

level that poses no appreciable risk to humans.

2. *Prenatal and postnatal sensitivity.* There is an indication of increased susceptibility (qualitative and quantitative) of rats and rabbits to *in utero* exposure to cymoxanil. In the rat developmental toxicity study, decreased fetal body weights and skeletal malformations were observed at 25 mg/kg/day LOAEL, which is below the maternal toxicity of 75 mg/kg/day LOAEL. In the rabbit developmental study increased skeletal malformations were observed at 8 mg/kg/day LOAEL, also below the maternal NOAEL of 32 mg/kg/day. In the 2-generation reproduction study there was an indication of increased qualitative susceptibility in the offspring, since there was decreased pup viability at a maternally toxic dose.

3. *Conclusion.* There is a complete toxicity data base for cymoxanil and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. EPA determined that the 10X SF to protect infants and children should be reduced to 1X. The FQPA factor is reduced to 1X because in the developmental and postnatal studies (including a developmental neurotoxicity study in rats) the effects are well characterized and conservative NOAELs were established for all developmental and offspring effects. In addition, the doses selected for risk assessment are lower than the NOAELs from these studies and are protective of any potential prenatal and post-natal effects. Therefore, there are low levels of concern and no residual uncertainties for prenatal and postnatal toxicity.

In response to the notice of filing of July 6, 2001, WWF urged EPA to apply the full 10X FQPA safety factor to cymoxanil. According to WWF the data for cymoxanil is inadequate to address potential endocrine disruption and there is evidence of increased susceptibility in the prenatal developmental rabbit study. WWF claimed the multigeneration reproduction study in rats is inadequate because it was conducted before the 1996 guideline changes which added additional endpoints responsive to estrogenic and/or androgenic endocrine disruption. In addition, WWF noted that inferences about endocrine disruption based on current guidelines are still not fully adequate to evaluate endocrine disruption. In particular, the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) recommended the inclusion of more endpoints relevant to thyroid disruption and measurement of estradiol, testosterone,

luteinizing hormone, follicle stimulating hormone, T4 and thyroid stimulating hormone levels in multigeneration studies. WWF further argued for the inclusion of certain adrenal hormones such as ACTH and corticosterone (the primary glucocorticoid in rodents) to fully address the endocrine disruption issue. In addition, WWF believes that there is an increased developmental susceptibility to rabbits fetuses. WWF questioned the conclusions reached by the Office of Pesticide Programs' Hazard Identification Assessment Review Committee (HIARC) Jan 20, 1998 that there is no sensitivity in fetuses compared to maternal animals. Developmental malformations were observed at 8 mg/kg/day, which is below the maternal NOAEL of 16 mg/kg/day. These results were discounted due to uncertainties regarding the source of the parental rabbits. In another rabbit study, developmental malformations were observed at the same dose (8 mg/kg/day) as in the previous study, however, HIARC did not consider this to show increased susceptibility because the effects were observed at 8 mg/kg/day, which is also a maternal toxic dose.

On June 18, 2002, HIARC reviewed the WWF comments and concluded that possible endocrine-related effects on testicular and/or epididymal tissues are fully characterized and well defined in mouse, subchronic and chronic rat and dog studies with clear NOAELs. Further, in the reproduction toxicity study in rats, testicular effects were seen, however, these effects did not affect any measured reproductive parameters, indicating no adverse effects on reproduction. Additional measurements recommended by EDSTAC and WWF are unlikely to provide any significant additional information for cymoxanil since NOAELs are clearly defined for the testicular and/or epididymal effects and there are no indications of endocrine disruption in other organs e.g., thyroid (thyroid weight changes and hyperplasia), adrenal toxicity.

Prior to receipt of WWF letter, the HIARC on August 21, 2001, reevaluated the toxicology data base and modified certain study reviews resulting in the selection of new endpoints. The reevaluations resulted in the qualitative and quantitative evidence of increased susceptibility to rabbit fetuses (as suggested by WWF) and rat fetuses. In addition, reevaluation of rat reproduction toxicity study resulted in the qualitative increased susceptibility to offspring. A conservative NOAEL from the rabbit developmental study was used for establishing the aRfD. Nonetheless, it was concluded that

reliable data supported applying no additional safety factor since endpoints chosen for risk assessments adequately protect infants and children with regard to the prenatal and/or postnatal toxicity that has been identified.

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 as used by the USEPA Office of Water are used to calculate DWLOCs: 2 liter (L)/70 kg (adult male), 2L/60 kg (adult female), and 1L/10 kg (child). Default body weights and drinking water consumption values vary on an individual basis. This variation will be taken into account in more refined screening-level and quantitative drinking water exposure assessments. Different populations will have different DWLOCs. Generally, a DWLOC is calculated for each type of risk assessment used: Acute, short-term, intermediate-term, chronic, and cancer.

When EECs for surface water and ground water are less than the calculated DWLOCs, OPP concludes with reasonable certainty that exposures to the pesticide in drinking water (when considered along with other sources of exposure for which EPA has reliable data) would not result in unacceptable levels of aggregate human health risk at this time. Because EPA considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, EPA will reassess the potential impacts of residues of the pesticide in drinking water as a part of the aggregate risk assessment process.