

TABLE 1.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY—Continued

Guideline No.	Study Type	Results
870.6300	Developmental neurotoxicity (rat)	Maternal toxicity NOAEL = 50 mg/kg/day Maternal toxicity LOAEL = 100 mg/kg/day, based on slight decrease body weight, body weight gains (17%) and food consumption. Offspring NOAEL = 50 mg/kg/day Offspring LOAEL = 100 mg/kg/day, based on decreased pup survival, decreased pup weight and body weight gain during early lactation (less than 6%), increases in morphometric measurements (anterior/posterior cerebrum for males, cerebellar height for females) at PND 79–83, and decreased retention in the water maze task for adult females (latency 158% of control levels) seen at the LOAEL of 100 mg/kg/day.
870.7485	Metabolism and pharmacokinetics (rat)	Cymoxanil was readily absorbed and 86 to 94% of the administered dose was excreted in 96 hours. The majority of the administered dose was recovered in the urine (64 - 57%) with smaller amounts excreted in the feces (16 - 24%) and carcass (<1%). There were no sex-related differences in the absorption, distribution and metabolism of cymoxanil. In urine about 37 - 55% of the dose was free and/or conjugated [¹⁴ C]glycine and 2 cyano-2-methoxyiminoacetic acid (IN-W3595; about 7 to 33% of the dose). Intact cymoxanil was not isolated in urine. In feces intact ¹⁴ C cymoxanil (<1%) and IN W3595 was detected, but the majority of radioactivity was ¹⁴ C glycine (about 9 - 13%). Based on the data, the metabolic pathway involves hydrolysis of cymoxanil to IN W3595, which is then degraded to glycine, which in turn is incorporated into natural constituents or further metabolized.

B. Toxicological Endpoints

The dose at which the NOAEL from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern. However, the LOAEL is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intra species differences.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (aRfD or cRfD) where the RfD is equal to the NOAEL divided by the appropriate UF (RfD = NOAEL/UF).

Where an additional safety factors is retained due to concerns unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic population adjusted dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA SF.

For non-dietary risk assessments (other than cancer) the UF is used to determine the level of concern. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) = NOAEL/exposure) is calculated and compared to the level of concern.

The linear default risk methodology (Q*) is the primary method currently used by the Agency to quantify carcinogenic risk. The Q* approach assumes that any amount of exposure

will lead to some degree of cancer risk. A Q* is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (e.g., risk is expressed as 1×10^{-6} or one in a million). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a “point of departure” is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure ($MOE_{cancer} = \text{point of departure/exposures}$) is calculated. A summary of the toxicological endpoints for cymoxanil used for human risk assessment is shown in the following Table 2.

TABLE 2.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR CYMOXANIL FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute dietary (females 13–50 years of age)	NOAEL = 4 mg/kg/day UF = 100 aRfD = 0.04 mg/kg/day	FQPA SF = 1X aPAD = aRfD FQPA SF = 0.04 mg/kg/day	Developmental toxicity study - rabbit Developmental LOAEL = 8 mg/kg/day based on increased skeletal anomalies of the cervical and thoracic vertebrae (hemivertebrae) and ribs; at 32 mg/kg/day, cleft palate was also observed.