from 8 to 11 percent for males and 6 to 14 percent for females at the mid-dose, and about 24 percent for males and 29percent for females at the HDT. Doserelated increasing levels of liver toxicity, including regenerative changes, were observed. In the female mice at the HDT, the incidence of malignant hepatocellular carcinomas and hyperplastic nodules was significantly increased in comparison with controls. The increased incidence of carcinomas exceeds the testing laboratory's historical control range. There were no increases in tumors 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 in the midand high-dose male and female rats. There was a 4 to 8 percent weight loss in the HDT males.

Acephate has been tested in a wide array of genotoxicity assays. The evidence indicates that acephate produced positive responses in gene mutation *in vitro* 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.

Based on this information regarding animal carcinogenicity, the Agency concludes 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).

Triadimefon

After a full evaluation of all the data and supporting information regarding animal carcinogenicity, EPA has concluded that exposure to triadimefon results in the induction of hepatocellular adenomas in both male and female NMRI mice. Male and female NMRI mice were fed 0, 50, 300, or 1,800 ppm of triadimefon for 21 months. At the HDT, the incidence of hepatocellular adenomas was increased in both male and female mice by pairwise comparison between the HDT and controls. A positive dose-related significant trend for adenomas was found in both sexes. The incidence of hepatocellular adenomas for each sex exceeded the testing laboratory's historical control range for adenomas in NMRI mice.

In another study, male and female CF1-W74 mice were fed 0, 50, 300, or 1,800 ppm of triadimefon for 24 months. The HDT was considered appropriate for assessing carcinogenicity based on increased hematological changes; statistically significant increases in liver weights accompanied by histopathological changes and weight gains at the HDT were significantly lower than in controls.

Initially, the tumor profile was thought to provide no indication that triadimefon had an influence on total tumor incidence, on the number of mice with tumors or on incidence of single tumor types; however, the pathology report indicated that more mice had hyperplastic liver nodules at the HDT than mice in the other treated groups or the controls. The Peer Review Committee recommended that in light of the NMRI study results outlined above, and that the original analysis of the study results was performed before the current criteria were put into place, the liver nodules should be re-read with updated criteria.

The new histopathological information for the CF1-W74 mouse study was submitted subsequent to the completion of the latest Triadimefon Peer Review document. Only a small number of slides were available for reexamination, and the results were deemed inconclusive. However, they are suggestive of an effect on tumor incidence in the liver and are consistent with the findings in the NMRI study that the liver is a principal site for tumor induction. Lesions which were originally classified as hyperplastic or regenerative nodules were reclassified as either hepatocellular adenomas or carcinomas. In males, 3, 3, 2, and 3 adenomas and 1, 4, 4, and 4 carcinomas were found out of 6, 8, 7, and 13 liver samples examined at doses of 0, 50, 300, and 1,800 ppm, respectively. This suggests that triadimefon may contribute to the induction of liver tumors and there may be a carcinoma component.

In a 104-week study, male and female Wistar rats were fed 0, 50, 300, or 1,800 ppm of triadimefon. Triadimefon induced a positive dose-related trend in the incidence of thyroid follicular cell adenomas/adenomas multiple in male Wistar rats. Positive dose-related trends were achieved in both sexes for combined incidences of thyroid follicular cell cystic hyperplasia and adenomas/adenomas multiple.

Hepatocellular adenomas are considered to be evidence of cancer because hepatocellular adenomas can progress to hepatocellular carcinomas. Malignancy (carcinoma) implies a more extensive disease process. Thus, hepatocellular adenomas represent an earlier stage than carcinomas in the progression of cancer induction. This is one of the major reasons that the National Toxicology Program (NTP) has used to justify combining these two tumor types for an overall analysis of carcinogenicity (in addition to analyzing them separately). For triadimefon, the possible progression to carcinoma was suggested in the CF1-W74 mouse study and is strongly supported by carcinoma induction in close structural analogues, e.g., etaconazole, uniconazole, cyproconazole, tebuconazole, and fenbuconazole.

Based on the above data and supporting information regarding animal carcinogenicity, it is concluded that exposure to triadimefon results in the induction of hepatocellular adenomas in both male and female NMRI mice. A positive dose-related significant trend for adenomas was also found in both sexes. This conclusion is bolstered by the extensive structural activity support from closely structurally related triazole compounds tested in many mouse studies that showed increased incidences of not only adenomas but carcinomas as well. It is also noted that although the analysis was inconclusive, there was a carcinoma response by triadimefon in the CF1-W74 mouse study. In addition, triadimefon induced a positive doserelated trend in the incidence of thyroid follicular cell adenomas/adenomas multiple in male Wistar rats. Positive dose-related trends were achieved in both sexes for combined incidences of thyroid follicular cell cystic hyperplasia and adenomas/adenomas multiple.

The relevance of these data to an evaluation of triadimefon's potential for human carcinogenicity is discussed in the Peer Review document of Triadimefon (September 26, 1990).

Iprodione

After a full evaluation of the data and supporting information regarding animal carcinogenicity, EPA concludes that exposure to iprodione resulted in an increased incidence of hepatocellular malignant carcinomas in male mice and combined hepatocellular adenomas/ carcinomas in both sexes of mice, ovarian lutenomas in female mice, and