

mice. A summary of results of chronic toxicity studies in rats, mice, and dogs indicates that the primary target organ from chronic exposure is liver, with effects on hematology parameters and body weight.

In a 12-month chronic oral toxicity study, dogs were fed capsules containing butafenacil that resulted in daily test substance intakes of 0, 20, 100, 500, or 1,000 mg/kg/day. The administration of butafenacil caused findings only at 500 and 1,000 mg/kg/day. These effects consisted of loss in the body weight of male animals at 1,000 mg/kg/day. Hematology parameters were slightly affected at 500 and 1,000 mg/kg/day. Based on body weight loss at 1,000 mg/kg/day, the increase in relative liver weight at 1,000 mg/kg/day and the hematological effects at 500 and 1,000 mg/kg/day, the maximum tolerance dose (MTD) was achieved at 1,000 mg/kg/day and the NOAEL for chronic toxicity in dogs is 100 mg/kg/day.

In an 18-month oncogenicity study, mice were fed diets containing butafenacil that resulted in average daily test substance intakes of 0, 0.12, 0.36, 1.18, 6.78 mg/kg/day. The treatment of mice with butafenacil for 18 months revealed effects on hematology parameters in males at 1.18 and 6.78 mg/kg/day, increased liver weights at 6.78 mg/kg/day in both sexes and histopathological findings indicating that the liver was the target organ of toxicity. The MTD was achieved at 6.78 mg/kg/day. Dose responsive non-neoplastic changes in the liver occurred at 1.18 mg/kg/day in males and at 6.78 mg/kg/day in both sexes. Butafenacil was not carcinogenic in this study. Based on the hematology and liver effects, the NOAEL for chronic toxicity in mice was established at 0.36 mg/kg/day in males and 1.20 mg/kg/day in females.

In a 2-year chronic toxicity and carcinogenicity study, rats were fed diets containing butafenacil that resulted in average (sexes combined) daily test substance intakes of 0, 0.42, 1.22, 4.10, or 12.2 mg/kg/day. Treatment had no effect on survival and there were no treatment-related clinical signs. There were no effects on food consumption and body weight. Hematology and clinical chemistry data were comparable in all groups. Necropsy revealed no changes in organ weights.

The treatment of rats with butafenacil for 24 months indicated the liver as the target organ, with non-neoplastic histopathological findings in the liver in both sexes at 4.10 and 12.2 mg/kg/day. Based on the liver effects, the MTD was

achieved at 12.2 mg/kg/day. No increased incidence of tumor formation was noted, indicating that butafenacil was not carcinogenic in this study. Based on the liver effects at 4.10 and 12.2 mg/kg/day, the NOAEL was established at 1.14 mg/kg/day (1.14 mg/kg/day in males and 1.30 mg/kg/day in females).

6. *Animal metabolism.* The major initial metabolic processes in rat involve the hydrolysis of the allyl ester to form the free carboxylic acid compounds. Parent compound was of significant abundance only in the feces from the high dose group. Subsequent metabolic routes involve reduction, hydroxylation, and opening of the uracil ring. The phenyl and uracil rings remain connected and all major metabolites have the unchanged phenyl structure.

7. *Metabolite toxicology.* Toxicity studies, including acute oral, mutagenicity, and 28-day feeding studies were conducted with major metabolites found in environmental studies. An acute oral and a mutagenicity test were conducted. The acute oral LD₅₀ was at least >2,000 mg/kg and all mutagenicity studies were negative. The 28-day feeding study was conducted with major metabolites at 0, 300, 2,000, and 10,000 ppm. The target organ was confirmed as the liver for all test materials. Based on the data from the studies and reasons cited, none of these metabolites is considered to be of toxicological concern.

8. *Endocrine disruption.* Butafenacil does not belong to a class of chemicals known or suspected of having adverse effects on the endocrine system. There is no evidence that butafenacil has any effect on endocrine function in development or reproductive studies. Furthermore, histological investigation of endocrine organs in chronic dog, mouse, and rat studies did not indicate that the endocrine system is targeted by butafenacil.

9. *Neurotoxicity.* In an acute neurotoxicity study in rats, butafenacil was administered orally by gavage at 0 or 2,000 mg/kg. All animals survived and body weight development and food consumption were not affected by treatment. There were no toxicologically relevant clinical signs nor changes in observations and functional tests conducted as part of the functional observational battery. No treatment-related effects on any of the different motor activity parameters were seen. Macroscopical and microscopical examination of the multiple areas of the central and peripheral nervous system, the eyes, optic nerves, and skeletal muscle of the male and female, control and treated animals did not reveal any

treatment-related neuropathic changes. In conclusion, butafenacil was devoid of any acute neurotoxicity when administered to rats at a single oral dose of 2,000 mg/kg. The NOAEL was greater than 2,000 mg/kg body weight.

C. Aggregate Exposure

1. *Dietary exposure.* Dietary exposure from butafenacil potentially exists through both food commodities and drinking water. Each exposure pathway is addressed below.

i. *Food.* Chronic and acute dietary exposure evaluations for butafenacil were performed using average field trial residues and assuming 100% crop treated. Cotton is the only raw agricultural commodity included in the assessment. All dietary exposure evaluations were made using the Dietary Exposure Evaluation Model (DEEM) and the USDA's Continuing Survey of Food Intake By Individuals (1994-96). Chronic exposure was compared to a chronic NOAEL of 100.0 mg/kg body weight/day (bwt/day) from a 1-year dog study. The acute NOAEL is 100 mg/kg in a rabbit teratology study based on maternal body weight loss and increased post-implantation loss. A 100X-uncertainty factor was assumed for both chronic and acute values. Both chronic and acute exposures were expressed as a percent of a reference dose of 1.0 mg/kg/day.

Secondary residues in animal commodities were calculated by constructing diets for beef and dairy cattle, poultry and swine in order to calculate anticipated residues in meat, fat, milk and pork. The beef cattle diet was used to calculate meat, fat and organ meats. The dairy cattle diet was used to estimate residues in milk. The swine diet was used for secondary residues in pork commodities and the poultry diet was used for residues in poultry commodities. Each diet was calculated using averaged field trial residues. Beef (cattle and dairy), and swine transfer factors were derived from a lactating goat 14C-metabolism study.

The results were favorable in both acute and chronic assessment scenarios. Acute and chronic exposure values were negligible (less than 0.01% of the acute and chronic reference dose of 1 mg/kg bwt/day).

The major contributors to chronic exposure (children 1-6 years old) were milk, accounting for 48% of the total exposure, cottonseed oil accounting for 28%, and meat (beef) products accounting for 25% of the total. In the U.S. population, the percentage contribution to the chronic exposure from meat (beef) products and milk were each 34% and cottonseed oil