

CPPU is low by all routes. The lowest subchronic study no observed effect level (NOEL) value is 16.8 milligrams/kilogram/day (mg/kg/day) obtained from the dog 90-day toxicity study. Chronic studies indicate that CPPU is not carcinogenic. The lowest chronic dietary NOEL is 7 mg/kg/day from male rats fed CPPU for 104 weeks. CPPU showed no evidence of developmental toxicity in rats and rabbits. In a rat reproduction study, reproductive effects were only observed at maternally toxic doses. Finally, genetic toxicity studies indicate that CPPU is not genotoxic. For the purposes of dietary risk analysis, 0.07 mg/kg/day is proposed for the chronic Population Adjusted Dose (cPAD). The cPAD is based on a chronic endpoint of 7 mg/kg/day which is the NOEL for males from the rat chronic/oncogenicity feeding study and an uncertainty factor of 100. No acute toxicity endpoint could be identified and therefore an acute dietary risk assessment is considered unnecessary.

1. *Acute toxicity.* The acute toxicity of CPPU is low by all routes. The battery of acute toxicity studies place CPPU into Toxicity Category III. CPPU has low acute toxicity when administered orally, dermally or via inhalation to rats. It is not a skin irritant and is only a mild eye irritant. CPPU is not a skin sensitizer.

2. *Genotoxicity.* The genotoxic potential of CPPU was studied *in vitro* in bacteria and mammalian cells and *in vivo* in the unscheduled DNA synthesis test. The test systems assayed did not show any evidence of genotoxicity except in the bacterial mutagenicity assay, strain TA1535, without metabolic activation. The weight of the evidence indicates that CPPU does not possess significant genotoxicity concerns.

3. *Reproductive and developmental toxicity.* Developmental effects of CPPU were studied in rats and rabbits and multigenerational effects on reproduction were studied in rats.

i. *Rat developmental.* In the developmental toxicity study conducted with rats, CPPU was administered by gavage at levels of 0, 100, 200 and 400 mg/kg/day. The maternal and developmental no observed adverse effect levels (NOAELs) are 200 mg/kg/day based on reduced body weights, body weight gain and food consumption and an increased incidence of alopecia in dams. There were no developmental effects.

ii. *Rabbit developmental.* In the rabbit developmental study, gavage doses of 0, 25, 50 and 100 mg/kg/day were administered. Maternal toxicity (decreased body weight and body weight gains) was observed at 50 mg/kg/day and above. The maternal NOAEL is

25 mg/kg/day and the developmental NOAEL is 100 mg/kg/day. There were no developmental effects.

iii. *Reproduction.* In the rat reproduction study, CPPU was administered in the diet at levels of 0, 150, 2,000, and 7,500 ppm for two generations. There were no adverse effects of CPPU on reproductive success. Parental toxicity consisted of clinical signs, inhibition of body weight gain, reduced food consumption, and macroscopic and microscopic effects in the kidney. Reproductive toxicity at the highest dose consisted of slightly reduced live litter sizes in the F₂ litters. In the pups, body weights and survival (late lactation period) were reduced and at the high dose, pup mortality and emaciation was increased. The parental, pup, and reproductive NOAELs are 150 ppm, 150 ppm, and 2,000 ppm, respectively.

4. *Subchronic toxicity.* Subchronic toxicity studies have been conducted with CPPU in the rat, mouse, and dog.

i. *Rats.* CPPU technical was tested in rats in a 3-month study at dietary levels of 0, 200, 1,000 and 5,000 ppm. Observations were decreased body weight, body weight gain and food efficiency. The NOAEL in males is 5,000 ppm (400 mg/kg/day) and in females is 1,000 ppm (84 mg/kg/day).

ii. *Mice.* A 13-week feeding study in mice was conducted at dose levels of 0, 900, 1,800, 3,500 and 7,000 ppm. Effects included decreased body weight and food consumption, increased relative liver weight and lymphocytic cell infiltration in the kidneys. The NOAEL is 3,500 ppm (609 mg/kg/day in males and 788 mg/kg/day in females).

iii. *Dogs.* A 13-week dietary toxicity study was conducted in beagle dogs at dose levels of 0, 50, 500 and 5,000 ppm. Effects included decreased body weight gain, food consumption and food efficiency. The NOAEL for both sexes was 500 ppm (16.8 mg/kg/day in males and 19.1 mg/kg/day in females).

5. *Chronic toxicity.* CPPU has been tested in chronic studies in dogs, rats, and mice.

i. *Rats.* In a 104-week chronic/oncogenicity study in rats, CPPU was administered at dose levels of 0, 150, 2,000 and 7,500 ppm in the diet. Findings were decreased body weight, body weight gain and food consumption, and organ weight and histopathological effects in the kidney. No oncogenicity was found. The NOAEL for this study is 150 ppm (7 mg/kg/day in males and 9 mg/kg/day in females).

ii. *Mice.* CPPU was administered in the diet to mice for 78-weeks at dose levels of 0, 10 and 1,000 mg/kg/day.

Observations were decreased body weight and body weight gain, food consumption, increased kidney weights and incidence of chronic kidney histopathological lesions. The NOAEL for both sexes is 10 mg/kg/day.

iii. *Dogs.* In a 12-month study, CPPU was administered in the diet to dogs at dose levels of 0, 150, 3,000 and 7,500 ppm. Observations included reduced body weight, body weight gain and food consumption and various hematology changes. The NOAEL for both sexes was 3,000 ppm (87 mg/kg/day in males and 91 mg/kg/day in females).

iv. *Carcinogenicity.* CPPU did not produce carcinogenicity in chronic studies with rats or mice. The oncogenicity classification of CPPU will be "E" (no evidence of carcinogenicity for humans).

6. *Animal metabolism.* A rat metabolism study indicates that CPPU is almost completely absorbed and most of the ¹⁴C-CPPU-derived radioactivity is rapidly eliminated primarily via the urine. The majority of the metabolism of CPPU was via hydroxylation of the phenyl ring. The sulfate conjugate of hydroxyl CPPU was the major metabolite excreted in the urine, accounting for as much as approximately 96% of the urinary radioactivity. Tissue residues accounted for less than 1% of the administered dose at 168 hours post-dosing.

7. *Metabolite toxicology.* Metabolites occur at levels below 0.1 ppm and therefore are below levels required to be assayed in animal testing.

8. *Endocrine disruption—Potential endocrine effects.* No special studies to investigate the potential for endocrine effects of CPPU have been performed. However, as summarized above, a large and detailed toxicology data base exists for the compound including studies in all required categories. These studies include acute, sub-chronic, chronic, developmental, and reproductive toxicology studies including detailed histology and histopathology of numerous tissues, including endocrine organs, following repeated or long-term exposures. These studies are considered capable of revealing endocrine effects. The results of all of these studies show no evidence of any endocrine-mediated effects and no pathology of the endocrine organs. Consequently, it is concluded that CPPU does not possess estrogenic or endocrine disrupting properties.

C. Aggregate Exposure

1. *Dietary exposure.* This dietary risk assessment was conducted by InfoScientific.com for KIM-C1, LLC. The dietary exposure assessment was