

3. *Magnitude of residues.* Five residue trials have been conducted in Bavaria, Germany during 1996 and 1997. The hops were treated up to 8 times per season at a rate of up to 4.3 kg active ingredients/hectare (a.i./ha) (up to 23 kg a.i./ha per season), considering a 14 day PHI. After kiln drying, the measured residues in hops ranged from 25 to 65 ppm. Folpet was not detectable in any of the processed hop commodities (LOD for spent hops = 0.01 ppm; beer = 0.003 ppm). The generated data support the requested tolerance.

B. Toxicological Profile

1. *Acute toxicity.* In studies using laboratory animals, in general folpet has been shown to be of low acute toxicity: The acute oral LD₅₀ and the acute dermal LD₅₀ in rats were greater than 5,000 mg/kg. The acute rat inhalation LC₅₀ (4-hour) was 0.48 mg/l. Folpet was irritating to the eyes of rabbits. It was not irritating to rabbit skin in a standard dermal irritation study but was a dermal sensitizer in a guinea pig maximization study. Based on these results, folpet is expected to be classified as TOXICITY CATEGORY IV for acute oral and dermal toxicity, and skin irritation, and as TOXICITY CATEGORY II for acute inhalation toxicity, and eye irritation.

2. *Genotoxicity.* Folpet was tested for genotoxic effects in several standard tests. Folpet is neither mutagenic nor genotoxic in mammals. In some of the *in vitro* studies mutagenic events were observed, such as gene mutations/DNA damage in bacteria and mammalian cells, chromosomal aberrations in mammalian cells and mitotic recombination in yeast. However, folpet does not present a genotoxic risk based on the fact that folpet degrades with a half-life of 0.97 seconds *in vivo*. This fast detoxification effectively eliminates systemic exposure to folpet or thiophosgene.

3. *Reproductive and developmental toxicity.* In an oral developmental study with New Zealand rabbits, the maternal and developmental no observed adverse effect level (NOAEL) was 10 mg/kg/day based on decreased food consumption, increased number of fetuses and litters with hydrocephalus and associated skull malformations at the lowest observed adverse effect level (LOAEL) of 20 mg/kg/day. In the rat developmental study the developmental no observed effect level (NOEL) was 60 mg/kg and the lowest observed effect level (LOEL) was 360 mg/kg.

A two-generation reproductive study in rats produced a parental NOEL of 34.5 mg/kg/day. There was a marginal decrease in the body weight of the F₁ offspring at birth and during lactation

but no other changes in physical, functional, or behavioral endpoints were observed. The NOEL in the F₂ of 40 mg/kg/day was based on decreased body weight gain and decreased fertility of the males. The LOEL in this study was 180 mg/kg.

For both developmental and reproductive bioassays, the effects elicited by folpet are considered secondary to its primary effect: irritancy of the gastrointestinal tract. Folpet is absent in the systemic circulation and its initial ring degradate, phthalimide, has been shown not to be a developmental toxin.

4. *Subchronic toxicity.* In a 90-day feeding study in rats, the NOEL was established at 3,000 ppm and the LOEL was 10,000 ppm. Noted effects were decreased brain weight and decreased total blood protein including albumin.

In a subchronic dermal toxicity study, folpet was applied to rats at dose levels of 0, 1, 10, and 30 mg/kg body weight for 6 hours per day, 5 days a week, for a total of 21 days over a period of 30 days. All folpet treated rats developed pronounced dermal irritation in a dose-related manner. Systemic toxicity based on decreased body weight gain was observed at 10 and 30 mg/kg dose levels, but without clearly separating this effect to the severe skin damage.

5. *Chronic toxicity.* A 2-year feeding chronic toxicity/carcinogenicity study in rats was conducted with folpet at dietary concentrations of 0, 200, 800, or 3,200 ppm. For chronic toxicity, the NOAEL was 200 ppm (9 mg/kg/day) and the LOAEL was 800 ppm (35 mg/kg) based on hyperkeratosis/acanthosis and ulceration/erosion of the non-glandular stomach in males and females. No evidence of carcinogenicity was observed in this study.

A 2-year feeding chronic toxicity/carcinogenicity study in CD-1 mice showed a statistically significant, dose-related increase in the incidence of duodenal adenocarcinomas with an increase of about 50% at the highest dose tested (1,429 mg/kg/day). A similar response was seen in a chronic feeding study with B6C3F1 mice at the highest dose tested (HDT) of 1,000 mg/kg.

In previous assessments, the Agency has concluded that folpet is a Group B2 carcinogen, based on the increased incidences of duodenal adenomas and carcinomas in males and females of two strains of mice.

6. *Animal metabolism.* Results from the livestock and rat metabolism studies showed that orally administered folpet was rapidly absorbed, hydrolyzed and metabolized, followed by rapid elimination, predominantly via the urine. The major fecal degradate was

phthalamic acid, while phthalic acid was a minor degradate. Most of the applied dose was excreted within 24 hours.

7. *Metabolite toxicology.* There are no folpet metabolites identified in plant or animal commodities, which require regulation.

8. *Endocrine disruption.* The standard battery of required toxicity studies has been completed. These studies include an evaluation of the potential effects on reproduction and development and an evaluation of the pathology of the endocrine organs following repeated or long-term exposure. There is no evidence which suggests that folpet is an endocrine disrupter. The existing studies are generally considered to be sufficient to detect any endocrine effects.

C. Aggregate Exposure

1. *Dietary exposure.* Potential dietary exposures from food under the existing tolerances for domestic uses (avocados) and imported commodities (apples, cranberries, cucumbers, grapes, lettuce, melons, onions, strawberries, and tomatoes), were estimated using the Dietary Exposure Evaluation Model (DEEM) for acute and chronic exposure based on the U.S. Department of Agriculture's (USDA) 1989–1992 individual consumption data. Residue data were based on field trials and percent crop information along with processing factors from submitted studies. No data from USDA's Pesticide Data Program (PDP) were available for folpet.

i. *Food.* Acute dietary exposure was compared to the acute population adjusted dose (aPAD), which utilizes 25.3% for females (15–50 years) at the 99th percentile, the only population group of concern for the acute Reference Dose (aRfD = 0.03 mg/kg/day, using the NOAEL of 10 mg/kg from the rabbit study, and the FQPA safety factor of 3X).

The results of the chronic (non-cancer) dietary analysis indicate that the chronic Population Adjusted Dose (cPAD) was below 1% for the U.S. population and its most sensitive subgroups based on a cRfD of 0.09 mg/kg/day.

Concerning the dietary cancer risk, the Agency's calculated upper bound risk was 9.8×10^{-8} , based on a Q* of 0.00186 mg/kg/day⁻¹, using field trial data, processing factors and percent crop treated information. This risk level is far less than EPA's level of concern of 1×10^{-6} .

Based on USDA's consumption data not more than 0.0022% of the U.S. population diet is constituted of hops