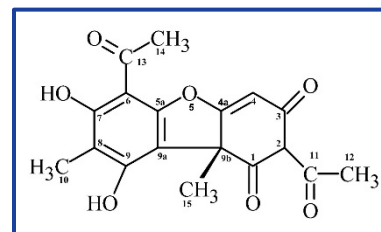


SUMMARY

Background: The complex chemical compound (+)-usnic acid is produced naturally by certain lichen species. It has been used in traditional medicines and marketed in the United States as an ingredient in dietary supplements claiming to promote weight loss. The U.S. Food and Drug Administration received reports that one such supplement appeared to be associated with adverse events affecting the liver, ranging in severity from mild hepatotoxicity (liver damage) to liver failure and death. In two companion NTP studies, the effects of 3-month dietary exposures to *Usnea* lichens (TOX-105) or (+)-usnic acid (the current report) were evaluated in male and female rats and mice to identify potential toxicity in humans.



Methods: Groups of 10 male and 10 female rats and mice were fed rodent feed containing (+)-usnic acid for 3 months at concentrations of 30, 60, 120, 360, and 720 parts per million (ppm) for rats and 15, 30, 60, 180, and 360 ppm for mice. Other groups were not exposed to the chemical and served as control animals (0 ppm). At the end of the study, tissues from more than 40 sites were examined for signs of disease. Systemic evaluations of body weight, survival, and female estrus cyclicity were also conducted.

Results: All rats in all exposure groups survived to the end of the study, and both male and female rats lost weight at the highest exposure concentration. Exposure to 120 ppm or higher led to hepatotoxicity in male rats only, as evidenced by increased incidence and severity of hepatocellular (liver) degeneration and hepatic inflammation. Female estrus length was extended in the highest exposure group. Survival and body weight were not affected in male or female mice from any exposure group, nor was estrus cycle disruption observed. However, moderate increases in serum creatinine, blood urea nitrogen, serum alanine aminotransferase, and alkaline phosphatase (indicators of liver toxicity) were observed in male mice. Damage to DNA was evident in male and female mice from a 2-week exposure to 600 ppm.

Conclusions: Under the conditions of this 3-month feed study, dietary exposure to (+)-usnic acid resulted in hepatotoxicity in male rats. (+)-Usnic acid was relatively nontoxic to female rats and male and female mice at the exposure concentrations used in this NTP study.
