

TABLE 2.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY—Continued

| Guideline number | Study Type | Results |
|------------------|---------------------------------------|--|
| 870.7485 | Metabolism and pharmacokinetics (rat) | Overall recovery of administered radioactivity exceeded 95%, most (74–93%) of which was eliminated in the feces. Approximately 4–15% of the administered radioactivity was excreted in the urine over 168 hours while tissue residues were negligible, thereby implying limited absorption. No radioactivity was detected in expired air. Excretion of radioactivity was >90% complete by 48 hours. Up to six components were detected in the urine of rats from both dose groups, the most prevalent being an hydrolysis product, CGA-293731 which represented >90% of urinary radioactivity. Urinary elimination of metabolites was quantitatively greater in female rats than in males. Only minor amounts (near detection limits) of parent compound were detected in the urine of high-dose males. Based upon biliary elimination, ~74–79% of the dose entered the hepatobiliary pathway but was eliminated via the feces. An increase in parent compound in feces of the high-dose group was indicative of saturated absorption and/or saturated metabolism, but could not be definitively resolved due to the absence of biliary elimination studies at the high dose. Biliary elimination studies revealed that approximately 60–64% of the administered low dose was detected in 0–4 hour pooled bile samples and that the majority of fecal radioactivity could be attributed to biliary metabolites |
| 870.7485 | Mechanistic studies | Effects on enzymes of cultured mouse, rat, and/or human hepatocytes involved with heme biosynthesis |
| 870.7485 | Mechanistic studies | Effects on liver microsomal and plasma protox activity and its metabolic conversion |
| 870.7485 | Mechanistic studies | Effects on porphyrin profile in rats; treatment induced porphyria, consisting of accumulation of selected porphyrins in the liver, spleen, and plasma and increased excretion in urine and feces |
| 870.7485 | Mechanistic studies | Test substance interferes with heme biosynthesis in rats, as evidenced by dose-dependent, pronounced porphyria in the liver, spleen, and plasma; increased porphyrin excretion, and decreased activity of various isoenzymes of the hepatic microsomal cytochrome P450 system |
| 870.7485 | Mechanistic studies | Test substance interferes with heme biosynthesis in mice, as evidenced by dose-dependent, pronounced porphyria in the liver, spleen, and plasma; increased porphyrin excretion, and decreased activity of various isoenzymes of the hepatic microsomal cytochrome P450 system |
| 870.7485 | Mechanistic studies | Effects on porphyrin profile in mice; treatment induced porphyria, consisting of accumulation of selected porphyrins in the tissue and plasma, and increased excretion of heme precursors |

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 margin of exposure (MOE). 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. A UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences.

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 factors (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 level of concern (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) = $NOAEL / \text{exposure}$) is calculated and compared to the LOC.

A summary of the toxicological endpoints for butafenacil used for human risk assessment is shown in Table 3 of this unit: