

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

Guideline No.	Study Type	Results
870.4100	Chronic toxicity dogs	NOAEL = 1.29(m), 1.14(f) mg/kg/day LOAEL = 27.75 (m), 26.82(f) mg/kg/day based on increased alkaline phosphatase, kidney, and liver weight in both sexes, increased cholesterol in males, decreased T3, T4, and ALT values in both sexes, and increased incidences of microscopic lesions in the brain, eye, kidney, spinal cord, sciatic nerve, and liver.
870.4300	Chronic toxicity/ oncogenicity in rodents (rat)	NOAEL = 1.2 (m), 1.5 (f) mg/kg/day LOAEL = 19.3 (m), 24.4(f) mg/kg/day based on methemoglobinemia and multi-organ effects in blood, kidney, spleen, heart, brain, eye, liver and uterus. No evidence of carcinogenicity
870.4300	Carcinogenicity mice	NOAEL = <7.4 ((m), 9.4 (f) mg/kg/day LOAEL = 7.4 (m), 38.4 (f) mg/kg/day based on increased incidence and severity of cataracts. No evidence of carcinogenicity
870.5100 870.5395 870.5375	Gene Mutation Cytogenetics	Ames Assay <i>S. typhimurium</i> not mutagenic <i>In vivo</i> mammalian cytogenetics—micronucleus assay (mouse) not mutagenic. <i>In vitro</i> mammalian cytogenetics— Chinese hamster lung fibroblasts (V79) cells not mutagenic.
870.5375 870.5550	Other Effects	<i>In vitro</i> cytogenetics chromosomal analysis of cultured CHO cells—not mutagenic. Unscheduled DNA synthesis in rat hepatocytes <i>in vitro</i> —not mutagenic.
870.6200	Acute neurotoxicity screening battery	NOAEL = <75 (m and f) mg/kg/day LOAEL = 75 (m and f) mg/kg/day based on clinical signs in females (uncoordinated gait and decreased activity) and decreased motor activity in males.
870.6200	Subchronic neurotoxicity screening battery	NOAEL = 7.30 (m), 8.40 (f) mg/kg/day LOAEL = 38.1 (m), 42.6 (f) mg/kg/day based on microscopic lesions (including axonal swelling in brain and spinal cord).
870.6300	Developmental neurotoxicity	Maternal NOAEL = 40.8 mg/kg/day LOAEL = not determined (no adverse effects seen). Offspring NOAEL = <1.7 mg/kg/day LOAEL = 1.7 mg/kg/day based on decreased pre-weaning body weight and body weight gain.
870.7485	Metabolism and pharmacokinetics	Rapidly absorbed and metabolized following oral exposure to either single or multiple doses. The urine was the major route of excretion with small amount excreted via feces. Significant amounts of radiolabel were eliminated as CO ₂ and CH ₄ . A maximum of 7% of the total recovered radiolabel was found in the tissues and residual carcass. Twenty-five metabolites arising from the fluorophenyl portion of the molecule were detected in excreta, and 17 of these were identified. The total amount of radiolabel identified ranged from [Fluorophenyl-UL- ¹⁴ C] FOE 5043 67%-86%; [Thiadiazole-2- ¹⁴ C] FOE 5043 84%-92%; and [Thiadiazole-5- ¹⁴ C] FOE 5043 53%-69%. All unidentified residues in excreta were characterized.
n/a	Metabolism/Mechanism	Hypothesis of an extrathyroidal mechanism of action for FOE 5043 (flufenacet) Hypothesis of an extrathyroidal mechanism of action for FOE 5043-supplement to above.
n/a	Metabolism/Metabolite	Evaluated a hypothesis that the neurotoxicity observed in dogs dosed with high levels of FOE 5043 was caused by metabolic limitations.

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.

The Agency imposed an additional 10X safety factor to account for uncertainties arising because available data support the possibility of decreases in thyroid hormones at dose levels similar to those used in the submitted rat developmental neurotoxicity study (DNT) as well as the lack of a NOAEL

in the rat developmental neurotoxicity study. To address these concerns the Agency will require a special comparative assay on thyroid hormone levels in neonatal and adult rats as a condition of registration. The Agency also had a concern for a lack of a NOAEL in the rat developmental neurotoxicity study and for the decrease in morphometric measurements in adult females which were not measured at the lowest dose. The doses and endpoints for various risk assessments and the uncertainty factors applied are expected to adequately address uncertainties