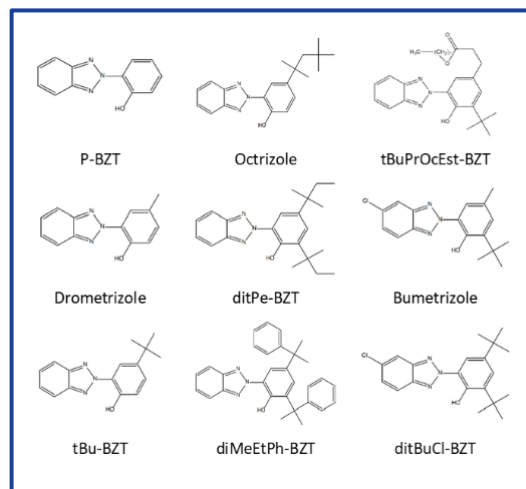


SUMMARY

Background: Phenolic benzotriazoles (PBZTs) are chemical additives used to protect industrial and consumer products from ultraviolet (UV) degradation. Due to their high production volumes, widespread use, and potential occupational and general public exposure, toxicity studies were conducted since limited toxicological data are available for many of these compounds. The effects of oral exposure to nine PBZTs in male rats were studied to identify potential toxicity that could be relevant to humans. The nine PBZTs selected for these studies included: 2-(2H-benzotriazol-2-yl)phenol (**P-BZT**); 2-(2H-benzotriazol-2-yl)-4-methylphenol (**drometrizole**); 2-(2H-benzotriazol-2-yl)-4-tert-butylphenol (**tBu-BZT**); 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol (**octrizole**); 2-(2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylpropyl)phenol (**ditPe-BZT**); 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (**diMeEtPh-BZT**); 3-(2H-benzotriazol-2-yl)-5-(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid, octyl ester (**tBuPrOcEst-BZT**); 2-(5-chloro-2H-1,2,3-benzotriazol-2-yl)-6-(1,1-dimethylethyl)-4-methylphenol (**bumetrizole**); and 2-(5-chloro-2H-benzotriazol-2-yl)-4,6-bis(1,1-dimethylethyl)phenol (**ditBuCl-BZT**).



Methods: Groups of five male rats were orally administered 0, 30, 100, 300, or 1,000 milligrams per kilogram body weight per day (mg/kg/day) of P-BZT, drometrizole, tBu-BZT, octrizole, ditPe-BZT, diMeEtPh-BZT, tBuPrOcEst-BZT, bumetrizole, or ditBuCl-BZT in 0.5% aqueous methylcellulose via gavage for 2 weeks. Control animals received 0.5% aqueous methylcellulose with no chemical added (0 mg/kg/day). Body weight measurements were recorded throughout the study and clinical observations were recorded daily. Organ weights were measured and livers and kidneys were analyzed for gene expression changes after the 2-week exposure. Blood samples were evaluated for changes in clinical pathology (clinical measures in the blood) and to assess plasma concentrations of each PBZT. Tissues from nine sites from every animal were examined for signs of disease.

Results: There was no effect on survival in rats administered any of the nine PBZTs. Lower body weights were observed in rats administered tBuPrOcEst-BZT. Liver toxicity was observed in rats administered seven of the nine PBZTs, with varying degrees of severity. Increased liver weights and lesions, such as hepatocyte hypertrophy (an increase in the size of individual liver cells), were observed in the P-BZT, drometrizole, and tBu-BZT rat groups. Rats administered ditPe-BZT, tBuPrOcEst-BZT, and ditBuCl-BZT also showed increased liver weights and increased incidences of hepatocyte hypertrophy, accompanied by changes in serum biomarkers and liver gene expression. Rats administered bumetrizole had increased liver weights, with no other observed changes. Minimal to no effects were observed in rats administered octrizole or diMeEtPh-BZT. In addition, increases in kidney weights and lesions in kidney tissues were observed in rats administered tBuPrOcEst-BZT. Rats administered P-BZT, ditPe-BZT, and ditBuCl-BZT also exhibited increases in kidney weights. Tests evaluating the potential for PBZTs to damage DNA were mostly negative, except in rats administered tBuPrOcEst-BZT, which were equivocal.

Conclusions: Under the conditions of these 2-week gavage studies, oral administration of seven out of nine phenolic benzotriazoles resulted in toxicological effects on the liver, characterized by increased liver weights, hepatocyte hypertrophy, and alterations in liver-related gene expression. The most potent liver toxicants were ditPe-BZT, tBuPrOcEst-BZT, and ditBuCl-BZT, with effects observed at the lowest tested dose of 30 mg/kg/day. Kidney effects were also observed in rats administered tBuPrOcEst-BZT, which exhibited an increased incidence of lesions and increased kidney weights. Kidney weight increases occurred following administration of three other PBZTs without corresponding lesions. PBZTs will require further study to better understand the differential responses across the class as observed here.