testicular interstitial cell tumors in male rats.

Iprodione was administered to CD-1 mice (50/sex/group) at levels of 0, 160, 800, or 1,400 ppm for at least 99 weeks (or until the 52-week interim sacrifice of 15 additional mice/sex/group). At the terminal sacrifice, there was a significantly increased incidence of benign and malignant liver cell tumors in both sexes compared to the control. Analysis indicates that male mice had significant difference in the pair-wise comparisons of the 1,400-ppm dose group with the controls for liver adenomas, carcinomas and combined adenomas and/or carcinomas. Female mice had significant increasing trends in liver adenomas, carcinomas, and combined adenomas and/or carcinomas. All males in all dose groups (including concurrent controls) displayed a higher incidence of carcinomas than observed in historical controls. Although there was no increase in the incidence of testicular tumors in the male mice, there was a dose-related increase in the incidence of interstitial cell hyperplasia at the 800- and 1,400-ppm dose levels.

In female mice, iprodione was associated with significant dose-related increasing trends in liver adenomas, carcinomas and combined adenomas and/or carcinomas; there were significant differences in pair-wise comparisons with the high-dose level with controls for liver adenomas and combined adenomas and/or carcinomas. The increased incidences of hepatocellular tumors at the 1,400-ppm level generally exceeded the available historical control data for these tumor types in mice of this strain. Additionally, iprodione was associated with a significant increasing trend in ovarian lutenomas, and there was a significant difference in the pair-wise comparison of the 1,400-ppm dose group with the control group and historical controls. EPA considers the dose levels used in this study to be adequate for testing the carcinogenicity of iprodione in mice.

Iprodione was administered in the diet to 60 Sprague-Dawley rats/sex/group for 2 years at dose levels of 0, 150, 300, or 1,600 ppm. There was a 52-week interim sacrifice of 10 additional rats/sex/group. At the interim sacrifice, males at the high-dose level displayed an increase in the incidence of lesions in the adrenals, and there was an increase in the incidence of centrilobular hepatocyte enlargement in males at the 300 and 600 dose levels; females displayed an increased incidence of centrilobular hepatocyte enlargement at the highest dose tested.

In male rats fed iprodione for 2 years, there was a significant dose-related increasing trend and a significant difference in the pair-wise comparison of the 1,600-ppm dose group with the controls for testicular interstitial cell benign tumors. The incidence of both unilateral and bilateral benign interstitial cell tumors was increased at this dose level compared to historical control data. In addition to the neoplastic lesions, interstitial cell hyperplasia in the testes, reduced spermatozoa in the epididymis, and absent/empty secretory colloid cells or reduced secretion in the seminal vesicles were observed at the 300- and 1,600-ppm dose levels. Atrophy of the seminiferous tubules in the testes, with atrophy of the prostate and absence of spermatozoa in the epididymis, were observed at 1,600 ppm. Centrilobular hepatocyte enlargement was increased in males at the high-dose level. Adrenal lesions were observed in both sexes at the 300- and 1,600- ppm dose levels, although males displayed more lesions than females.

In females rats fed iprodione at the high-dose level for 2 years, there were no significant compound-related tumors observed, although there was an increased incidence of tubular hyperplasia in the ovaries and increased sciatic nerve fiber degeneration compared to the controls. The dose levels chosen for this study were considered appropriate for assessing the carcinogenicity of iprodione in rats.

Iprodione is structurally related to vinclozolin and procymidone. Procymidone has been associated with the appearance of tumors in both sexes in the reproductive organs and the liver, but did not have mutagenic activity in several tests. Vinclozolin, which is currently being tested for its carcinogenic potential, has been associated with adverse effects on the reproductive organs and liver. With the exception of the mouse lymphoma (forward mutation) assay, vinclozalin was negative for mutagenicity. In mutagenicity studies, iprodione was not mutagenic in the Ames assay, the CHO/HGPRT mammalian cell forwarded mutation assay, the in vitro chromosome aberration assay in CHO cells, the *in vitro* sister chromatid exchange assay in CHO cells and the dominant-lethal test in mice. However, iprodione was positive in the *Bacillus subtilis* assay for DNA damage without metabolic activation.

Imazalil

After a full evaluation of the data and supporting information regarding animal carcinogenicity, EPA concludes that exposure to imazalil is associated with an increased incidence of adenomas and combined adenomas/adenocarcinomas of the livers of male Swiss mice and with a significant dose-related increasing trend in hepatocellular adenomas and combined adenomas and/or carcinomas.

Imazalil base was administered in the diet to groups of 50 male and 50 female Swiss mice and treated for 100 to 101 weeks at levels of 0, 50, 200, or 600 ppm. Male mice had a significant dose-related increasing trends in hepatocellular adenomas and/or carcinomas. There was a significant difference in the pair-wise comparison of the 200-ppm dose group with the controls for hepatocellular adenomas. There were also significant differences in the pair-wise comparisons of the 600-ppm dose group with the controls for hepatocellular adenomas and combined adenomas and/or carcinomas. EPA has concluded that the malignant carcinoma response at the 600-ppm dose level was biologically relevant and related to imazalil exposure despite the lack of pair-wise statistical significance compared to controls. There was over a doubling of the concurrent control incidence and a positive trend for carcinomas. The male carcinoma incidence was also outside the historical control data provided by the submitting company. It was noted that about 50% of the significantly positive combined incidence was contributed by carcinomas. Also, there appears to be a progression towards malignancy across the dose groups.

Female mice had significant dose-related increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

Nonneoplastic changes in the liver were also observed in male mice at all dose levels. At the 200-ppm level, males had a significant increase in the incidence of focal cellular changes, large vacuoles, and swollen sinusoidal cells in the liver. At the highest dose tested, males also had a significantly increased incidence of pigmentation in the sinusoidal cells of the liver and focal cellular changes in the pancreas, increased absolute and relative liver weight, and decreased body weight and body weight gain. Female mice did not exhibit any cellular changes in the liver, although there was some effect on body weight at the 600-ppm dose and slight increases in liver weights at the highest dose tested as well.

There is extensive structure-activity relationship (SAR) support for the