

8EHQ-0197-13874

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Document Processing Center (7407)
(Attn: Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

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RE.: TSCA Section 8(e) Notice: R&D Pesticidal Chemical, CGA-185072

Dear Section 8(e) Coordinator:

Ciba-Geigy Corporation (Ciba) requests that the specific chemical name and CAS Registry Number shown in brackets in this letter be treated as Confidential Business Information. We enclose a sanitized copy of this letter for the public file.

In accordance with EPA's March 16, 1978 policy statement on Section 8(e) reporting under the Toxic Substances Control Act and EPA's June 1991 TSCA Section 8(e) Reporting Guide, Ciba wishes to bring to your attention **preliminary information** from several mammalian toxicity studies conducted at some contract laboratories and in the laboratories of Ciba-Geigy Limited in Basel, Switzerland, with the chemical substance, [

]. This substance, also known internally under the designation CGA-185072, may be referred to generically in the public file as "substituted heterocyclic acetic acid ester."

1. Skin Sensitization in Guinea Pigs

~~Groups of ten albino Guinea pigs of each sex were administered CGA-185072 or the vehicle (control) to test for allergenic potential using the optimization test of Meurer and Hess. The test included an induction phase, consisting of ten intradermal injections, and the challenge phase, consisting of one intradermal injection and two epicutaneous applications, given at 14 days after the last sensitizing injection. The test substance was demonstrated to be a skin sensitizer in Guinea pigs since all treated animals showed positive skin reactions after the epidermal challenge.~~

CSRAO/OPPT
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2. 28-Day Oral Cumulative Toxicity Study in Rats

Groups of ~~four~~ ~~male and female~~ rats were administered CGA-185072 at daily doses of 0, 10, 100, or 1000 ~~ppm~~ ~~in the diet~~ for 28 days. Treatment-related effects were quite marked but mainly limited to the 1000 ~~ppm~~ ~~in the diet~~ level. These high dose animals had hunched posture, piloerection, and frequent urination ~~and~~ ~~urinary~~ ~~excretion~~ ~~within~~ ~~two~~ ~~weeks~~. Depressed body weight and food consumption, elevated water consumption, and changed hematologic profile, including ~~leukopenia~~ ~~and~~ ~~lymphopenia~~, and slight anemia, were noted at this dose level. Histopathologic changes seen at the top dose included: atrophy of splenic white pulp, necrosis of the thymus, focal necrosis of the bone marrow, ~~degeneration~~ ~~or~~ ~~erosion~~ of the gastric mucosa, acute or chronic renal tubular lesions, and renal papillary necrosis and acute inflammation. Blood chemistry changes, probably reflecting the liver and kidney histopathologic findings, were reported for the top dose animals. In addition, the renal papillary lesion was also noted in one female rat at 100 ~~ppm~~ ~~in the diet~~.

3. 3-Month Oral Toxicity Study in Rats

Groups of ~~four~~ ~~male and female~~ rats per sex were administered CGA-185072 at 0, 20, 100, 1000, or 6000 ppm in the diet for 90 days. A single high dose male was found dead on week 9. Polymia (male only), increased water consumption, and decreased kidney weights were observed at this dose level. Some of the high dose ~~male~~ ~~rats~~ ~~appeared~~ ~~to~~ ~~be~~ ~~changed~~ at necropsy. Histopathologic examination revealed high dose effects of hydronephrosis accompanied by inflammation with necrosis in the renal parenchyma in many tubules and necrosis of acini in renal papilla in two males. In addition, urinary bladder epithelium hyperplasia was seen in males at both 1000 and 6000 ppm.

4. 13-Week Feeding Study in dogs

Groups of four Beagle dogs were scheduled to receive CGA-185072 in the diet at 0, 100, 1000, or 40000 ppm for 90 days. However, the top feeding level was decreased in three steps. Due to low food consumption, within the first eighteen days from 40000 ppm to 15000 ppm, but still resulted in numerous treatment effects including tremors and hematologic changes such as anemia and low platelet counts. Increased erythropoiesis and changes in erythropoiesis were seen in both the bone marrow and spleen of many high dose animals while severe erythrophagocytosis was noted in the spleen of one male. Inflammatory reactions, possibly due to severe changes in hemopoiesis, were observed in different organs (heart, intestine, kidney, thyroid) at the top dose. Other histopathologic changes seen at this dose included perivascular mixed inflammatory cell infiltration and multilayer necrosis in the liver, subcutaneous lymphatic vessels in the liver, and atrophy in the thyroid. At 1000 ppm, only the liver (one female) and thyroid (one male) showed any histologic changes.

5. 52-Week Feeding Study in Dogs

Groups of four Beagle dogs of each sex were scheduled to receive CGA-185072 in the diet at 0, 75, 1500, or 15000 ppm for a year. However, due to excessive toxicity at 15000 ppm, the top dose was reduced to 10000 ppm after four weeks. In spite of the reduction in dose level, one top dose female died at week 15 and one top dose male was taken off treatment from week 22 to week 29 due to body weight loss and severe anemia. The female that died early showed moderate bone marrow hypoplasia with septicemia.

6. 24-Month Carcinogenicity Study in Rats

Groups of eighty albino rats of each sex were administered CGA-185072 in the diet at 0, 10, 100, 1000, or 2000 ppm for up to two years. Ten and fifty animals per sex per group were designated for termination after one and two years of exposure, respectively, to evaluate carcinogenic potential. Twenty animals per sex per group were designated for providing clinical laboratory samples throughout the two years. Lymphoid hyperplasia of the thymoid was observed in a few high dose males while thyroid follicular epithelial hyperplasia occurred at significantly higher incidence in females at 1000 and 2000 ppm than the controls.

7. 18-Month Carcinogenicity Study in Mice

Groups of sixty albino mice of each sex were administered CGA-185072 at 0, 10, 100, 1000, or 5000 ppm for up to 18 months, with ten of the sixty mice per group reserved for blood sampling. Chronic inflammatory changes were observed in the mucosa and the smooth wall of the urinary bladder in high dose males and sometimes in association with the presence of calculi or ulceration.

8. Developmental Toxicity (Teratogenicity) Study in Rats

Groups of twenty-four mated albino rats were administered CGA-185072 by oral gavage at 0, 10, 100, or 400 mg/kg each day on days 6 through 15 of gestation. Decreased fetal body weight and delayed skeletal maturation were observed at the high dose in the presence of depressed maternal food consumption and body weight.

9. Developmental Toxicity (Teratogenicity) Study in Rabbits

Groups of twenty mated rabbits were administered CGA-185072 by oral gavage at 0, 10, 60, or 300 mg/kg each day on days 7 through 19 of gestation. Tremors, reduced locomotor activity, one abortion, and five found-deaths were seen among the high dose dams during the dosing period. Only a slight delay in skeletal ossification was noted in fetuses at the high dose.

10. Two-Generation Reproduction Study in Rats

Groups of twenty-five albino rats were administered CGA-185072 in the diet at 0, 50, 500, 5000, or 10000 ppm through the entire study period. The adult animals were exposed to the test substance for 100 days prior to a mating period of 21 days for each generation. Adult males were terminated subsequent to the mating period while females were only terminated after weaning of their offspring. Four deaths occurred at 1000 ppm among parental males in the F1 generation. The high-dose F1 animals had numerous changes in several zones of the kidney and urinary bladder. The high-dose pups had reduced weights (F1 and F2) and increased incidence of pelvis dilatation in the kidney (F1 only).

CGA-185072 is a research and development compound being evaluated for pesticidal purposes. Some of these evaluations are being conducted in the United States, under the supervision of technically qualified personnel, knowledgeable in handling potentially hazardous chemicals.

In response to these findings, Ciba will do the following:

1. Modify the Material Safety Data Sheet to reflect these findings.
2. Notify persons working with this compound of the new findings in accordance with notification requirements of OSHA's Hazard Communication Standard (29 CFR 1910.1200).
3. Provide copies of the study final reports after we receive them.

Please contact the undersigned if you require additional information.

Very truly yours,



Anthony Di Battista