

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

| Guideline No. | Study Type | Results |
|---------------|---|---|
| 870.5500 | <i>In vitro</i> unscheduled DNA synthesis (primary rat hepatocytes) | Negative response up to 50 µg/mL. Cytotoxicity at 100 - 500 µg/mL. |
| 870.6200 | Acute neurotoxicity screening battery (rat) | NOAEL = 2,000/1,000 mg/kg/day (M/F) LOAEL = >2,000/2,000 mg/kg/day (M/F) based on F = piloerection |
| 870.6200 | Subchronic neurotoxicity screening battery (rat) | NOAEL = 1050.0/1272.5 mg/kg/day (M/F) LOAEL = >1050.0/1272.5 mg/kg/day (M/F) |
| 870.6300 | Developmental neurotoxicity (rat) | Maternal NOAEL = 1,442 mg/kg/day LOAEL = >1,442 mg/kg/day Offspring NOAEL = 14 mg/kg/day LOAEL = 147 mg/kg/day based on decreased body weights on PND 4 and decreased body weight gain on PNDs 1-4) |
| 870.7485 | Metabolism and pharmacokinetics (rat) | BAS 510 was readily absorbed and excreted following single oral 50 mg/kg; at single 500 mg/kg or 15 doses of 500 mg/kg, absorption was saturated. Excretion mainly by feces (80-98%). Biliary excretion 40-50% of fecal activity at 50 mg/kg, 10% at 500 mg/kg. Urine, about 16% at 50 mg/kg, 3-5% at 500 mg/kg. Absorption about 56% at 50 mg/kg and 13-17% at 500 mg/kg. Excretory patterns similar by gender or radiolabel position. Metabolites (hydroxylation and conjugation products) were consistent with Phase I oxidation reactions followed by Phase II conjugation with glucuronic acid or sulfate, or by conjugation of the parent with glutathione with cleavage to sulfate metabolites. |
| 870.7600 | Dermal penetration (rat) | Maximum % absorption: 0.01 mg/cm ² = 10.93 (24 hour exposure, 24 hour sacrifice) 0.10 mg/cm ² = 3.76 (24 hour exposure, 24 hour sacrifice) 1.00 mg/cm ² = 1.48 (10 hour exposure, 72 hour sacrifice)] |
| | Special studies: Hepatic enzyme induction (rat) | 1. Hypertrophy of zone III hepatocytes 2. >20% increase in liver weight 3. Increase in CYP450 activity 4. Slight to extensive microscopic SER proliferation 5. Not a peroxisome proliferator 6. Enzymes in CYP450 subfamily not induced 7. No notable microscopic increase in size or number of peroxisomes CONCLUSION: Inducer of total CYP450 activity |
| | Special Study: Hormone and enzyme induction (rat) | 1. Slight (statistically significant) decrease in circulating T ₃ and T ₄ only in males 2. Increase in circulating TSH levels both sexes 3. Increase in all 3 liver microsomal glucuronyltransferases CONCLUSION: disruption of thyroid homeostasis by decreasing circulation T ₃ and T ₄ and increasing TSH; likely the result of hepatic microsomal glucuronyltransferase induction |
| | Special Study: Reversibility study (dietary): 4-week administration followed by 4 weeks recovery or 13 weeks recovery (rat) | 4 weeks dosing: at 2500 and 15000 ppm: increase in TSH (68% and 87%) ; increase in absolute and relative thyroid weights hypertrophy of thyroid follicular epithelial cells and diffuse follicular hyperplasia, increase in absolute and relative liver weights and centrilobular hypertrophy as well as liver portal fatty changes. 4 weeks dosing + 4 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. 4 weeks dosing + 13 weeks recovery: no increases in TSH; increase in absolute and relative thyroid weights; thyroid hypertrophy and hyperplasia decreased to control values; all liver effects reversed to control. CONCLUSION: induction of liver microsomal enzyme system resulting in increased glucuronidation of thyroxine, resulting in an increase in TSH secretion as a compensatory response of the physiological negative feedback system; increased TSH resulted in increased thyroid weight. |

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 (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 (acute RfD or chronic RfD) where