2-3-82

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 5 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: February 3, 1982

SUBJECT: EPA Reg.#201-279; 201-281; Bladex; Rat teratology study; PP#9F2232; petition proposing a tolerance of 0.1 ppm for the pesticide, 2-[[(4-chloro-6-(ethyl-amino)-5-triazin-2-yl]amino-2-methyl-propionitrile, be established to cover negligible residues in or on Soybeans. CASWELL#188C Acc.#070584

FROM: William Dykstra, Toxicologist
Toxicology Branch/HED (TS-769)

TO: Robert Taylor (25)
Registration Division (TS-767)
and
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Recommendations:

1) The requested tolerance is not toxicologically supported. Toxicology Branch requires historical control data in the strain of rat used in the rat teratology study to further evaluate the results of the study. The occurrence of eyes small or absent in the 25 mg/kg/day dose group, diaphragmatic hernia, and other findings are suggestive of teratogenic effects.

2) A rabbit teratology study and a mouse oncogenicity study are required to be submitted within a reasonable period of time.

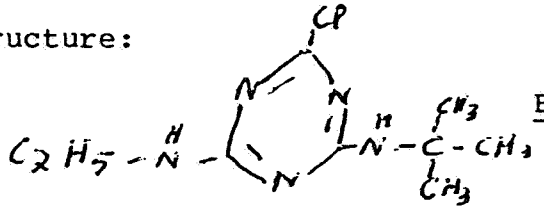
A. Substance Identification

1. Name: 2-[[(4-chloro-6-(ethylamino)-5-triazin-2-yl]amino]-2-methylpropionitrile

2. Purity: >90%

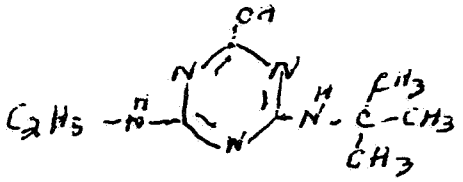
3. Synonyms: Bladex

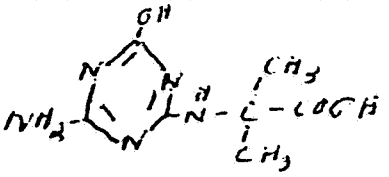
4. Structure:



Bladex

Plant metabolite DW4385 + Plant metabolite DW4394





B. Related Petitions: 9G0844, 0F0998, 3G1377, 5F1532, 5E1565, 5F1599, 6F1729

C. Tolerances established under 40 CFR 180.307.

D. Previously Submitted Toxicity Data

1. Memo of 3/15/71 from G. Whitmore in PP#0F0998

- °2-year rat chronic/oncogenic study: oncogenic potential: negative; NOEL = 12 ppm
- °2-year dog feeding study: NOEL = 50 ppm
- °3-generation rat reproduction: NOEL = 80 ppm
- °Major plant metabolite DW4394: 13-week rat feeding study; NOEL = 10,000 ppm (highest dose)
- °Major plant metabolite DW4385: 13-week rat feeding study; NOEL = 10,000 ppm (highest dose)
- °Acute oral (tech) = 334 mg/kg

2. Memo of 10/8/77 from D. Ritter in PP#6F1729

   °Rabbit teratology: negative up to 3.2 mg/kg/day; IBT invalid
   °Mouse dominant lethal assay: negative
   °Host-mediated assay: negative
   °Mouse bone marrow assay: negative

3. Memo of 5/11/77 from M. Rogoff regarding Nitrosamine action; Shell Bladex: No detectable amounts of nitrosamine at a detection level of 1.0 ppm. Recommend that any registration or tolerance actions on subject pesticide which are held pending resolution of the nitrosamine problem be released from each action moratorium.

4. Memo of 10/14/81 from W. Dykstra to R. Taylor, PP#9F2232

   a. I.B.T. No. 8580-11112, Teratogenic study with SD15418 Bladex technical in Albino Rabbits, is invalid.

E. Toxicity Data Submitted with Petition

1. Technical Bladex (SD15418) Teratology Study in Rats (Westhollow Research Center Project No. 61230; December, 1981)

   Groups of 30 mated female rats (Fischer 344) were dosed orally with 0, 1, 2.5, 10 or 25 mg SD15418/kg body weight on days 6-15 of gestation. Vitamin A, 128 mg/kg body weight, was given on days 9-15 of gestation as the positive control. Body weights and unusual clinical signs were recorded during gestation. On day 20 of gestation, necropsies were done and the litters evaluated on females dosed with the test compound or vehicle control until 20 pregnant females with live litters were obtained from each group, and on all surviving females dosed with the positive control chemical. The remaining animals were killed and discarded. The uterine horns were weighed and the contents were examined for evidence of fetal toxicity or teratogenic response.

   Results:

   All groups showed a body weight gain over the period of gestation. However, significant reductions in body weight gain were seen in the 10 mg (on gestation day 12) and the 25 mg (on gestation days 12 and 15) dose groups and in the positive control group (on gestation days 12, 15 and 20) when compared to the negative controls ($p \leq 0.05$).

Analysis of the carcass weights (gestation day 20 body weights minus gravid uterine weights) revealed a significant reduction in the 25 mg of SD 15418/kg group and the positive control group as compared to the negative control ($p \leq 0.05$).

No significant differences were seen between animals in the negative control and SD 15418 treated groups for the parameters measured i.e., the number of corpora lutea, implantations, resorptions, live or dead fetuses, fetal body weights, fetal crown-rump length and sex ratio. In the positive control group (Vitamin A), a significant decrease in fetal body weight and increase in the number of dead fetuses per litter as compared to the negative control group were observed.

No significant increases of external abnormalities were observed in the SD 15418 treated groups as compared to the negative control group, however the incidence of eyes small or absent is suggestive of a teratogenic effect.

The positive control group had significant increases in the incidences of numerous abnormalities including eye defects [(small eye(s), absent eye(s) or open eye(s), club hind limb, and cleft palate.

Several litters in the various dose groups consisted of a single fetus which was examined for visceral or for skeletal abnormalities, depending upon the abnormalities noted at the external examination.

Fewer than 20 litters were examined in three of the dose groups, because a single fetus was present which was processed for skeletal examination only. Examinations of Bouin-fixed fetuses of all test groups including the positive control group showed low incidences of abnormalities such as displaced esophagus, diaphragmatic hernia, small liver protrusion, undescended testis and displaced testis. SD 15418 treated groups had no significant increases in the incidences of visceral abnormalities compared to the negative controls, however the occurrence of diaphragmatic hernia is also suggestive of a teratogenic effect. The positive control group showed significant increases in the incidences of absent eye(s), cleft-palate, displaced esophagus, dilated renal pelvis, dilated ureter and wavy ureter.

One litter in the 25 mg of SD 15418/kg group and in the positive control group consisted of a single fetus which was processed for visceral abnormalities only. Delayed ossification or delayed development were commonly observed in the bones of most test groups e.g., dumbbell or bipartite centra of the thoracic vertebrae, lumbar vertebrae and sternebrae. But significant increases in the incidence of delayed ossification

for some of those bones were only observed in the positive control group as compared to the negative controls. A significantly increased incidence of the skeletal variation of lumber spur was observed among litters of rats dosed with 25 mg of SD 15418/kg or with Vitamin A. The positive control group also showed significant increases in the incidences of other skeletal variations (i.e., cervical spur on the 7th cervical vertebrae, increased number of lumbar vertebrae and extra rib(s) on the 14th thoracic vertebrae). The presence of extra ribs or spurs in rats is regarded as being indictive of fetotoxicity.

Conclusion:

Toxicology Branch requires historical control data in the strain of rat used in the rat teratology study to further evaluate the results of the study. The occurrence of eyes small or absent in the 25 mg/kg/day dose group, diaphragmatic hernia, and other findings are suggestive of teratogenic effects.

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