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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Hydroxyatrazine: Evaluation of a Rat Chronic Feeding/Oncogenicity Study Interim Report

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CONCLUSIONS

Dose levels being tested in the study are 0, 10, 25, 200, and 400 ppm or roughly 0, 0.5, 1.25, 10, and 20 mg/kg/day of G-34048 (hydroxyatrazine technical).

By 52 weeks, significant adverse effects had occurred in the urinary tract (particularly the kidney and bladder) of rats at dietary concentrations of 200 and 400 ppm. Urinary tract effects were noted in both sexes. Treatment-related reduced survival was reported in both sexes of the high dose group as were treatment-related changes in body weight gain, food consumption, and hematologic and clinical chemistry parameters.

There did not appear to be any treatment-related increases, relative to the control group, in benign or malignant neoplasms at 52 weeks. However, only selected tissues were examined microscopically and no individual animal data were provided in the study report.

The tentative NOEL for systemic effects in the two-year study at 52 weeks is 25 ppm (about 1.25 mg/kg/day) and the tentative LOEL is

200 ppm (about 10 mg/kg/day). A NOEL and LOEL of 100 ppm (about 5 mg/kg/day) and 300 ppm (about 15 mg/kg/day) respectively were determined in a 90-day rat feeding study with hydroxyatrazine technical (MRID 412935-01). However, the dietary concentrations tested in the 90-day study (0, 10, 100, 300, and 600 ppm) did not include a 25 ppm concentration. Urinary tract toxicity was also noted in the 90-day study.

The final report of the two-year study must be received and evaluated before more definitive NOELs and LOELs for systemic and oncogenic effects can be established. The interim report is considered to be Core Supplemental data.

The way in which the results of the Hydroxyatrazine two year rat feeding study will be incorporated into the hazard evaluation and risk assessment of Atrazine has not yet been determined.

ACTION REQUIRED

The 52 week interim report of a hydroxyatrazine rat chronic feeding/oncogenicity study (which is being conducted voluntarily) has been submitted for evaluation by the sponsor, Ciba-Geigy Corp., Greensboro, NC.

Title: 2-Year Dietary Chronic Toxicity/Oncogenicity Study with G34048 [Hydroxyatrazine Technical] in Rats. An Interim Report. Completed on 1/26/93, by E. Chow and S.B. Emeigh Hart, (Lab Study No. F-00125).

The study is being conducted by Ciba-Geigy's Environmental Health Center, Farmington, CT and was initiated on 8/20/91.

TOXICOLOGY BRANCH I EVALUATION

Study Design Summary

Daily dietary concentrations of 0, 10, 25, 200, or 400 ppm are being tested in this study. At study initiation, the control and high dose groups contained 80 CD Sprague-Dawley derived rats/sex and all other groups contained 70 rats/sex. Animals were six weeks of age at the start of the study. The test material is a white powder with a purity of 97.1%. For the 52 week test interval, test substance concentration homogeneity and concentration were determined, body weight, food consumption, water intake, mortality, and clinical signs were monitored, and clinical laboratory tests (hematology, clinical chemistry, and urinalysis) were performed.

Twenty rats from the control and high dose groups and ten rats from each of the other groups were designated for sacrifice at 52 weeks. Some had already died by this time. At interim sacrifice, organ weights were obtained from scheduled sacrifices and a necropsy and

microscopic examination (of selected tissues) were performed on all animals dying scheduled or unscheduled by 52 weeks.

Findings at 52 Weeks

Only summary tables were provided for evaluation. No individual animal data were submitted.

Systemic Toxicity
Major findings reported by the study authors are as follows:

1. The urinary tract (particularly the kidney and urinary bladder) was adversely affected by treatment with the test material at dose levels of ≥ 200 ppm.

Absolute and relative kidney weights were increased in both sexes at 400 ppm and altered kidney appearance/content was noted in this group at necropsy. Also noted in high dose animals were crystalline materials and enrichment of G-34048 (the test material) in urinary sediments, and effects on urinary parameters. At necropsy, calculus was noted in several places in the urinary tract.

The study authors reported various microscopic lesions in the kidneys of males (≥ 200 ppm) and of both sexes at 400 ppm including dilatation/inflammation/fibrosis with crystal deposits, or accelerated chronic nephropathy. Urinary bladder lesions (fibrosis and hyperplasia) were reported in both sexes at ≥ 200 ppm.

2. Survival was reduced at 400 ppm in both sexes and clinical signs characteristic of renal affects or moribund animals were observed at this dose concentration. The study authors attributed reduced survival to the renal affects.

3. Cumulative body weight gain was decreased slightly in females at 200 ppm and by 22% and 44% respectively, relative to the control group, in males and females at 400 ppm.

4. Food consumption was decreased in both sexes at the high dose.

5. Hematologic and clinical chemistry parameters were affected (possibly related to renal effects) in both sexes at 400 ppm.

Oncogenicity

Only selected tissues were evaluated microscopically. These were kidneys, urinary bladders and pituitaries from all animals, and ovaries, mammary glands, and all skin-associated masses/lesions from all females.

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Masses. Although it appears that the only masses/lesions subjected to histologic examination were skin-associated masses/lesions from females, the small total numbers of masses observed at necropsy for either sex showed no obvious relationship to treatment (see table below).

MASSES OBSERVED AT NECROPSY AT 52 WEEKS[1,3]

	Males					Females				
Dose Group[2]	C	1	2	3	4	C	1	2	3	4
Number Examined	23	14	13	16	38	22	13	12	11	35
Mass Location										
Skin	3	2	2	0	2	5	3	3	1	3
Harderian Gland				1			1			
Pericardial Sac					1					
Diaphragm Muscle					1					
Lung								1		
Liver								1		
Ovary										1
Eye/Optic Nerve				2			2			
Total	3	2	2	3	4	5	6	5	1	4

1 From all deaths, scheduled & unscheduled
2 C=0 ppm (control), 1=10 ppm, 2=25 ppm, 3=200 ppm, 4=400 ppm of G-34048 (hydroxyatrazine tech)
3 Fat masses were not included in above tabulations (Males had epididymal fat masses at 25 ppm (1) and 400 ppm (1) and a female had an abdominal fat mass at 200 ppm.

Neoplasms. There did not appear to be any treatment-related increases in benign or malignant neoplasms at the 52 week time point. Neoplasms observed are presented in the tables below.

NEOPLASMS REPORTED AT 52 WEEKS[1]

MALES Dose Groups[2]	C	1	2	3	4
Lymphoma Kidney or Urinary bladder (malignant)	0/23	0/14	2/13	0/16	1/37 or 38
Pituitary Gland Adenoma (benign)	0/22	2/13	0/13	0/16	4/38
Animals with Neoplasms	0	2	1	0	5

1 From all deaths, scheduled & unscheduled
2 C=0 ppm (control), 1=10 ppm, 2=25 ppm, 3=200 ppm, 4=400 ppm of G-34048 (hydroxyatrazine tech)

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NEOPLASMS[1] REPORTED AT 52 WEEKS[2]

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FEMALES Dose Groups[3]	C	1	2	3	4
Mammary Gland Adeno-carcinoma (malignant)	3/22	0/13	1/12	0/11	2/35
Adenoma (Benign)	1/22	1/13	0/12	0/11	1/35
Fibro-adenoma (benign)	3/22	2/13	1/12	1/11	1/35
Hyper-plasia w/atypia all grades	1/22	1/13	0/12	2/11	3/35
Lobular Hyper-plasia all grades	1/22	1/13	2/12	2/11	3/35
Skin Squamous Cell Carcinoma (malignant)	0/22	0/13	1/11	0/11	0/35
Ovary Sertoli cell (benign)	0/22	0/13	0/12	0/11	1/33
Hyper-plasia Sertoli Cell all grades	4/22	2/13	4/12	1/11	3/33
Hyper-plasia Thecal/ Inter-stitial all grades	5/22	5/13	5/12	4/11	16/33
Pituitary Gland Adenoma (benign)	7/22	2/13	3/12	1/11	2/35
Animals w/ Neoplasms	9	4	6	2	5

1 Incidences of hyperplasia in some neoplastic tissues are also included
2 From all deaths, scheduled & unscheduled
3 C=0 ppm (control), 1=10 ppm, 2=25 ppm, 3=200 ppm, 4=400 ppm of G-34048 (hydroxyatrazine tech)

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