

TABLE 1B.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY FOR S-METOLACHLOR (PC CODE 108800)—Continued

Guideline No.	Study Type	Results
870.5100	Gene Mutation Test	There was no indication that S-metolachlor technical induced a mutagenic effect in any tester strain either in the presence or the absence of S9 activation.
870.5395	Cytogenetics Micronucleus test	There was no evidence that S-metolachlor technical induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.
870.5550	Other Effects Unscheduled DNA synthesis	S-metolachlor technical was negative for genotoxicity but positive for cellular proliferation when tested up to overtly toxic and cytotoxic doses in this <i>in vivo/in vitro</i> rat hepatocyte RDS/UDS assay.
870.7485	Metabolism and pharmacokinetics	S-metolachlor has a high affinity for and a long half-life in blood (especially RBC) which might contribute to the retarded depletion of tissue residues.
870.7485	Metabolism and pharmacokinetics Unacceptable	The 72 hour mean recovery of radioactivity in urine, feces, and carcass following administration of 0.5 mg/kg of Phenyl-U- ¹⁴ C CGA-24705 was 43.1%, 47.0%, and 7.4% in males and 54.0%, 39.4%, and 4.1% in females, respectively. In contrast, both sexes excreted more of the label in the feces (M:F 59.7%:53.4%) than in the urine (M:F 29.4%:39.8%) during the same period following administration of the same dose of Phenyl-U- ¹⁴ C CGA-77102 (the S-enantiomer) (MRID 44491401).

B. Toxicological Endpoints

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the lowest dose at which adverse effects of concern are identified (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 factor (SF) 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 LOC. 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 LOC.

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 ($MOE_{cancer} = \text{point of departure} / \text{exposures}$) is calculated. EPA's Health Effects Division's Cancer Assessment Review Committee has classified metolachlor as a Group C carcinogen with risk quantitated using a non-linear approach. The NOAEL of 15 mg/kg/day from the rat combined chronic toxicity/carcinogenicity study is based on neoplastic nodules/hepatocellular carcinomas seen at the highest dose tested of 150 mg/kg/day. The Agency notes that the tumor NOAEL of 15 mg/kg/day is comparable to the NOAEL of 9.7 mg/kg/day selected for establishing the chronic reference dose for metolachlor. It is assumed that the chronic dietary PAD is protective for cancer dietary risk. Therefore, a separate cancer aggregate risk assessment was not conducted, and cancer DWLOC values were not calculated. A summary of the toxicological endpoints for S-Metolachlor used for human risk assessment is shown in Table 2 of this unit: