of increased susceptibility following *in utero* exposure of rats to folpet. There was evidence of qualitative susceptibility following *in utero* exposure to folpet in a developmental toxicity study in rabbits where hydrocephaly and related skull malformations were seen in fetuses at the same dose that caused minimal maternal toxicity (decrease in food consumption; maternal and developmental NOAEL=10 mg/kg/day, maternal and developmental LOAEL=20 mg/kg/day). In another developmental toxicity study in rabbits, there was evidence of quantitative susceptibility since fetal effects (delayed ossification) were seen at a

dose lower than that which produced maternal toxicity (maternal NOAEL/LOAEL=40/160 mg/kg/day, developmental NOAEL/LOAEL=10/40 mg/kg/day). There was no quantitative or qualitative evidence of increased susceptibility in either of the two-generation reproduction studies. In one study, comparable offspring toxicity (reduced fertility in males of F1 generation) was seen in the presence of maternal toxicity (decrease in body weight and food consumption in F1 generation). In the other two-generation reproduction study, offspring toxicity was seen at a higher dose than that which caused maternal toxicity.

The developmental 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 dermal (with a 2.7% absorption rate), and short and intermediate-term inhalation exposure routes (100% absorption assumed). The maternal NOAEL based on decrease in food consumption in dams from the same rabbit developmental study was used for assessing risk from short- and intermediate-term incidental oral exposure routes and short- and intermediate-term dermal exposure routes. 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 from long-term dermal and inhalation exposure as well (D285511, D286709, D286682).

In 1986, HED's Cancer Peer Review Committee (CPRC) classified Folpet as B2 (Probable Human Carcinogen) based on small intestine and fore stomach tumors in mice and recommended a linear approach ($Q_1$*) for quantification of cancer risk (TXR No. 0054914). In 2010, at the registrant's request, the Cancer Assessment Review Committee (CARC) re-evaluated folpet's cancer classification in accordance with the EPA's March 2005 *Final Guidelines for Carcinogen Risk Assessment* (EPA/630/P-03/001F). The CARC re-classified folpet as "Not likely to be carcinogenic to humans at doses that do not cause an irritation response in the mucosal epithelium" (TXR No. 0055509). This decision was based on the following weight-of-evidence considerations: (i) The occurrence of small intestine and forestomach tumors in male and/or female mice (two strains); (ii) The weight-of-evidence suggests that folpet induces small intestine tumors by a nongenotoxic mode of action involving cytotoxicity and regenerative cell hyperplasia that exhibits a clear dose threshold. This mode of action is also applicable to forestomach tumors; (iii) There were no treatment-related tumors following folpet exposure in rats; and (iv) Folpet is an *in vitro* mutagen that is not active in the whole animal because it reacts with thiols or proteins that rapidly deactivate it or its highly reactive breakdown product, thiophosgene. Future quantification of cancer risk will be through a non-linear (RfD) approach since there are sufficient data to ascertain the mode of action for the tumor response. This is different from the linear $Q_1$* approach used in previous risk assessments.

Toxicity Data Requirements

The toxicity database for folpet is incomplete. In accordance with the 2007 revised 40CFR Part 158 toxicology data requirements, the neurotoxicity battery and an immunotoxicity study are required. However, HED's Hazard and Science Policy Council (HASPOC) determined that the neurotoxicity battery (acute and subchronic neurotoxicity) is not required based on the available hazard and exposure information. The dicarboximide fungicides class of chemicals is severely irritating to the mucous membranes of the eyes, respiratory system, and digestive system, and skin. The Agency is

regulating at a dose that is protective of the irritation via the oral route. Therefore, it is unlikely that neurotoxicity would be observed at a dose lower than which causes irritation via the oral route. The concern for neurotoxicity is low for folpet. The HASPOC also determined that a 90-day inhalation study is required due to the potential for occupational and residential inhalation exposure from the use pattern of Folpet and the low MOEs obtained using an oral point of departure (POD) (TXR No. 0056407).

Hazard Conclusions

Endpoint selection and uncertainty factors may need to be re-evaluated during registration review to ensure that points of departure reflect current policy. While there are outstanding studies as indicated above, the Agency believes the existing database is adequate for risk assessment.

**Residue Chemistry**

The nature of the residue in plants is adequately understood. The HED Metabolism Committee has concluded that the residue of concern in plants is folpet *per se* (F. Fort, 7/24/95, HED Metabolism Committee Decision Memorandum). There are two plant metabolites of folpet, phthalimide (PI) and phthalic acid (PAI), but they are not regulated because phthalimide (PI) is not of toxicological concern, and phthalic acid (PAI) is not a carcinogen and is far less toxic than the parent.

The nature of the residue in ruminants is adequately understood. Folpet is degraded by loss of the one carbon trichloromethyl moiety. This part of the molecule becomes extensively metabolized and the carbon becomes incorporated into thiazolidine and natural products. The thiazolidine metabolite is a likely detoxification product of thiophosgene (formed from the trichloromethylthio moiety of folpet) and the cysteine moiety of glutathione. With the carboxyl group on the ring it is likely to be rapidly excreted. It is far less toxic than thiophosgene. The remaining phenyl part of the molecule is mostly metabolized to phthalimide (PI) and phthalamic acid (PAM; rat metabolite not found in the avocado metabolism study). No folpet *per se* was found in any ruminant tissue. The concern for the phthalamic acid (PAM) metabolite is no greater than for phthalimide (PI) and phthalic acid (PAI) (email communication from R. Kent to B. Cropp-Kohlligian dated 7/20/12).

A tolerance is established under 40 CFR §180.191(a) for residues of folpet (N-(trichloromethylthio)phthalimide) in/on hops, dried cones at 120.0 ppm. A tolerance with regional registration is established under 40 CFR §180.191(c) for residues of folpet (N-(trichloromethylthio)phthalimide) in/on avocado at 25.0 ppm. Tolerances with no U.S. registrations are also established under 40 CFR §180.191(a) for residues of folpet (N-(trichloromethylthio)phthalimide) in/on apple at 5.0 ppm; cranberry at 15.0 ppm; cucumber at 2.0 ppm; grape at 50.0 ppm; grape, raisin at 80.0 ppm; lettuce at 50.0 ppm; melon at 3.0 ppm; onion, bulb at 2.0 ppm; strawberry at 5.0 ppm; and tomato at 25.0 ppm. No tolerances have been established on livestock commodities. The tolerance expression will need to be updated in accordance with current policy. The tolerance in/on avocado may be too high and may need to be reassessed under registration review to be more closely aligned to the available residue chemistry data.

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).

Apples, avocados, cranberries, cucumbers, grapes, lettuce, melons, onions, strawberries, and tomatoes were evaluated in the 1999 Folpet Reregistration Eligibility Decision (RED). Subsequently, the domestic use of folpet on hops and the registration of a new formulation for folpet for use on avocados in Florida were evaluated in the most recent HED risk assessment (D285511, D286709, and D286682). In the most recent risk assessment, HED recommended that the currently registered FOLPAN 80 WDG (66222-48; dated 1/7/10) should be amended as follows: (1) The maximum rate of application on hops should be revised to be 2 lb ai/A/application; (2) The PHI for avocados should be revised to 7 days; (3) 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.

The following are residue data requirements specified in the Residue Chemistry Chapter of the Folpet RED (D254864) which have since been satisfied/waived:

Guideline 860.1200 Direction for Use

- Once adequate residue data are available for avocados, the registrant should amend labels to specify: 1) the maximum single application and maximum seasonal application rate in lb ai/A that are supported by the residue data; 2) the minimum application volume per acre; and 3) a practical PHI that is supported by the residue data. Product 66222-8 must be canceled by the registrant or all data requirements must be fulfilled. The requirements for avocado have been satisfied (D264065) and Product 66222-8 was cancelled 3/10/00 according to PRISM OPPIN.

Guideline 860.1300 Nature of the Residue - Livestock

- A ruminant metabolism study is required for the tolerance with no U.S. registration petition on apples, since wet apple pomace can be used for animal feed. This data requirement has been satisfied (D255675).

Guideline 860.1380 Storage Stability

- Avocado: Storage stability data under two week refrigerated conditions must be submitted before the required avocado magnitude of the residue is fulfilled (D237945 and D241080,). This data requirement has been satisfied (D269339 and D274283). Based on the storage stability data, the tolerance in/on avocado may be too high and may need to be reassessed under registration review to be more closely aligned to the available residue chemistry data.
- Cucumber and Melon: Additional information regarding the use and study conduct is required before a favorable recommendation for a tolerance with no U.S. registration on cucumbers can be made. Supporting storage stability data and field trial information must be submitted prior to a favorable recommendation for a melon tolerance with no U.S.

registration. These data requirements have been waived (D264061). Cucumber and melon storage stability data requirements waived provided the registrant amends foreign labels to specify a maximum single application rate of 1.75 kg/hectare, a maximum seasonal application rate of 10.5 kg/hectare, and a minimum re-treatment interval of 7 days (RTI issue esp. in Guatemala and Honduras).

- Tomato: Additional information regarding the storage of the tomato samples must be submitted before a favorable recommendation for a tolerance with no U.S. registration on tomatoes. This data requirement has been satisfied (D258193).

The following are residue data requirements specified in the Residue Chemistry Chapter of the Folpet RED (D254864) which have not been previously satisfied/waived and are currently listed as outstanding but are no longer needed as explained herein:

Guideline 860.1340 Residue Analytical Methods - Livestock

- An analytical method for the determination of folpet and any metabolites of concern identified in the ruminant metabolism study is required for the tolerance with no U.S. registration petition on apples, since wet apple pomace can be used for animal feed. These data remain outstanding but are not needed as explained below.

Guideline 860.1480 Magnitude of the Residue - Livestock

- A cattle feeding study is required for the tolerance with no U.S. registration petition on apples, since wet apple pomace can be used for animal feed. These data remain outstanding but are not needed. Wet apple pomace (40% dry matter) is fed only to dairy cattle (10% of diet) according to the HED guidance concerning the construction of maximum reasonably balanced diets (Table 1 Feedstuffs, October 2006 version). Based on an estimated maximum reasonably balanced diet for dairy cattle of 1.2 ppm (4.6 ppm estimated median residue in wet apple pomace (from CODEX median value of 1.8 ppm in/on apples x 2.6 concentration factor for wet apple pomace)) and the results of the ruminant metabolism data (MRIDs 44807701 and 44807702; D255675), there is no reasonable expectation of finite residues of concern in meat and milk. These findings should be discussed fully in the Registration Review Risk Assessment.

**Conclusions**

The qualitative nature of folpet residues in the registered crops and livestock is adequately understood based on acceptable metabolism studies. With regards to crops, folpet is the only residue of concern for the tolerance expression and dietary risk assessment. There is no reasonable expectation of finite residues of concern in livestock. Adequate analytical enforcement methods are available.

With regards to domestic use on avocado and hops, provided the FOLPAN 80 WDG label is amended as recommended in the most recent HED risk assessment (D285511, D286709, and D286682), available residue chemistry data are adequate.

The tolerance expression will need to be updated in accordance with current policy. The tolerance in/on avocado may be too high and may need to be reassessed under registration review to be more closely aligned to the available residue chemistry data.

**Recommended label amendments:**

FOLPAN 80 WDG (66222-48; dated 1/7/10) should be amended as follows: (1) The maximum rate of application on hops should be revised to be 2 lb ai/A/application; (2) The PHI for avocados should be revised to 7 days; (3) 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.

## Dietary Exposure and Risk

### Dietary Risk

The most recent dietary exposure assessment (D287372) used 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. This dietary exposure assessment evaluated folpet residues in food but not drinking water.

Highly refined dietary exposure analyses were performed on food only. The assumptions for most of the commodities (apples and apple juice; cranberries; cucumbers; grapes, grape juice, wine, raisins; lettuce; melons; onions; strawberries; and tomatoes) were anticipated residue levels based on field trial data (acute analysis used residue distributions and chronic analysis used average values) and the percent crop treated estimate for imported crops consumed in the U.S. For avocados, the assumptions of the acute and chronic dietary exposure analyses were the anticipated maximum residue level based on field trial data 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 and chronic dietary exposure analysis were tolerance level residues and 100% crop-treated. At the 99.9$^{th}$ 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 less than 1% of the chronic PAD was used for the General U.S. Population and all other population subgroups. Dietary cancer risk from folpet was 7.2E-08 based on the $Q_1^*$ for folpet of $1.86 \times 10^{-3}$ $(mg/kg/day)^{-1}$. The CARC re-evaluated Folpet in 2010 and it has a new classification. Folpet was classified as "Not likely to be carcinogenic to humans at doses that do not cause an irritation response in the mucosal epithelium." Folpet should be regulated based on a non-linear risk assessment.

### Drinking Water

According to the most recent HED risk assessment, 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 17days, and some mobility based on $K_F$ ranging 1.2-5.0 for most soil types (sand, loam, and clay soils) 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 considered the residues of concern in/on avocado after application of folpet (F. Fort, 7/24/95 HED Metabolism Committee Decision Memorandum) and determined that phthalimide (PI) and phthalic acid (PAI) were not residues of concern and HED now finds that the concern for the phthalamic acid (PAM; rat metabolite not found in avocado metabolism study) metabolite is no greater than for phthalimide (PI) and phthalic acid (PAI) (email communication from R. Kent to B. Cropp-Kohlligian dated 7/20/12). Consistent with the determination in plants, HED now considers the residue of concern in water to be folpet only based primarily on the toxicity of the metabolites. This position may be confirmed by the Residues of Concern Knowledgebase Subcommittee (ROCKS) during Registration Review if needed.

The potential groundwater and surface water exposures to folpet were assessed based on screening models, which provide Tier I computer-generated Estimated Drinking Water Concentrations (EDWCs). In the most recent HED risk assessment, risks from potential exposure to folpet in drinking water from all sources were evaluated by comparing these modeled EDWCs against calculated drinking water levels of comparison (DWLOCs). The assessment indicated that the EDWCs for folpet residues in surface and ground water did not exceed the Agency's calculated DWLOC values. The Agency no longer relies on DWLOCs and drinking water estimates may need to be updated for the dietary assessment.

Conclusions

HED has previously assessed dietary exposures and risks from these exposures were below the Agency's level of concern. New acute and chronic dietary risk assessments may need to be conducted using the newest version of the Dietary Exposure Evaluation Model DEEM-FCID™, Version 3.16 which uses food consumption data from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/ WWEIA) and incorporate potential changes to the folpet toxicological points of departure (PODs) and uncertainty factors. Since the CARC re-evaluated Folpet in 2010 and folpet has a new classification, the Q1* approach is no longer required. Folpet should be regulated based on a non-linear risk assessment. The Agency no longer relies on DWLOCs and drinking water estimates may need to be incorporated directly into the dietary assessments.

The most recent drinking water assessment is adequate based on current methodologies but may need to be revised.

If new dietary risk assessments are conducted under registration review, updated foreign use pattern information and percent crop treated data for domestic and foreign uses may be needed for reliable anticipated residue estimates and dietary risk refinements.

## Occupational and Residential Exposure

The most recent occupational and residential exposure (ORE) assessment was performed in conjunction with the April 2004 human-health risk assessment for use on hops and avocados (D285511). Folpet is currently registered for agricultural uses on hops and avocados (the use on avocados is restricted to Florida only), formulated as FOLPAN® 80 WDG (water dispersible granule, 80% ai); and on avocados (Florida only), formulated as FOLPAN® 50 W (wettable powder, 50% ai). These products are labeled to be applied as broadcast applications at maximum rates of 3 pounds ai per acre (lb ai/A) for avocado (up to 5 applications made in 2-week intervals) and 2.4 lb ai/A for hops (up to 4 applications made in 28-day intervals). Only the FOLPAN 80 WDG label prohibits application via any type of irrigation system or by air. The restricted entry interval (REI) is 24 hours.

In the residential setting, folpet is currently registered as a fungicide/preservative in wood sealants for use on exterior wood surfaces including residential/recreational decks and playsets. It is also registered as a preservative for flexible vinyl flooring materials and olefin, nylon and polyester carpet yarns and fibers.

Occupational Non-Cancer Inhalation Handler and Post-Application Exposure Results
The inhalation handler exposure assessment for the agricultural uses resulted in MOEs ranging from 20 to 13,000. The level of concern (LOC) for this chemical is 100, based on its toxicological database. For the scenario resulting in the MOE of 20, the addition of personal protective equipment (PPE) in the form of a respirator increases the MOE to 100, which is not of concern.

For the antimicrobial uses, occupational exposures were last evaluated in the 1999 RED as total MOEs which were calculated by comparing the sum of the dermal and inhalation doses to the NOAEL of 10 mg/kg/day. This evaluation indicated that the handler risks of mixing/loading wettable powder during paint preservation had total MOEs of 12 and 130. The total MOE of 12 was calculated assuming baseline PPE (i.e. no gloves or respirators worn) and the total MOE of 130 assumed the use of gloves and dust/mist respirators. Because the total MOE was less than the required MOE of 100 for baseline PPE, the risks were considered to be of concern and the requirement for gloves and respiratory protection was added to the labels.

A quantitative post-application inhalation exposure assessment was not performed for folpet. However, there are multiple potential sources of post-application inhalation exposure to individuals performing various activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html). The Agency is currently evaluating the SAP report. EPA is also evaluating the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new

policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for folpet.

Spray drift is always a potential source of 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 ground–based applications of folpet. The Agency 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 (see the Agency's Spray Drift website for more information at http://www.epa.gov/opp00001/factsheets/spraydrift.htm). On a chemical by chemical basis, the Agency is now requiring interim mitigation measures for aerial applications that must be placed on product labels/labeling. Other potential sources of residential exposure include volatilization of pesticides and re-suspension of dusts and/or particulates that contain pesticides.

Occupational Non-Cancer Dermal Handler and Post-Application Exposure Results

The dermal handler exposure assessment for the agricultural uses resulted in MOEs ranging from 8.6 to 6,300. The level of concern (LOC) for this chemical is 100, based on its toxicological database. For the scenarios resulting in MOEs of 8.6 and 75, the addition of (PPE) in the form of gloves and coveralls increases the MOEs to 240 and 2,100, respectively. This mitigation was required in the 1999 Folpet RED.

The MOEs resulting from post application exposure estimates range from 82 to 1,600 on the day of application, and reach 100 on the second day after application for training and harvesting hops. The recommended 48 hour REI for folpet would mitigate the MOE of 82, which would otherwise be of concern using the current 24 hour REI.

As discussed above for inhalation exposures, occupational exposures resulting from the antimicrobial uses were last evaluated in the 1999 RED as total MOEs.

Occupational Cancer Risk

As previously mentioned, until 2010, folpet was classified as a B2 carcinogen (probable human carcinogen). To quantify cancer risk, the $Q_1$ was multiplied by the estimated lifetime average daily doses from occupational exposure. The occupational handler cancer risk estimates for the agricultural uses of folpet ranged from 4.1E-07 to 2.9E-04, while those for post-application exposure ranged from 4.7E-07 to 5.0E-06.

When the CARC re-evaluated Folpet in 2010, it was classified as "Not likely to be carcinogenic to humans at doses that do not cause an irritation response in the mucosal epithelium." Therefore, future quantification of cancer risk will be based on a non-linear approach.

Residential Exposure

The non-cancer inhalation handler exposure assessment resulted in MOEs ranging from 1,100 to 9,400, and the dermal handler exposure assessment resulted in MOEs ranging from 420 to 430. The MOE estimates of dermal post application exposure for exposure to treated wood range from 270 (for children) to 550 (for adults) on the day of application. For children, the incidental oral MOE

estimate from hand-to-mouth exposure to treated wood is 270. Because the level of concern (LOC) for this chemical is 100, based on its toxicological database, these risk estimates are not of concern. The dermal and incidental oral exposures for toddlers playing on folpet preserved flooring materials and carpets had not been previously assessed and will need to be assessed during registration review.

The residential handler cancer risk estimates range from 7.6E-08 to 1.0E-07, while the post-application cancer risk estimate is 2.1E-07
In accordance with the Food Quality Protection Act of 1996 (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, and is not of risk concern. For adult handlers, dermal and inhalation exposures co-occur, and because a common toxicological endpoint (developmental malformations) was selected, these exposures were combined; the total MOEs range from 300 to 410, and are not of risk concern. Handler and post application 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.

Conclusions for Residential and Occupational Exposure
Due to recent residential and occupational exposure science policy updates, existing residential and occupational scenarios may have to be reassessed. These updates include changes to data sources and default assessment inputs for both handler and post-application assessments. In addition, the assessment may need to be updated to reflect any potential changes to the points of departure (PODs) and uncertainty factors for folpet.

**Aggregate Exposure and Risk**
Since folpet may be applied to decks/playsets as well as to agricultural crops, there is potential exposure to this fungicide in the residential setting as well as through the diet. In the previous risk assessment, the short-term aggregate assessment included exposure from the dietary, drinking water, and residential pathways. The aggregate MOE estimates for food and residential use ranged from 160 to 300, which was not of risk concern. The drinking water estimates did not contribute significantly to the aggregate risk estimate.

An aggregate cancer assessment was also conducted for combined exposure to folpet and captan through the oral route (based on their shared metabolite thiophosgene). The aggregate exposure from folpet and captan residues in food and water did not exceed the EPA's level of concern for cancer risk for the U.S. population

**Public Health and Pesticide Epidemiology Data**

For this evaluation, the OPP Incident Data System (IDS) was utilized to retrieve pesticide incident data on the active ingredient folpet. Based on the low frequency and severity of incident cases reported for folpet, there does not appear to be a concern at this time that would warrant further investigation (D403989). The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

**Tolerances and International Harmonization**

The U.S., CODEX, and Canadian residue definitions for folpet are harmonized. Mexico adopts U.S. tolerances and/or Codex MRLs for export purposes.

U.S. tolerance levels are not fully harmonized with CODEX and may need to be reassessed. (See International Residue Limits table in the Appendix). Only the folpet tolerances and CODEX MRLs for lettuce, melon, and strawberry are currently harmonized. Only avocado and tomato U.S. tolerances and Canadian MRLs are currently harmonized. Updated foreign use pattern information may be needed for further harmonization.

**Endocrine Disruption**

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), folpet is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. Folpet was included on that list and has been issued an order to conduct the Tier 1 testing. Once all required Tier 1 and Tier 2 data have been received and reviewed, the endpoints and safety factors used for risk assessment purposes will be examined and a new risk assessment performed if necessary. For further

information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

**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 folpet and captan share the common metabolite thiophosgene, its role in folpet's and captan's toxicity has not been determined because thiophosgene is transient and not easily measurable. Therefore, the EPA has not assumed that folpet has a common mechanism of toxicity with captan or any 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/.

**Human Studies**

The occupational exposure and risk assessment for folpet relied in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies required a review of their ethical conduct and have received the appropriate review by the Human Studies Review Board (HSRB). Many such studies, involving exposure to many different pesticides, comprise generic pesticide exposure databases such as the PHED and the Agricultural Reentry Task Force (ARTF) Database. EPA has reviewed all the studies in these multi-pesticide generic exposure databases, and on the basis of available evidence has found them to have been neither fundamentally unethical nor significantly deficient relative to standards of ethical research conduct prevailing when they were conducted. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied.

**Environmental Justice**

Potential areas of environmental justice concerns, to the extent possible, were considered in the human-health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.hss.energy.gov/nuclearsafety/env/guidance/justice/eo12898.pdf). OPP typically considers the highest potential exposures from the legal use of a pesticide when conducting human-health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who might be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

## Data Requirements

*Toxicology:*

- Guideline 870.7800 Immunotoxicity
- Guideline 870.3465 90-day Inhalation

*Residue Chemistry:*

- No data requirements

*Occupational and Residential Exposure (ORE):*

- Guideline 875.2300 Indoor Surface Residues – needed to evaluate dermal and incidental oral exposure in children exposed to transferable folpet residues from
  - Treated decks.
  - Treated carpet
  - Treated hard surfaces
- Guideline 875.1200 Dermal Exposure Indoor - needed to evaluate dermal exposure to handlers applying folpet containing paints and stains using brushes, rollers or airless sprayers.
- Guideline 875.1400 Inhalation Exposure Indoor - needed to evaluate inhalation exposure to handlers applying folpet containing paints and stains using brushes, rollers or airless sprayers.

## Recommended Label Amendments

The currently registered FOLPAN 80 WDG label (EPA Reg. No 66222-48) should be amended as follows:

1. The maximum rate of application on hops should be revised to be 2 lb ai/A/application;
2. The PHI for avocados should be revised to 7 days;
3. If the application rate is not revised, then REI should be revised from 24 to 48 hours to reach an acceptable MOE for training hop vines.

## Risk Assessment Updates Required Under Registration Review

*Hazard Conclusions:*

- Endpoint selection and uncertainty factors may need to be re-evaluated to ensure that points of departure (PODs) reflect current policy and to incorporate any new endpoints or uncertainty factors selected based on the required toxicity studies.

*Dietary and Drinking Water Exposure and Risk*:

- New acute and chronic dietary risk assessments may be needed if there are changes to the folpet toxicological PODs, uncertainty factors, or drinking water assessment. If new dietary risk assessments are conducted under registration review, updated foreign use pattern information and percent crop treated data for domestic and foreign uses may be needed for reliable anticipated residue estimates and dietary risk refinements.

*Residue Chemistry:*

- The tolerance expression will need to be updated in accordance with current policy. The tolerance in/on avocado may be too high and may need to be reassessed under registration review to be more closely aligned to the available residue chemistry data.

*Tolerances and International Harmonization:*

- U.S. tolerance levels are not fully harmonized and may need to be reassessed for CODEX harmonization. Updated foreign use pattern information may be needed for further harmonization.

*Occupational and Residential Exposure (ORE) and Risk:*

- The residential and occupational exposure assessments may need to be updated to reflect current SOPs and to incorporate any new endpoints or uncertainty factors selected based on the required toxicity and indoor ORE studies.

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# Appendix

**Table 1. Doses and toxicological endpoints selected for various exposure scenarios for Folpet: (This table is from the 2004 Risk Assessment.)**

| 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<br>UF = **100**<br>**Acute RfD = 0.1** mg/kg/day | FQPA SF = **1X**<br>**aPAD** = acute RfD / FQPA SF<br>= **0.1** mg/kg/day | Rabbit Developmental Toxicity<br>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<br>UF = **100**<br>**Chronic RfD** = **0.09** mg/kg/day | FQPA SF = **1X**<br>**cPAD** = chronic RfD / FQPA SF<br>= **0.09** mg/kg/day | Combined Chronic Toxicity/ Carcinogenicity Study in Rats<br>LOAEL = **35** mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females. |
| Short-and Intermediate-Term Incidental Oral (1-30 days, 1-6 months) | NOAEL (maternal) = **10** mg/kg/day | **Residential** LOC for MOE = **100** | Rabbit Developmental Toxicity<br>LOAEL = **20** mg/kg/day based on a decrease in food consumption |
| Short- and Intermediate-Term Dermal (1 to 30 days, 1-6 months) | NOAEL (developmental[1])= **10** mg/kg/day<br>(dermal absorption rate = **2.7 %** | **Residential** LOC for MOE = **100**<br>**Occupational** LOC for MOE = **100** | Rabbit Developmental Toxicity<br>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**<br><br>**Occupational** LOC for MOE = **100** | Combined Chronic Toxicity/ Carcinogenicity Study in Rats<br><br>LOAEL = **35** mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females. |
| Short- and Intermediate-Term Inhalation (1 to 30 days, 1-6 months) | NOAEL (developmental) = **10** mg/kg/day (*) | **Residential** LOC for MOE = **100**<br><br>**Occupational** LOC for MOE = **100** | Rabbit Developmental Toxicity<br>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**<br><br>**Occupational** LOC for MOE = **100** | Combined Chronic Toxicity/ Carcinogenicity Study in Rats<br><br>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).<br>The **$Q_1$* is** $1.86 \times 10^{-3}$ $(mg/kg/day)^{-1}$.[2] | | |

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.
[1]Note that the maternal NOAEL was used to assess toddler dermal exposure.
[2]In 2010 in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC re-classified Folpet as "Not likely to be carcinogenic to humans at doses that do not cause an irritation response in the mucosal epithelium." Since the CARC determined that there was a plausible MOA for the mouse tumors, folpet should be regulated based on a non-linear risk assessment.

## Table 2. Folpet Toxicology Data Requirements

| Test | | Technical | |
|---|---|---|---|
| | | Required | Satisfied |
| 870.1100 | Acute Oral Toxicity | yes | yes |
| 870.1200 | Acute Dermal Toxicity | yes | yes |
| 870.1300 | Acute Inhalation Toxicity | yes | yes |
| 870.2400 | Primary Eye Irritation | yes | yes |
| 870.2500 | Primary Dermal Irritation | yes | yes |
| 870.2600 | Dermal Sensitization | yes | yes |
| 870.3100 | Oral Subchronic (rodent) | yes | yes |
| 870.3150 | Oral Subchronic (nonrodent) | yes | yes |
| 870.3200 | 21/28-Day Dermal | yes | yes |
| 870.3250 | 90-Day Dermal | yes | yes |
| **870.3465** | **90-Day Inhalation** | **yes** | **no** |
| 870.3700 | Developmental Toxicity (rodent) | yes | yes |
| 870.3700 | Developmental Toxicity (nonrodent) | yes | yes |
| 870.3800 | Reproduction | yes | yes |
| 870.4100 | Chronic Toxicity (rodent) | yes | yes |
| 870.4100 | Chronic Toxicity (nonrodent) | yes | yes |
| 870.4200 | Oncogenicity (rat) | yes | yes |
| 870.4200 | Oncogenicity (mouse) | yes | yes |
| 870.4300 | Chronic/Oncogenicity (mouse) | yes | yes |
| 870.4500 | Chronic/Oncogenicity (rat) | yes | yes |
| 870.5100 | Mutagenicity—Gene Mutation - bacterial | yes | yes |
| 870.5xxx | Mutagenicity—other genotoxic effects | yes | yes |
| 870.5375 | Mutagenicity—Structural Chromosomal Aberrations | yes | yes |
| 870.6100 | Acute Delayed Neurotox. (hen) | no | ..... |
| 870.6100 | 90-Day Neurotoxicity (hen) | no | ..... |
| **870.6200** | **Acute Neurotox. Screening Battery (rat)** | **no** | * |
| **870.6200** | **Chronic Neurotox. Screening Battery (rat)** | **no** | * |
| 870.6300 | Develop. Neurotox | no | ..... |
| 870.7485 | General Metabolism | yes | yes |
| 870.7600 | Dermal Penetration | yes | yes |
| **870.7800** | **Immunotoxicity** | **yes** | **no** |

*Neurotoxicity studies waived by HASPOC (TXR No. 0056407)

**Table 3. Folpet Acute Toxicity Studies:**

| Guideline No. | Study Type | MRID #(s) | Results | Toxicity Category |
|---|---|---|---|---|
| 81-1 | Acute Oral - Rat | 00144057 | $LD_{50}$ = 43.8 g/kg(M); 19.5 g/kg(F) | IV |
| 81-2 | Acute Dermal - Rabbit | 00141728 | $LD_{50}$ = >5.0 g/kg | IV |
| 81-3 | Acute Inhalation - Rat (Nose Only) | 44286301 | $LC_{50}$ = 1.535 (M); >1.99 (F) ; > 1.89 (M+F) mg/L | III |
| 81-3 | Acute Inhalation - Rat (Whole Body) | 40592301 | 0.34mg/L(M);1.00mg/L(F); 0.48mg/L(M+F) | II |
| 81-4 | Primary Eye Irritation - Rabbit | 00160444 | intermediate irritation | III |
| 81-5 | Primary Skin Irritation - Rabbit | 00160430 | no irritation | IV |
| 81-6 | Dermal Sensitization- Guinea Pig | 00160431 | sensitizing | N/A |

**Table 4. Toxicity Profile for Folpet**

| Guideline | Study Type - Dose Levels | Results |
|---|---|---|
| 870.4300 | 2-Yr Feeding/Carcinogenicity Rat: (1985) MRID: 00015160 Doses: 0, 200, 800, 3200 ppm in Crl:CD (SD)BR albino rats (0, 10, 40, 160 mg/kg/day). | Systemic Toxicity NOAEL= 200 ppm (10 mg/kg/day). Systemic Toxicity LOAEL= 800 ppm (40 mg/kg/day), ulceration/erosion, hyperkeratosis of stomach in M & F.<br><br>Increased incidence of C-cell adenoma & carcinoma of thyroid in M & Leydig cell tumors of testes). Results of diet analysis requested for a formal determination. |
| 870.4300 | 2-Yr Feed/Carcinogenic Rat (Fischer 344): MRID #: 00157493 (1986) Doses: 0, 500, 1000 & 2000 ppm in diet (0, 25, 50, 100 mg/kg/day) | Systemic Toxicity NOAEL = 500 ppm (25 mg/kg/day). Systemic Toxicity LOAEL = 1000 ppm (50 mg/kg/day) based on hyperkeratosis of nonglandular epithelium of stomach in both sexes.<br><br>Increased benign fibroepithelial tumor of the mammary glands & C-cell adenoma of the thyroid. |
| 870.4100 | 2-Year Feeding Rat:(1981) MRID: 00098054 Doses: 0, 200, 800,3200 ppm (0, 10, 40, 160 mg/kg/day). | One year interim: Less than 3% loss to death during first year. This study was discontinued after 60 weeks due to mix- up in test diets by the testing lab. |
| 870.4100 | 2-YR FEEDING RAT:(1989) MRID: 43640201 | Systemic Toxicity NOAEL = 250 ppm (M: 12 and F: 15 |

| Table 4. Toxicity Profile for Folpet | | |
|---|---|---|
| **Guideline** | **Study Type - Dose Levels** | **Results** |
| | Doses: 0, 250, 1500 and 5000 ppm (mg/kg body/day: males= 0, 12, 81 and 291; females= 15, 100 and 351) for 24 months. | mg/kg/day)<br>Systemic Toxicity LOAEL = 1500 ppm (M: 81 and F: 100 mg/kg/day) based on an increase in incidence and severity of hyperkeratosis of the esophagus and non- glandular epithelium of the stomach. |
| 870.4100 | 17- Month Feeding Rat(1961) MRID: 00064323<br>Doses: 1000,3200, 10000 ppm (50, 160, 500 mg/kg/day). | Systemic Toxicity NOAEL = 3200 ppm (160 mg/kg/day).<br>Systemic Toxicity LOAEL = 10000 ppm (500 mg/kg/day) increased spleen & testicle weights at 12 months. Increased thyroid weights at 17 months. |
| 870.4200 | LIFETIME CARCINOGENICITY MOUSE: (1985) MRID: 00151075<br>Doses: 0, 1000, 5000 and 10000 ppm (0, 150, 750, 1500 mg/kg/day) in B6C3F1 str., reduced week 22 to 0, 1000, 3500 & 7000 ppm (0, 150, 525, 1050 mg/kg/day). | Systemic Toxicity NOAEL < 1000 ppm (150 mg/kg/day). (LDT; hyperkeratosis, acanthosis, & hyperplasia). Systemic Toxicity LOAEL = 1000 ppm (150 mg/kg/day) duodenal carcinoma and stomach papilloma both sexes, malignant lymphoma in high dose female only. |
| 870.4200 | LIFETIME CARCINOGENICITY MOUSE (CD-1): (1982)<br>MRID: 00125718<br>Doses: 1000, 5000 and 12000 ppm (150, 750, 1800 mg/kg/day). | Systemic Toxicity NOAEL < 1000 ppm (150 mg/kg/day) decreased body weight. Positive carcinogen based on a dose related increase in incidence of intestinal adenomas and adenocarcinomas in both sexes. These neoplasms are rare in (CD-1) mice. |
| 870.4100 | 1-YR FEEDING DOG (capsule): (1986) MRID: 00161315<br>Doses: 0, 10, 60, 120 mg/kg in beagle dogs | Systemic Toxicity NOAEL = 10 mg/kg/day.<br>Systemic Toxicity LOAEL = 60 mg/kg/day (decreased food consumption & body weight gain; decreased serum cholesterol & serum proteins). Test material analyses requested from sponsor. |
| 870.3800 | 2-Generation Reproduction Rat (Charles River CD (SD): (1986) MRID#: 40135901<br>Doses: 0, 250, 1,500 or 5,000 ppm<br>(calculated mg/kg/day during the 14 weeks pre-mating period: males FO= 19.1, 112 and 370; males F1 = 25.1, 150 and 520; females FO= 22.5, 134 and 436; and females F1 = 28.4, 168 and 565). | Parental Systemic Toxicity NOAEL = 250 ppm males FO= 19.1, males F1 = 25.1, females FO= 22.5, females F1 = 28.4 mg/kg/day<br>Paternal Systemic Toxicity LOAEL = 1,500 ppm<br>males FO= 112, males Fl = 150,<br>females FO= 134, females Fl = 168 mg/kg/day)<br>based on diffuse hyperkeratosis of the non-glandular epithelium in both sexes of both generations.<br><br>Offspring Systemic Toxicity NOAEL = 1,500 ppm males FO= 112, males Fl = 150, females FO= 134, females Fl = 168 mg/kg/day Offspring Systemic Toxicity LOAEL = 5,000 ppm males FO= 370, males Fl = 520, females FO= 436, females Fl = 565 mg/kg/day<br>based on lower pup body weights primarily in the F1 litter generation.<br><br>Reproductive Toxicity NOAEL = 5,000 ppm males FO= 370, males Fl = 520, females FO= 436, females Fl = 565 mg/kg/day<br>Reproductive Toxicity LOAEL >5,000 ppm<br>males FO= 370, males Fl = 520,<br>females FO= 436, females Fl = 565 mg/kg/day. |
| 870.3800 | 2-GENERATION REPRODUCTION RAT (Sprague- Dawley): (1985)<br>MRID #: 00151489 & 40051401<br>Doses: 0, 200, 800, 3600 ppm (nominal; 0, 10, 40, 180bmg/kg/day) in the diet (0, 150, 690, 3200 ppm analytical concentration; 0, 8, 35, 160 mg/kg/day), | Parental Systemic Toxicity NOAEL= 690 ppm (35 mg/kg/day).<br>Parental Systemic Toxicity LOAEL = 3200 ppm (160 mg/kg/day based on decreased weight gain in F1offspring. |

| Table 4. Toxicity Profile for Folpet | | |
|---|---|---|
| **Guideline** | **Study Type - Dose Levels** | **Results** |
| | | Reproductive Toxicity NOAEL = 690 ppm (35 mg/kg/day). Reproductive Toxicity LOAEL = 3200 ppm (160 mg/kg/day) based on decreased fertility in males. |
| 870.3700 | DEVELOPMENTAL TOXICITY RAT: (1983) MRID: 00132457 & 00144420 Doses: 10, 60,360 mg/kg/day (gavage) in Crl: COBS- CD-(SD) BR strain. | Maternal Systemic Toxicity NOAEL= 10 mg/kg/day. Maternal Systemic Toxicity LOAEL= 60 mg/kg/day (reduced body weight).<br><br>Developmental Systemic Toxicity NOAEL= 60 mg/kg/day Developmental Systemic Toxicity LOAEL = 360 mg/kg/day (possible incomplete ossification of one or both pubes and/or eschia). |
| 870.3700 | DEVELOPMENTAL TOXICITY RAT: (1983) MRID: 00132456 (Range Finding Study) Doses: 20, 80, 320, 640 mg/kg/day. | Maternal Systemic Toxicity NOAEL = 20 mg/kg/day. Maternal Systemic Toxicity LOAEL = 80 mg/kg/day (reduced body weight).<br><br>Developmental Toxicity NOAEL = 80 mg/kg/day. Developmental Toxicity LOAEL = 320 mg/kg/day (reduced live fetal body weight/litter). |
| 870.3700 | DEVELOPMENTAL TOXICITY RAT (CD): (1985) MRID: 00155617 Doses: 0, 150, 550 & 2000 mg/kg/day by gavage | Maternal Systemic Toxicity NOAEL = 150 mg/kg/day. Maternal Systemic Toxicity LOAEL = 550 mg/kg/day (decreased body weight gain, soft feces 2/22).<br><br>Developmental NOAEL = 150 mg/kg/day. Developmental LOAEL= 550 mg/kg/day based on increased number of small fetuses, significant increases in enlarged fontenelles, reductions of the squamosal bones, and unossified 5$^{th}$ metatarsal. |
| 870.3700 | Developmental Toxicity Study in (HY/CR Albino) NZW rabbits. (1985) MRID#:00156636,45047607,45047608 Doses: 0, 10,40 or 160 mg/kg/day by gavage at | Maternal Systemic Toxicity NOAEL= 40 mg/kg/day. Maternal Systemic Toxicity LOAEL= 160 mg/kg/day based on decrease in body weight gain and food consumption.<br><br>Developmental Systemic Toxicity NOAEL = 10 mg/kg/day Developmental Systemic Toxicity LOAEL = 40 mg/kg/day based on delayed ossification of sternebrae and lack of ossification of caudal vertebrae distal to caudal vertebra #15. |
| 870.3700 | Developmental Toxicity Study in Rabbits (1966) MRID #: 00043391 (Published study). Doses: 0, 80 mg/kg by gavage | NOAELs couldn't be established. Reported as negative for teratogenicity. Summary data only. |
| 870.3700 | DEVELOPMENTAL TOXICITY RABBIT (NZW): (1985) MRID: 00151490 Doses: 0 & 60 mg/kg (gavage) by "pulse dose". | Only one dose was utilized Maternal Systemic Toxicity NOAEL< 60 mg/kg/day Maternal Systemic Toxicity LOAEL= 60 mg/kg (decreased food consumption & body weight gain during gestation). Developmental Systemic Toxicity NOAEL< 60 mg/kg/day Developmental Systemic Toxicity LOAEL = 60 mg/kg (Irregularly shaped fontanelles). |
| 870.3700 | DEVELOPMENTAL TOXICITY RABBIT (NZW): (1984) MRID: 00160432 & 00160434 Doses: 0, 10, 20, 60 mg/kg/day (gavage). | Maternal Systemic Toxicity NOAEL= 10 mg/kg/day. Maternal Systemic Toxicity LOAEL = 20 mg/kg/day (Decreased food consumption & body weight gain during gestation). At 60 mg/kg/day decreased food consumption & body weight gain, hydrocephalus and related skull malformations. Positive for teratogenicity.<br><br>Developmental Systemic Toxicity NOAEL = 10 mg/kg/day. Developmental Systemic Toxicity LOAEL = 20 mg/kg/day (Increased incidence of hydrocephalus & |

**Table 4. Toxicity Profile for Folpet**

| Guideline | Study Type - Dose Levels | Results |
|---|---|---|
| | | domed skull & irregularly shaped fontanelles). |
| 870.3100 | 13-WEEK FEEDING RAT (1957)<br>MRID #: 00081263<br>Doses: 1000, 3200, and 10000 ppm in diet (50, 160, 500 mg/kg/day). | Systemic Toxicity NOAEL = 3200 ppm (160 mg/kg/day)<br>Systemic Toxicity LOAEL = 10000 ppm (500 mg/kg/day)<br>5% decrease in body weight. |
| 870.3150 | 13-WEEK FEEDING DOG (1985)<br>MRID: 00147135<br>Doses: 0, 790, 1800, & 4000 mg/kg/day by capsule | Systemic Toxicity NOAEL < 790 mg/kg/day<br>(LDT; decreased weight gain in males and females, testicular atrophy in males). |
| 870.3150 | 28 Day Feeding Dog (Capsule)- (1983)<br>MRID #: 00161314 & 263771<br>Doses: 0, 20, 60, 180 & 540 mg/kg | Systemic Toxicity NOAEL < 20 mg/kg Systemic Toxicity LOAEI = 20 mg/kg/day (decreased body weight gain in male & female). |
| 870.3100 | 13-WEEK FEEDING MOUSE | Not available |
| 870.3100 | 28-Day Feeding Mouse. (1978)<br>MRID: 00125719<br>Doses: Not specified<br>Pilot Study | Food intake was depressed at all levels for females and at 5000 ppm (750 mg/kg/day) and higher in males. Female body weight depressed at 16000 ppm (2400 mg/kg/day)and 20000 ppm (3000 mg/kg/day); males depressed at 5000 ppm (750 mg/kg/day) & higher. |
| 870.6200 | ACUTE NEUROTOXICITY RAT | Not available |
| 870.6200 | 90-DAY NEUROTOXICITY RAT | Not available |
| 870.3200 | 28-DAY DERMAL TOXICITY RAT (1988)<br>MRID: 40750802<br>Doses: I, I0 & 30 mg/kg/day | Systemic Toxicity NOAEL =1 mg/kg/day.<br>Systemic Toxicity LOAEL = 10 mg/kg/day in male & female rats. Dermal irritation occurred at all doses but systemic toxicity as reduced body weight gain occurred only at => I0 mg/kg/day. |
| 870.3465 | 2I-Day Inhalation Rat (I975)<br>MRID: OOI60437<br>Doses: 0.048 mg/L/4hours/day, 5 days/week for 3 weeks. | No effects noted. Data insufficient for setting NOAEL or LOAEL. Only I dose; animals necropsied I2 days after last exposure; inadequate histopathology and clinical chemistry data |
| 870.5275 | Mutagenic- Sex Link Recessive in Drosophilia: (1981) MRID #: OOI43567<br>Doses: 0, 2, 3, or 2000 ppm in 1% glucose as food, 72 hours. | Positive for sex linked recessive lethals. |
| 870.5195 | Mutagenic- Lymphoma Mutation in L5I78Y/TK mouse lymphoma cells. (1980) MRID #: 00162394<br>Doses: Unknown | Positive for forward mutations in L5I78Y/TK mouse lymphoma cells. Higher concentration necessary in the presence of S-9 fraction. |
| 870.5500 | Mutagenic- Gene Mutation (1976) MRID #: 00046435<br>Doses: Unknown | Published study, summary data only. Reported as positive for gene mutation in Salmonella & E. coli; Reported as positive for DNA damage in B. subtilis rec assay. Unacceptable |
| 870.5275 | Mutagenic- Sex Link Recessive in Drosophila: MRID #:05003752<br>Doses: 0, 3.3 mM in DMSO. | Published study, summary data only. Reported as negative for sex linked recessive lethals. Unacceptable. |
| 870.5575 | Mutagenic- Recomb/Convers Assay: (1977) MRID #: 00124901 & 00132582<br>Doses: 0.003% incubation in S. cerevisiae D3. | Positive for recombinants with/without metabolic activation |
| 870.5380 | Mutagenic- Chromosome Aberration in Chinese hamster ovary cells (CHO): (1989) MRID #: 42122014<br>Methods: Folpet was tested up to toxicity in non-activated (2.5 ug/mL) & activated Chinese hamster ovary cells (CHO) (25.7 & 75.0 ug/mL) in 10 & 20 hour assays. | There was a 10-30 fold difference in toxicity sensitivity. The test article induced chromosomal aberrations at marginally cytotoxic concentrations of 0.75 ug/mL in the non-activated system, and 0.26 ug/mL in the 10 hour activation assay, but required 25.0 ug/mL in the 20 hour activation assay. |

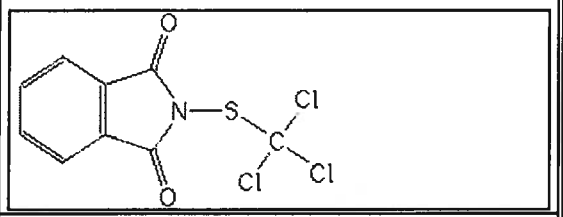
| Table 4. Toxicity Profile for Folpet | | |
|---|---|---|
| **Guideline** | **Study Type - Dose Levels** | **Results** |
| 870.5450 | Mutagenic- Dominant Lethal Test in the Mouse: (1977) MRID #: 00124901 & 00132582<br>Doses: 0, 1250, 2500 & 5000 mg/kg in the diet of ICR/SIM mice. | Negative for mutagenicity |
| 870.5300 | Mutagenic- In vivo Cytogenetic toxicity in Mouse: (1984) MRID #: 00149567<br><br>Doses: 0, 100, 1500 & 5000 ppm (nominal; 0, 15,225,750 mg/kg/day) in the diet of T-strain mice (76, 1340, 4310 ppm analytical; 0, 11, 201, 647 mg/kg/day). | NOEL for survival not established.<br>Developmental NOEL= 76 ppm (analytical: 11 mg/kg/day)<br>No effect on the incidence of coat color spots -negative for mutations. Significant pup mortality at all doses levels. Decreased survival of pups during lactation. Increased melanocyte toxicity in pups at 4310 ppm (647 mg/kg/day), decreased weight gain in dams at 4310 ppm (647 mg/kg/day). |
| 870.5300 | Mutagenic-In vivo Cytogenetic in Mouse (1984) MRID #: 00148625<br>Doses: 0, 700, 2300 or 7000 ppm (0, 105,345, 1050 mg/kg/day) in the diet of T-strain mice (range finding study). | Decreases in the number and % of live born pups, maternal weight gain. |
| 870.5375 | Mutagenic-Chromosome Aberration in Rats(1983) MRID #: 00160445<br>Doses: 0.15- 2.0 g/kg (gavage). | Not a clastogen at HDT. No measure of cytotoxicity in bone marrow. Dose used not supported by evidence that the HDT was an MTD. |
| 870.5395 | Mutagenic- Micronucleus Assay in the Mouse (CD-I): MRID #: 00150558 (1985)<br>Doses: 0, 10, 50, 250 mg/kg by gavage. | No evidence of mutagenicity or effect on PCE/NCE ratio. Dose not supported by range-finding data. |
| 870.5500 | Mutagenic- Reverse Mutation: (1978) MRID #: 253165 | Positive direct acting mutagen. Both batches tested were equally mutagenic. Effect of metabolic activation not assessed. |
| 870.5550 | Mutagenic- DNA Repair Test: (1977) MRID # 00124901 & 00132582<br>Doses: 0.1 mg/disc in B. subtilis & E. coli. | Positive for DNA damage without metabolic activation. |
| 870.5550 | Mutagenic- Unscheduled DNA Synthesis in WI 38 Fibroblasts: (1977)<br>MRID #: 00124901 & 00132582<br>Doses: 10-8 to 10-4M in WI 38 fibroblasts. | Positive in the presence of metabolic activation only. |
| 870.5500 | Mutagenic- Reverse Mutation: (1977)<br>MRID #: OOI2490I & 00132582 | Positive for reverse mutations in Salmonella TAIOO, TAI535 & TAI538, & in E. coli WP2. Rat liver S-9 had no effect on mutagenicity. |
| 870.7485 | Metabolism Study in Sprague-Dawley Rats: (199I) MRID: # 42I22OI6<br><br>Doses: 50, and 5000 ppm (3, 7 mg/kg/day dietary admix), | The 5,000 ppm level had been shown to cause the tumors in mice but not in rats. The studies suggested that Folpet was tumorigenic in the mouse and not in the rat because: greater intake in the mouse and greater target tissue exposure to active metabolites that the mouse could not detoxify; greater local effects on mouse upper gastrointestinal tract; and greater reliance by the mouse on glutathione for detoxification of Folpet. |
| 870.7485 | Metabolism Study: (1991) MRID #: 42122017<br>Doses: I4C-Folpet was administered orally to Sprague- Dawley rats in 3 studies:<br><br>1. single dose of I0 mg/kg;<br>2. single dose of 500 mg/kg;<br>3. On day 15, 10 mg/kg of 14C-Folpet after 14 consecutive days of unlabeled Folpet at IO mg/kg. Samples were examined for radioactivity for up to 120 hours post 14C-dosing. | 1. Single I4C-Folpet at 10 mg/kg was absorbed> 90% of the dose, there was rapid urinary excretion and by 120 hours, there was little detectable radioactivity.<br>2. Single 14C-Folpet at 500 mg/kg was about 60% absorbed with the urinary excretion rate being slower that after the 10 mg/kg dose (possibly due to rate-limiting absorption).<br>3. Single I4C-Folpet at 10 mg/kg following I4 daily non-labeled doses of I0 mg/kg yielded results similar to those observed after a single 14C dose.<br>4. No accumulation of Folpet was detected during the 5 days |

| Table 4. Toxicity Profile for Folpet | | |
|---|---|---|
| **Guideline** | **Study Type - Dose Levels** | **Results** |
| | | after dosing; concentrations of radioactivity in measured tissues were generally below the limit of detection at 10 mg/kg or were detected at very low levels at 500 mg/kg. 5. Phthalamic acid was determined to be the single active metabolite found in urine & it was suggested that its formation from Folpet may have been by trichloro- methylthio groups loss and hydrolytic cleavage of the "maleimide" ring. At 10 mg/kg, the major fecal metabolite was phthalamic acid and at 500 mg/kg, the radioactivity was primarily associated with unchanged 14C-Folpet (assumed to be unabsorbed test article). |
| 870.7485 | Metabolism- in vitro (Human): (1967) MRID #: 00070970 | Half-life in human blood is about 1 minute, degrades rapidly to phthalimide. |
| 870.7600 | Metabolism- Dermal Absorption in Sprague-Dawley Rats: (1990) MRID#: 42122018 Doses: 14C-Folpet was administered dermally to male doses of 10, 1, 0.1, and 0.01 mg/rat (200 uL volume of test suspension to 18.9 $cm^2$ of clipped skin) for up to 24 hours. Blood, urine, feces, carcass and skin radioactivity was measured (up to 24 hrs). | 1) Rapid absorption into the skin and carcass; 2) Low blood levels; 3) Primary excretion by urine with rate apparently inversely related to quantity applied and 4) Minor bile involvement in excretion as little in feces. |

## Chemical Structure

Folpet is the common name of the pesticide chemical (N-(trichloromethylthio) phthalimide). The chemical name and structure of folpet are presented in Table 5.

**Table 5. Test Compound Chemical Identity and Structure**

| | |
|---|---|
| **Compound** |  |
| **Common name** | Folpet |
| **Company experimental name** | Folpet or Folpan |
| **IUPAC name** | *N*-(trichloromethylthio)phthalimide;<br><br>*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. 66222-7)<br>Folpet 80 WDG (EPA Reg. No. 66222-48) |

Folpet's physicochemical properties are summarized in the Table 6 below.

**Table 6: Physicochemical Properties**

| Parameter | Value | Reference |
|---|---|---|
| **Melting Point** | 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<br>26 in toluene<br>3 in methanol | *The Pesticide Manual*, 11th Edition |
| **Vapor Pressure at 25°C** | $2.1 \times 10^{-2}$ mPa | *The Pesticide Manual*, 11th Edition |
| **Dissociation Constant (pKd) in water** | Not applicable since the TGAI is not an acid or base | |
| **Octanol/Water Partition Coefficient Log ($K_{ow}$)** | Log P=3.11 | *The Pesticide Manual*, 11th Edition |
| **UV/Visible Absorption Spectrum** | Media / λmax (nm) / absorbance / Molar coeff (€) dm³/mol/cm<br>Neutral 223 0.829 47100<br>Acid 223 0.925 52600<br>Base 225 1.397 19900<br>(99.5% PAI; UV/visible spectrophotometer) | MRID 45053701, D264048 |

# International Residue Limits

## Folpet (081601; 06/27/12)

| Summary of US and International Tolerances and Maximum Residue Limits | | | | |
|---|---|---|---|---|
| *Residue Definition*: | | | | |
| US | Canada | | Mexico[2] | Codex[3] |
| 40 CFR 180.191: Plant: Folpet (N-trichloromethylthio)phthalimide | *N*-(trichloromethylthio)phthalimide | | | Folpet |
| *Commodity* | *Tolerance (ppm) /Maximum Residue Limit (mg/kg)* | | | |
| | US | Canada | Mexico[2] | Codex[3] |
| Apple[1] | 5.0 | 25 | | 10 |
| Cranberry[1] | 15.0 | 25 | | |
| Cucumber[1] | 2.0 | 15 | | 1 |
| Grape[1] | 50.0 | 25 | | 10 |
| Grape, raisin[1] | 80.0 | | | 40 dried grapes (currants, raisins and sultanas) |
| Hop, dried cones | 120.0 | | | |
| Lettuce[1] | 50.0 | 25 | | 50 lettuce, head |
| Melon[1] | 3.0 | 15 | | 3 melons, except watermelon |
| Onion,bulb[1] | 2.0 | 25 onions | | 1 |
| Strawberry[1] | 5.0 | 25 | | 5 |
| Tomato[1] | 25.0 | 25 | | 3 |
| | | | | |
| *MRL With No US Registration* | | | | |
| Blackberries | | 25 | | |
| Blueberries | | 25 | | |
| Boysenberries | | 25 | | |
| Celery | | 30 | | |
| Cherries | | 25 | | |
| Citrus fruits | | 15 | | |
| Crabapples | | 25 | | |
| Currants | | 25 | | |
| Dewberries | | 25 | | |
| Garlic | | 15 | | |
| Gooseberries | | 25 | | |
| Huckleberries | | 25 | | |
| Leeks | | 25 | | |
| Loganberries | | 25 | | |
| Pumpkins | | 15 | | |
| Raspberries | | 25 | | |
| Squash | | 15 | | |
| Potato | | | | 0.1 |

| Summary of US and International Tolerances and Maximum Residue Limits | | | |
|---|---|---|---|
| *Residue Definition*: | | | |
| US | Canada | Mexico[2] | Codex[3] |
| Completed: M. Negussie; 07/02/2012 | | | |

[1]No U.S. registrations. These tolerances are for import only.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.
Note: The Committee noted concerns regarding the residue definition and requested the Delegation of the EC to further specify its concerns regarding the use of variability factors and intake concerns and make it available for the next CCPR session (37-96).

(c) *Tolerances with regional registrations.* Tolerances with regional registrations as defined in §180.1(l) are established for the fungicide folpet ( *N* -(trichloromethylthio)phthalimide) in or on the following raw agricultural commodity:

| | Parts per million | |
|---|---|---|
| **Commodity** | **US** | **Canada** |
| Avocado | 25.0 | 25 |