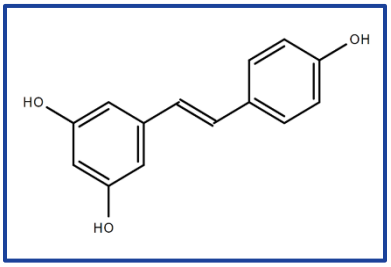
SUMMARY

Background: *Trans*-resveratrol is a naturally occurring compound found in various plants and plant-based products, such as red wine and dietary supplements. Humans are primarily exposed to *trans*-resveratrol via ingestion of these plant-based products. The compound is well known for its anti-inflammatory and antioxidant properties, which can provide health benefits; however, few studies have investigated whether exposure to trans-resveratrol has any harmful effects. In particular, the safety of *trans*-resveratrol use during pregnancy is unknown. NTP studied the effects of *trans*-resveratrol in male and female rats (including exposure during pregnancy) and mice to identify potential toxicity that could be relevant to humans. An oral route of exposure was chosen because human exposure occurs primarily through ingestion.



Methods: Groups of rats and mice were orally administered doses of *trans*-resveratrol mixed into 0.5% aqueous methylcellulose (a neutral substance) by gavage. The final doses were selected on the basis of preliminary 2-week studies. Groups of pregnant rats were administered doses of 78, 156, 312.5, 625, or 1,250 milligrams (mg) of *trans*-resveratrol per kilogram (kg) of body weight per day (mg/kg/day) during pregnancy and lactation. After weaning, randomly selected groups of 10 male and 10 female rat offspring were administered the same dose as their mother for 3 months. Separately, groups of 10 nonpregnant adult female mice and 10 adult male mice were administered *trans*-resveratrol doses of 156, 312, 625, 1,250, or 2,500 mg/kg/day for 3 months. Control animals for all studies were orally administered methylcellulose alone, with no chemical added (0 mg/kg/day *trans*-resveratrol). Body weight measurements and clinical observations were taken during the studies. At the end of the studies, tissues from more than 40 organs were examined for signs of disease in all control and high-dose animals. Affected organs were further examined in all dose groups.

Results: Pregnant rats in the dose groups administered 156 mg/kg/day or higher *trans*-resveratrol gained weight more slowly and had lower body weights compared to the control group. Male and female rat offspring in the highest dose groups 312.5 mg/kg/day or higher) temporarily had lower body weights than the control groups during lactation, although body weights were similar across dose groups by the end of the study. Noncancerous tissue abnormalities were observed in the kidneys and small intestines of male and female rat offspring. Male mice in the highest dose group and female mice in dose groups administered 625 mg/kg/day or more had increased liver weights. Female mice in dose groups administered 1,250 mg/kg/day or more had increased kidney weights and female mice in dose groups administered 625 mg/kg/day or more had increased incidences of noncancerous tissue abnormality in the nose (i.e., respiratory metaplasia in the olfactory epithelium). Tests evaluating the potential for *trans*-resveratrol to damage DNA were negative.

Conclusions: *Under the conditions of the 3-month studies, oral administration of trans-resveratrol resulted in noncancerous tissue abnormalities in the kidney and small intestine of rats and in the nose of mice. Lower body weights were observed in pregnant rats and rat offspring administered trans-resveratrol but not in adult mice. Changes in several organ weights were observed in adult mice. Effects related to trans-resveratrol were seen at doses 312.5 mg/kg/day or more in rats and 625 mg/kg/day or more in adult mice. No clear effects on reproductive health were observed, and there was no evidence of genetic toxicity.*