

9.0 CONTINUATION SHEET
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Submitter Tracking Number/Internal ID

7106 4575 1292 0337 7777
01-2-13

Continuation of 2.1

This is a follow-up to 8EHQ-99-14489.

Reporting is based on the neoplasms in the reproductive organs (i.e., uterus and uterine metastasizing adenocarcinoma, Leydig cell adenoma, and focal Leydig cell hyperplasia).

Abstract

AMS 13630 was administered via the diet to Wistar rats (50 males and 50 females per dose), in doses of 0, 50, 100, 350, and 2500 ppm over a period of up to 108 weeks. In addition, male and female Wistar rats (10 animals per dose and sex) were treated likewise with AMS 13630 and sacrificed after a treatment period of about 1 year.

There were no treatment-related clinical signs. Mortality was decreased in males and increased in females (non-significantly) at 2500 ppm.

At 2500 ppm, body weight development was significantly retarded and body weight-related food consumption was slightly increased in both sexes. Water consumption for all treated rats was comparable to controls.

There were no treatment-related ocular effects.

There were no treatment-related hematology or blood coagulation effects.

Treatment-related clinical chemistry findings, which were observed in the 2500 ppm dose group, were: 1) an increase in alkaline phosphatase in both sexes, 2) a decrease in cholesterol and triglycerides in both sexes, and 3) increased thyroid stimulating hormone serum concentrations in females.

There were no treatment-related urinalysis effects.

After one year of treatment with AMS 13630, the following treatment-related histological findings were observed in the 2500 ppm dose group: 1) minimal to moderate cytoplasmic vacuolation (micro vesicular and/or large vacuoles) of the Zona fasciculata cells with an increase in the incidence and/or severity in males, 2) minimal to slight diffuse adrenocorticocellular hypertrophy in three males, 3) minimal to moderate increase in the ovarian stroma, and 4) no metestrus/diestrus based on the morphology of the vaginal epithelium.

At terminal necropsy, the following treatment-related non-neoplastic histological findings were increased in the 2500 ppm dose group: 1) vacuolated enterocytes in the jejunum in both sexes, 2) diffuse hypertrophy/vacuolation the Zona fasciculata cells in the adrenal cortex in males, 3) atrophy/degeneration of the olfactory epithelium in the nasal cavity in males, and 4) colloidal aberration in the thyroid gland in males.

At terminal necropsy, the following treatment-related non-neoplastic age-dependent histological findings were decreased in the 2500 ppm dose group: 1) arteritis/periarteritis in the blood vessels of various organs in males, 2) chronic progressive nephropathy in the kidneys (reduced severity in males; reduced incidence in females), 3) diffuse transitional cell hyperplasia in the renal pelvis in both sexes, 4) mineralization in the kidneys in females, 5) squamous cell hyperplasia of the uterine cervix (also present in the 100 and 350 ppm dose groups), 6) peliosis in the adrenal cortex in females, 7) focal hyperplasia in the adrenal medulla in females, 7) pigment deposits in spleen and mesenteric lymph node in both sexes, and 8) epithelial hyperplasia in the thymus in both sexes.

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At 2500 ppm, there was a higher incidence of neoplasms in reproductive organs (i.e., uterus and uterine metastasizing adenocarcinoma, Leydig cell adenoma, and focal Leydig cell hyperplasia).

At 2500 ppm, there was a decrease in: 1) pituitary gland adenomas (pars distalis) in both sexes and 2) fibroadenomas and lobular hyperplasia of the mammary gland in females.

Several treatment-related clinical chemistry, gross, and histopathological changes seen after treatment at 2500 ppm are seen in the context of the known interference of AMS 13630 with lipid and steroid metabolism: 1) decreased cholesterol and triglyceride plasma concentrations, 2) significantly increased alkaline phosphatase plasma activity, 3) increased incidence of vacuolated enterocytes in the jejunum, 4) adrenocorticocellular hypertrophy, 5) increased incidence and/or severity in the vacuolation of Zona fasciculata cells in the adrenal cortex, 6) increased ovarian stroma, 7) no metestrus/diestrus, 8) increased incidence of uterine adenocarcinomas, and 9) decrease in pituitary gland adenomas.

In conclusion, under the conditions described, the administration of AMS 13630 to male and female rats was tolerated without adverse effects up to and including 350 ppm.