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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Acephate - Carcinogenicity in Animals

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Acephate; CAS Registry No. 30560-19-1; Chemical No. 103301

The Health Effects Division (HED) Carcinogenicity Peer Review Committee met on January 24, 1985 to evaluate the carcinogenicity data for Acephate. Full details and references are found in the Peer Review files.

A. Animal Carcinogenicity Studies

Male and female CD-1 mice were fed 0, 50, 250, or 1000 ppm of acephate for 105 weeks. Although fewer low-dose and mid-dose female mice survived to the end of the study compared with controls, the survival of the highest dose tested (HDT) female mice and all male mice was higher than that with the controls. Decreases in body weight gain ranged from 8-11% for males and 6-14% for females at the mid-dose, and about 24% for males and 29% for females at the HDT. Dose related increasing levels of liver toxicity, including regenerative changes were observed. The Committee agreed that all doses were tolerated for the entire lifespan.

In the female mice, at the HDT, the incidences of malignant hepatocellular carcinomas (12 out of 61 animals observed surviving past 52 weeks, i.e. 12/61) and hyperplastic nodules (15/61) were significantly increased in comparison with controls (1/64 and 2/64, respectively). The increased incidence of carcinomas exceeded the testing laboratory's historical control range (0 - 6%). The incidence of benign hepatocellular adenomas was low in this study (3/61 versus 0/64 for controls). There were no increases in tumors

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in the two lower dosed female groups or any of the male groups.

Male and female Charles River (CD) Sprague-Dawley rats were fed 0, 5, 50, and 700 ppm of acephate for 28 months. There was no dose-related effect on mortality although there was significant cholinesterase inhibition (brain, plasma, and RBC) in the mid- and high-dose male and female rats. There was also a 4-18% weight loss in the HDT males.

Although there was an elevated incidence of pheochromocytomas above controls in the treated males, there was no evidence of a dose-dependent increase. Furthermore, the incidence of pheochromocytomas was within the range of historical incidences reported for controls in the testing laboratory and in the literature for the strain tested. There was no evidence of either increased malignancy of lesions or decreased latency in the treated males. The incidence of pheochromocytomas in females was not increased. The conclusion reached was that the adrenal pheochromocytomas did not appear to be compound related.

B. Additional Information

Acephate has been tested in a wide array of genotoxicity assays. The evidence indicates that acephate produced positive responses in gene mutation assays with Salmonella, E. coli, and S. cerevisiae. Acephate has been reported to produce mutations in mouse lymphoma cells, sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells, and mitotic recombination in Saccharomyces. Several in vivo assays for SCEs and cytogenetic endpoints have been negative (negative results in in vivo situations for many organophosphates are not unusual due to the limiting cholinesterase inhibition). So while acephate is a mutagenic compound, its activity is difficult to detect in vivo.

C. Carcinogenicity in Animals

After a full evaluation of all the data and supporting information regarding animal carcinogenicity, it is concluded that exposure to acephate results in the induction of malignant hepatocellular carcinomas in female CD-1 mice. The incidence exceeded the historical control range of the testing laboratory. There is evidence that acephate is genotoxic based on in vitro studies, but this activity may be difficult to detect in vivo. The relevance of these data to an evaluation of acephate's potential for human carcinogenicity is discussed in the Peer Review document of Acephate (May 8, 1985).

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