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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Simazine - Carcinogenicity in Animals

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Simazine; CAS Registry No. 122-34-9; Chemical No. 080807

The Health Effects Division (HED) Carcinogenicity Peer Review Committee met on May 17, 1989 and October 25, 1989 to evaluate the carcinogenicity data for Simazine. Full details and references are found in the Peer Review files.

A. Animal Carcinogenicity Studies

Male and female Sprague-Dawley rats were fed 0, 10, 100, or 1000 ppm of simazine for 2 years. In female rats there was a statistically significant increase in mortality, and in male rats there was a statistically significant decrease in mortality, with increasing doses of simazine. Although the highest dose tested (HDT) appeared excessive for carcinogenicity testing based on deaths (females) and body weight gain reductions (28-45%, females; 27-36%, males), the appearance of tumors at the mid-dose (discussed below) in female rats suggested that the dosing does not detract from the observed tumor incidences at the HDT. The Committee also felt that there was too great an interval between the mid and high doses (100 to 1000 ppm).

When the shortened lifespan of the female rats was considered in the statistical analysis, the incidences of malignant mammary gland carcinoma at both the 100 and 1000 ppm dose groups were statistically significant compared to control ($p < 0.05$ and $p < 0.01$, respectively). There was a statistically significant increase in the combined mammary gland adenoma/carcinoma incidence compared to control as well ($p < 0.01$). The upper limit of the



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historical control range of the testing laboratory for mammary gland carcinoma was exceeded at 100 ppm, and greatly exceeded at 1000 ppm (HDT). The incidence of cystic glandular hyperplasia in the mammary gland was statistically significantly increased at the HDT, which correlates with the observed high tumor incidence at that dose. There was a statistically significant dose-related trend for mammary gland carcinomas and combined adenomas/carcinomas. There was a suggestion that the mammary gland carcinomas contributed to the increased mortality at the HDT.

In female rats, there was a significant increase in pituitary gland carcinomas at 1000 ppm based on pair-wise comparisons to control ($p < 0.05$) when time to death was considered. The pituitary tumors in the female rats were fatal with a possibly accelerated onset. The incidence of pituitary gland carcinomas was outside the historical control range of the testing laboratory.

There was a statistically significant dose-related trend for kidney tubule adenomas in female rats and carcinomas and combined adenomas/carcinomas in male rats; increased tumors were seen only at the HDT and were not significant by pair-wise comparison to controls. The incidence for adenomas in females in the historical control data from the testing laboratory was zero; the incidence of kidney tubule carcinomas in male rats was less clearly defined because of sporadic occurrences of the same tumor in control animals. The historical incidence of rat kidney tumors is described as uncommon.

Male and female CD-1 mice were fed 0, 40, 1000, or 4000 ppm of simazine for 95 weeks. The dosing was considered adequate for assessing the carcinogenic potential of simazine based on adequate body weight gain depressions. There was no increased incidence of tumors associated with simazine exposure to these mice.

B. Additional Information

Simazine is one of several s-triazine compounds used in agriculture as herbicides. It is structurally related to Atrazine, Cyanazine, and Propazine among others. Atrazine was associated with increased mammary gland tumors (primarily malignant tumors) in female Sprague-Dawley rats; early onset of mammary tumors was also observed. Cyanazine was also associated with increased mammary gland tumors (primarily malignant tumors) in female Sprague-Dawley rats. Propazine was associated with increased mammary gland tumors (primarily benign) in female Sprague-Dawley rats.

Simazine was found negative in the Salmonella assay for gene mutations; this is consistent with other tested s-triazines. However, it is reported that simazine is positive for gene mutations in the mouse lymphoma assay, the Drosophila sex-linked recessive lethal assay, the cell transformation assay in Syrian hamster embryo cells, and plant cytogenetic assays. Simazine is

also reported negative in several other assays including yeast assays, unscheduled DNA synthesis, sister chromatid exchanges, and for aneuploidy. These data suggest a possible mutagenic action for simazine. Cyanazine also has evidence of positive genotoxic activity in the mouse lymphoma assay for gene mutations and for unscheduled DNA synthesis in rat hepatocytes. Propazine also induces gene mutations in the cultured V79 cell assay for gene mutations.

C. Carcinogenicity in Animals

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, it is concluded that exposure to simazine results in increased incidences of malignant mammary gland carcinomas and malignant pituitary gland carcinomas in female Sprague-Dawley rats. These incidences exceeded the historical control range of the testing laboratory. The pituitary tumors were fatal with a possibly accelerated onset, and the mammary tumors also contributed to the increased mortality at the HDT. There was equivocal evidence of kidney tubule tumors (an uncommon tumor type) in both sexes. The structural analogues are strongly supportive as these compounds mostly induced malignant mammary gland tumors in Sprague-Dawley rats. There was some evidence of genotoxicity for simazine as well as some of the analogues. The relevance of these data to an evaluation of simazine's potential for human carcinogenicity is discussed in the Peer Review documents for Simazine (July 31, 1989 and May 24, 1990).

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