SUMMARY

Background: Black cohosh (*Actaea racemose L.*) can be used as a botanical dietary supplement to alleviate female gynecological symptoms, such as premenstrual syndrome and changes associated with menopause, and to stimulate labor. Women may be exposed to black cohosh primarily through ingestion throughout their lifetime, including during pregnancy and lactation. To emulate a potential human exposure scenario in which a woman might use black cohosh throughout pregnancy and lactation, or throughout her lifetime, the effects of oral exposure to black cohosh root extract (BCE) in female rats (with exposure starting in utero) and female mice (with exposure starting in adolescence) were studied to identify potential toxicity or cancer-related outcomes.

Methods: Groups of 38 pregnant rats were orally administered 75, 250, or 750 milligrams (mg) BCE/kilogram (kg) body weight/day in methylcellulose throughout pregnancy and during the nursing of their offspring. Afterwards, groups of 50 female offspring were administered the same doses as their mothers for 2 years. Dosing did not continue in the 50 male offspring (i.e., they were exposed only during gestation and nursing). Fifty female mice were administered BCE at doses of 30, 100, 300, or 1,000 mg/kg/day for 2 years beginning in adolescence. Ten female mice per dose group were removed at 3 and 12 months for interim hematological (blood-related) evaluations and to assess the potential for BCE to damage DNA. Control animals for all studies were given methylcellulose alone with no chemical added (0 mg/kg/day BCE). At the end of each 2-year study, tissues from more than 40 sites from every animal were examined for signs of disease. Blood, bone marrow, and spleens from interim evaluation mice were collected and examined.

Results: Dosing of pregnant rats with BCE had no discernable effect on their health. During pregnancy and while nursing their offspring, dam body weights were marginally reduced in BCE-dosed groups. The number of offspring per dam was decreased in the highest dosed group. Both male and female offspring had reduced body weights across doses during and after the nursing period, which persisted to the end of the 2-year study. In the offspring exposed for 2 years, neoplasms (which can include benign or malignant growths) were observed in the uterus of female rats in the 250 mg/kg/day group. Other effects observed in rats exposed to BCE included lesions in the uterus and ovaries of females and forestomach (an organ that stores undigested food) of males. In female mice dosed with BCE, no effects on survival were observed, but body weights were lower with increasing dose. Female mice did not have dose-related neoplasms in any examined tissue. However, lesions were observed in the liver, thyroid gland, and vagina. Hematological changes associated with a condition called megaloblastic anemia [a blood disorder marked by the production of oversized red blood cells] were observed in mice from the 3- and 12-month interim evaluations. Tests to evaluate the potential for BCE to damage DNA were inconclusive.

Conclusions: *The NTP four-point scale rates the level of evidence that a substance has the ability to cause cancer in laboratory animals. Under the conditions of these 2-year gavage studies, there was equivocal (uncertain) evidence that BCE exposure has the ability to cause cancer in female rats, based on uterine neoplasms, and no evidence that it has the ability to cause cancer in male rats and female mice. In addition, BCE exposure caused increased incidences of lesions in the forestomach of male rats, the uterus and ovary of female rats, and the liver, thyroid gland, and vagina of female mice. The disruption of normal hematological processes was also observed in female mice at 3 and 12 months.*