

10 mg/kg/day and the LOAEL was 20 mg/kg/day, based upon an increase in the number of fetuses and litters with hydrocephaly and related skull malformations. Although the developmental malformations (hydrocephaly) and associated maternal toxicity occur at similar doses, such effects are toxic manifestations as a result of exposure.

In order to determine the critical period of treatment for the occurrence of hydrocephaly and other treatment-related fetal anomalies observed in the above study, another developmental toxicity study was conducted with the same strain of rabbit with the highest dose group (60 mg/kg/day) receiving folpet on gestation days 7-9, 10-12, 13-15, or 16-18. The incidence of hydrocephalus was higher than historical or concurrent controls, but lower than in the previous study. The maternal toxicity noted was a dose-related decreased food consumption and variable decrease in body weight gain. Significantly increased incidence of irregularly-shaped fontanelles and slightly increased incidences of angulated hyoid alae were noted in the 60 mg/kg/day dose group.

In a second rabbit developmental toxicity study, HY/CR strain rabbits received folpet on gestation days 7 through 19. For maternal toxicity, the NOAEL was 40 mg/kg/day and the LOAEL was 160 mg/kg/day, based on decreased body weights and food consumption as well as clinical signs. For developmental toxicity, the NOAEL was 10 mg/kg/day and the LOAEL was 40 mg/kg/day, based on delayed ossification of the sternebrae. There was no evidence of hydrocephaly observed in this study at dose levels greater than in the previous study.

In addition, the Agency examined the available studies for captan, the structural analog of folpet, and determined that there was no indication of increased susceptibility of rabbits or hamsters to pre- or post-natal exposure to captan. In prenatal developmental toxicity studies in rabbits and hamsters and reproduction studies in the rat, all conducted using captan as the test material, toxicity to the offspring occurred at equivalent or higher doses than maternal toxicity.

3. *Conclusion.* i. There is a complete toxicity data base for folpet and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. The Agency has determined that the FQPA Safety Factor can be reduced to 1X based upon the following weight-of-the-evidence considerations:

a. There was no evidence of quantitative or qualitative susceptibility in two developmental toxicity studies in the rat;

b. There was no evidence of enhanced susceptibility to the pups in two different 2-generation reproduction studies in the rat;

c. Folpet is not a cholinesterase inhibitor and, therefore, comments made at the June 26-27, 2002 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) meeting on the Determination of the Appropriate FQPA Safety Factor(s) in the Organophosphorous Pesticide Cumulative Risk Assessment: Susceptibility and Sensitivity to the Common Mechanism, Acetylcholinesterase Inhibition should not influence this uncertainty factor decision.

d. There is inconsistency between the two available developmental toxicity studies in the rabbit. When tested at lower doses, there is a concern for hydrocephaly. However, when this study was repeated in the same strain of rabbit at higher dose levels, no evidence of hydrocephaly was observed. Nevertheless, for purposes of risk assessment, the Agency has selected the developmental NOAEL of 10 mg/kg/day from the rabbit developmental study in which hydrocephaly was observed as the endpoint for evaluating acute risk.

e. Other than the one rabbit developmental toxicity study, there are no other signs from the available toxicology database of a concern for neurotoxic effects.

f. Furthermore, the Agency's exposure assumptions are conservative. The assessment assumes that all hops consumed in the United States are treated with folpet. In addition, the analysis presumes that all avocados grown in Florida are treated with this fungicide. The percent crop treated data for the imported commodities assumed that all crop exported to the U.S. from countries in which folpet is registered are treated with this chemical. Therefore, a figure of 1% crop treated was assumed for the following commodities: Apple, cranberry, cucumber, grape, lettuce, melon, onion, strawberry, and tomato.

ii. The Agency has also determined that a developmental neurotoxicity study for folpet is not warranted based upon the following considerations:

a. Although hydrocephalus was observed in one developmental toxicity study in the rabbit, it occurred at maternally toxic doses and was only seen in one species;

b. No alterations to the fetal nervous system were seen in the developmental

rat studies at the same doses that induce hydrocephaly in rabbits;

c. Although there are no acute or subchronic neurotoxicity studies available, there is no evidence of neurotoxicity or neuropathology in adult animals in any of the studies;

d. The available data indicate that the developmental neurotoxicity 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 2-generation reproduction study (NOAEL of 168 mg/kg/day), it is anticipated that in order to elicit any fetal nervous system abnormalities in the developmental neurotoxicity study, the selected dose levels would have to be higher than 160 mg/kg/day.

e. Since the dose level selections for the developmental neurotoxicity 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 and risk assessments is 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 developmental neurotoxicity study would change the current doses used for overall risk assessments.

E. Aggregate Risks and Determination of Safety

To estimate total aggregate exposure to a pesticide from food, drinking water, and residential uses, the Agency calculates DWLOCs which are used as a point of comparison against the model estimates of a pesticide's concentration in water (EECs). DWLOC values are not regulatory standards for drinking water. DWLOCs are theoretical upper limits on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food and residential uses. In calculating a DWLOC, the Agency determines how much of the acceptable exposure (i.e., the PAD) is available for exposure through drinking water [e.g., allowable chronic water exposure (mg/kg/day) = cPAD - (average food + residential exposure)]. This allowable exposure through drinking water is used to calculate a DWLOC.

A DWLOC will vary depending on the toxic endpoint, drinking water consumption, and body weights. Default body weights and consumption values