

3. *Reproductive and developmental toxicity.* The results of a series of studies indicated that there were no reproductive, developmental, or teratogenic hazards associated with cymoxanil.

In a 2-generation cymoxanil rat reproduction study, the no observed effect level (NOEL) for both parents and offspring was approximately 7 milligrams/kilogram/day (mg/kg/day), based on decreased body weight, weight gain and food consumption in adults and decreased pup weight in offspring at 32 mg/kg/day. There were no reproductive or fertility effects. Since offspring effects occurred only in the presence of maternal toxicity, it is considered a secondary effect to the health effects on the dam.

With cymoxanil, developmental studies conducted in rats demonstrated a NOEL of 10 mg/kg/day and a lowest observed effect level (LOEL) of 25 mg/kg/day for both adult and developmental effects. Maternal effects in rats included decreased weight, weight gain, and food consumption. Developmental effects were increases in fetal variations, which were the result of generalized delays in ossification, and overall malformations, although malformations detected were not dose-related. In rabbits, several developmental toxicity studies were conducted with cymoxanil. Based on the weight-of-evidence of all three studies, EPA considered there was no unique sensitivity of perinatal animals to the effects of cymoxanil, nor any anomalies of the fetal nervous system at maternally toxic doses up to and including 32 mg/kg/day (Cymoxanil Agency Risk Assessment, February 18, 1998).

4. *Subchronic toxicity.* Subchronic (90-day) feeding studies were conducted with rats, mice, and dogs. In addition, the following subchronic feeding studies were conducted: A 90-day in rats to evaluate neurotoxicity and 28-day feeding studies in rats and mice to evaluate immunotoxicity. A 28-day dermal study was conducted in rats.

In a subchronic toxicity/neurotoxicity study in rats with cymoxanil, the NOEL of 47.6 mg/kg/day in males was based on decreased body weights and minimal to mild testicular and epididymal effects at higher concentrations. In females, the NOEL of 59.9 mg/kg/day was based on effects on body weight, weight gain, and food efficiency at higher levels.

The subchronic NOEL for male mice administered cymoxanil was 8.25 mg/kg/day based on body weight and weight gain effects at 82.4 mg/kg/day and above. The NOEL for females was 121 mg/kg/day based on increases in

spleen and liver weights at 433 mg/kg/day and above.

For cymoxanil, dogs were the most sensitive species in subchronic studies. Reduced body weight gain and/or food consumption was observed at 3 mg/kg/day or greater in females and 5 mg/kg/day and above in males. Both sexes had red blood cells (RBC) changes decreased RBC counts, hemoglobin (Hb), and/or hematocrit (Hct) and increased incidence of ketonuria at the intermediate and high concentration, and changes in serum chemistry (decreases in various electrolytes and proteins) at the high dose. Males had testicular and epididymal effects at the highest concentration, 11 mg/kg/day (raised from 5 mg/kg/day at week 3); this was considered to be retardation of development due to markedly reduced body weight in this group. The NOEL for males was 3 mg/kg/day. There was no NOEL in female dogs in the 90-day study. Although, a NOEL was not established in the dog subchronic study, 3 mg/kg/day was found to be a NOEL in a subsequent chronic study in dogs.

Subchronic 28-day studies were conducted in rats and mice to evaluate the immunotoxicity potential of cymoxanil. Cymoxanil was not immunotoxic up to and including the highest dose tested which was 1,600 ppm in rats (108 and 117 mg/kg/day in males and females, respectively), 1,200 ppm (218 mg/kg/day) in male mice, and 2,400 ppm (552 mg/kg/day) in female mice.

Cymoxanil was applied to the skin of rats 6-hours/day for 28 days at doses of 0, 50, 500, and 1,000 mg/kg/day. There were no effects at any dose tested. The 28-day dermal NOEL was 1,000 mg/kg/day, the highest dose tested.

5. *Chronic toxicity.* Chronic studies with cymoxanil were conducted on rats, mice, and dogs to determine oncogenic potential and/or chronic toxicity of the compound. Effects generally similar to those observed in the 90-day studies were seen in the chronic studies. Cymoxanil was not oncogenic.

The chronic NOEL for cymoxanil in male rats was 4.08 mg/kg/day based on decreased body weight, weight gain, food efficiency, and non-neoplastic lesions in several organs including lung inflammation, spermatid degeneration, and retinal atrophy at 30.3 mg/kg/day or higher. In addition, male rats in the two highest groups displayed increased aggressiveness and hyperreactivity consistent with the compromised general health status (i.e. systemic toxicity) of those groups. In females, the NOEL of 5.36 mg/kg/day was based on decreased body weight, weight gain, food efficiency, and non-neoplastic

lesions in several organs including lungs, liver, intestines, mesenteric lymph nodes, sciatic nerve, and retina at 38.4 mg/kg/day or higher. Retinal atrophy and sciatic lesions are common spontaneous lesions associated with aging. These effects observed in cymoxanil test animals were considered aging-related effects. Spermatid degeneration occurs spontaneously in rats. While the incidence was increased in cymoxanil-treated rats, most were mild or minimal and none were more than moderate. Thus, the effects are considered a mild exacerbation of a spontaneously occurring lesion.

In mice, the chronic NOELs for cymoxanil were 4.19 and 5.83 mg/kg/day for males and females, respectively, based on changes in organ weights, gastrointestinal effects in females and liver, testes and epididymal effects in males at the LOEL. Similar to the rat, the testicular effects were considered an exacerbation of a spontaneous lesion, that occurred in one-quarter of the control mice. The LOELs were 42.0 and 58.1 mg/kg/day for males and females, respectively.

The chronic cymoxanil NOEL for male dogs was 3.0 mg/kg/day based on a temporary decrease in body weight and food consumption, and lower RBC count, hemoglobin, and hematocrit at 5.7 mg/kg/day. In female dogs the only finding was a transient effect on body weight, food consumption, and food efficiency at the highest dose tested, 3.1 mg/kg/day, only during the first week of the study. EPA considered the NOEL in females to be 3.1 mg/kg (Cymoxanil Agency Risk Assessment, February 18, 1998).

6. *Animal metabolism.* When administered by gavage to rats, cymoxanil was readily absorbed and eliminated. Absorption reached maximum concentrations in whole blood within 4 hours post-dosing. A rapid and almost complete elimination was observed in the urine and feces. The majority of radioactivity was recovered within 96 hours, mainly in urine but also in feces. Radioactivity in the tissues and carcass was less than 1%. In the urine and feces, the majority of the radioactivity was free and/or conjugated glycine. 2-Cyano-2-methoxyimino-acetic acid was also found in low levels in the urine and trace levels in the feces. Intact cymoxanil was less than 1% in feces and not detected in the urine. The metabolite profile in urine and feces was similar between sexes, among dose groups, and between dosing regimens (single vs. multiple).