

initial exposure. There was no evidence of erythema in the intact skin at either time point. The abraded skin on one animal showed a slight erythematous reaction at 24 hours; at 72 hours, two abraded areas were graded very slight and one moderate. The intact skin of one animal showed very slight edematous reaction at 24 hours. The abraded areas had either a very slight or slight edematous reaction at both time points. Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was considered to be only a slight irritant.

vi. *Dermal sensitization.* The dermal sensitization potential of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was tested using the modified Maguire method. Ten male Hartley Albino guinea pigs received four induction doses of 0.1 milliliter (mL) of 10% solution of the cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride in 8 days. Freund's Adjuvant was injected intradermally adjacent to the site at the time of the third application. On challenge 2 weeks after the last induction application, the test material produced a positive response in one animal. The positive control, a 10% solution of DER 331 epoxy resin, confirmed that the test system was operating appropriately. The study demonstrated that a 0.1 mL dose of a 10% solution of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride is not a dermal sensitizer in guinea pigs.

2. *Genotoxicity.* Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was mutagenic in the *in vitro* Chinese hamster ovary (CHO) cell hypoxanthine guanine phosphoribosyl transferase (HGPRT) forward mutation assay with activation but nonmutagenic without activation. Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was negative in the rat hepatocyte unscheduled deoxyribonucleic acid (DNA) synthesis assay. It was negative also in the mouse micronucleus test.

3. *Reproductive and developmental toxicity.* A dermal developmental toxicity study was conducted with Fischer 344 rats. Doses of 0, 250, or 500 mg/kg/day of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride as a 50% aqueous solution were applied to the dorsal skin daily on gestation days 6 through 15. No significant adverse effects from treatment with the test compound were found but the study was considered adequate because the doses were sufficiently high.

4. *Subchronic toxicity—i. Dermal subchronic study.* In a 13-week dermal subchronic study, New Zealand white rabbits were given dermal applications of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride for 13 weeks. The doses were 0, 50, 200, or 1,000 mg/kg/day. The only treatment related effect was a dose-dependent increase in ulcerative dermatitis, at the treatment site, that was correlated with the abrasions from clipping. The NOAEL for systemic toxicity was 1,000 mg/kg/day.

ii. *A 90-day oral subchronic study.* One study was conducted to determine the level of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride in the diet which would result in complete acceptance of the diet by rats. Ten rats/sex/group were administered the chemical in the diet at dosages of 0, 1, 2, or 4 mg/kg/day for 90 days. The only parameters evaluated were body weight, food consumption, and organ weight (absolute and relative). Male rats in the 4 mg/kg/day group had a significant decrease in body weight at approximately 36% of the weighing periods. This group also had a significant decrease in food consumption throughout the study. The absolute weight of the heart in the 4 mg/kg/day group males was significantly decreased. The relative weight of the brain and liver were increased in the 4 mg/kg/day group of females.

iii. *A 90-day oral subchronic study.* In another study, cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was administered in the diet to groups of 10 rats/sex/group at dosages of 0, 7.5, 15, 30, and 60 mg/kg/day for 90 days. Mean body weight was significantly decreased in all the treated males and females throughout the study. Overall mean body weight gain was decreased in all the treated groups. Mean food consumption was significantly decreased in the treated males, especially at the beginning of the study. Although all of the treated female groups had significantly reduced intake at some time during the study, females were not as frequently affected as males. Calculation of feed efficiency values for the overall study and for the latter half of the study showed that the major effect of decreased food intake on body weight occurred at the beginning of the study. However, the decrease in food efficiency does indicate that the chemical had a toxic effect on body weight that cannot be accounted for solely by decreased food consumption. The only other possible effect of treatment was an increase in the

incidence of minimal hepatocellular swelling in the 60 mg/kg/day group males (0/5 in the control vs. 3/5 in the 60 mg/kg/day group).

iv. *A 90-day oral subchronic study.* In a dog study, cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride was administered in gelatin capsules to four Beagle dogs/sex/group at dosages of 0, 7.5, 15, or 30 mg/kg/day for 90 days. One female in the 30 mg/kg/day was sacrificed due to general deterioration on the 84th day of the study; necropsy revealed ascites with evidence of liver toxicity. The only other toxicologically significant findings during the study included a significant decrease in the hematocrit (HCT), hemoglobin (Hgb), and white blood count (WBC) measurements in the 30 mg/kg/day group males and histopathological changes, especially in the liver, in the 30 mg/kg/day group males and females. The incidence and/or severity of several findings in the liver were increased in the 30 mg/kg/day group males and females during the following:

- Obliterative vasculitis and perivasculitis of the hepatic blood vessels.
- Perivascular and pericholangiolar infiltration of mononuclear cells.
- Hyperplasia of the reticuloendothelial cells lining the hepatic sinusoid.

5. *Endocrine disruption.* No specific tests have been conducted with cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride to determine whether the chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects. However, there are no significant findings in other relevant toxicity tests, *i.e.*, developmental toxicity, which would suggest cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride produces effects characteristic of the disruption of endocrine function.

C. Aggregate Exposure

Dietary exposure. The proposed use of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride as a preservative in end-use product formulations applied to growing crops is not expected to result in significant additional dietary exposure, due to the low concentration of cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride employed in the formulation and the extremely low probability of contact by the general public following treatment.

Cis-isomer of 1-(3-chloroallyl)-3,5,7-triaza-1-azoniaadamantane chloride,