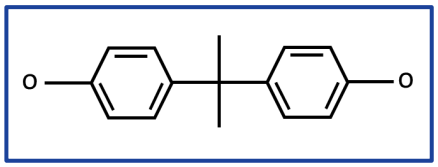
SUMMARY

Background: Bisphenol A (BPA) is an industrial chemical commonly used in plastics and resins, which has led to widespread, low-level exposure among humans. BPA exposure has been associated with health problems including infertility, weight gain, behavioral changes, early-onset puberty, prostate and mammary gland cancers, cardiovascular effects, and diabetes. The Consortium Linking Academic and Regulatory Insights on BPA Toxicity (CLARITY-BPA) is a multi-agency research program developed to address knowledge gaps and identify new methods or endpoints that could be relevant for understanding the potential human health effects of BPA exposure. This program has two research components, a "core" long-term study conducted at the National Center for Toxicological Research and a set of additional studies conducted by academic researchers using rats that were siblings of those used in the core study. This report focuses only on data from the first component, the core 2-year chronic study of potential BPA toxicity in rats.



Methods: The core study was conducted according to regulatory guidelines for toxicity testing. Pregnant rats were orally dosed with BPA at levels of 2.5, 25, 250, 2,500, or 25,000 micrograms per kilogram of body weight (µg/kg-bw) per day, starting 6 days after conception and continuing through the start of labor. The offspring were then divided into two groups and orally dosed with the same BPA dose daily, either continuously for 2 years (referred to as the "continuous-dose" group) or until the offspring stopped nursing at 21 days after birth (the "stop-dose" group). Results from the stop-dose group were used to assess the effects of early-life exposure to BPA. The continuous-dose group study also included pregnant rats and offspring that received 0.05 or 0.5 µg ethinyl estradiol/kg-bw per day. Ethinyl estradiol is a synthetic estrogen with well-known effects, and this component of the study allowed for comparison of the animals' responses with BPA exposure to the effects of the hormone. Naive rats (no treatment) and rats orally dosed with the vehicle only were included as controls. During the course of the study, samples were collected to examine a variety of parameters, including body weights, littering factors, age at vaginal opening, cell health in the vaginal lining, sperm factors, organ weights, and blood chemistry.

Results: Few treatment-related effects were observed following chronic exposure to BPA, in contrast with the estrogenic effects observed after exposure to ethinyl estradiol, which included a clear effect on the female mammary gland and reproductive tract. At the highest dose of BPA (25,000 µg/kg-bw), possible treatment-related effects were observed in both the continuous and stop-dose groups in the female reproductive tract (ovary, uterus, and vagina) and in the male pituitary (important gland located at the base of the brain). At lower BPA doses, some increases or decreases in the incidence of neoplastic lesions and noncancerous tissue abnormalities (e.g., apoptosis [cell death], hyperplasia [increased cell growth], inflammation) were statistically different from those in the vehicle control, including an increased occurrence of mammary tumors in the stop-dose lowest BPA group, but the response patterns were inconsistent across dose groups.

Conclusions: *Chronic oral exposure to BPA for up to 2 years resulted in few treatment-related effects in rats. BPA exposures below 25,000 µg/kg-bw per day did not present a clear pattern of consistent responses across doses within or across organs in the continuous- and stop-dose groups that would indicate an association with BPA exposure. Effects observed in the female reproductive tract and male pituitary at 25,000 µg BPA/kg-bw per day, however, may have been treatment related.*