

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

Guideline No.	Study Type	Results
870.6200	Dietary Neurotoxicity-CF-1 Mice L-660,599 Supplementary Study	Neurotoxicity NOAEL <0.1 mg/kg/day. One of the low-dose males had tremors, hunched posture and piloerection on day 14.
870.6300	Developmental Neurotoxicity-Rat MK-0244	Maternal Toxicity NOAEL=3.6/2.5 mg/kg/day (highest dose tested). Developmental Neurotoxicity NOAEL=0.10 mg/kg/day (lowest dose tested). The LOAEL is 0.60 mg/kg/day based on the dose-related decrease in open field motor activity in females at postnatal day 17.
870.7485	Metabolism-Rat MAB _{1a}	Radiolabeled MAB _{1a} benzoate is rapidly absorbed, distributed and excreted following oral and i.v. administration. The feces was the major route of excretion in oral and i.v. groups, while <1% of the administered dose was recovered in the urine 7 days post dosing. Tissue distribution and bioaccumulation appeared minimal. The metabolism of MAB _{1a} benzoate appears to involve primarily <i>N</i> -demethylation to AB _{1a} . AB _{1a} was the only metabolite detected in the feces while unmetabolized parent compound represented a large amount of the radioactivity.
870.7485	Bioequivalence-Dog MK-0243 solvate/ monohydrate	The study demonstrated that MK-0243 benzoate MTBE solvate and MK-0243 benzoate monohydrate were bioequivalent in male dogs following oral administration as indicated by similar plasma levels for the two compounds.
870.7485	Bioequivalence-Dog MK-0243 benzoate/HCL salts	The study demonstrated that benzoate and HCl salts are bioequivalent after oral administration in male beagle dogs.
870.7600	Dermal Absorption-Rhesus Monkey MAB _{1a} , MK-244	Dermal Absorption was approximated at 1.79% of the administered dose.

Key: MK-0243 = hydrochloride (adduct) or salt of emamectin; MK-0244 = benzoic acid (adduct) or salt of emamectin.

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 intraspecies differences.

As explained below in Unit III.D.3, EPA determined that the special FQPA SF be reduced to 1x. However, EPA also determined that an additional 3x Modifying Uncertainty Factor (UF_M) is required for application of the endpoint (based on the 15-day mouse neurotoxicity study) to acute- and short-term scenarios, to account for the steepness of the dose-response curve

and the severity of effects at the LOAEL (death and neuropathology). A 3x UF_M was judged to be adequate (as opposed to a 10X) because: (1) A NOAEL was established in this study; (2) although the effects of concern are seen after repeated dosing, the NOAEL here is used for a single exposure risk assessment; and (3) the most sensitive endpoint in the most sensitive species is selected. For intermediate- and chronic/long-term scenarios, EPA determined that a 10x UF_M is required to account for steepness of the dose-response curve, severity of effects at the LOAEL (death and neuropathology), and the use of a short-term study for long-term risk assessment.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) 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 x 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