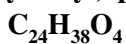


Di (2-ethylhexyl) phthalate



[CAS No. 117-81-7]

Reproductive toxicant: Group 1

Cohort studies conducted by different research groups have shown positive associations between exposure to di (2-ethylhexyl) phthalate (DEHP) and increased pregnancy loss or incidence of preterm birth with dose-response relationships¹⁻⁷⁾. In addition, deteriorating effects on neurobehavioral endpoints in the second generation⁸⁻¹⁴⁾ and semen indices¹⁵⁻²²⁾ are consistently observed in general. Many animal studies have shown reproductive effects including testicular toxicity and increased fetal death²³⁻²⁸⁾. Based on this evidence, DEHP is classified as a Group 1 reproductive toxicant. The current occupational exposure limit (OEL) of DEHP was set based on epidemiological and animal studies conducted before the 1990s, in which the calculated no-observed-adverse-effect level (NOAEL) were 508 mg/m³ (65 mg/kg/day) for rats and 468 mg/m³ (60 mg/kg/day) for dogs. However, a recent human study showed an exposure-associated change in sperm indices at 110.6 µg/m³ of DEHP under occupational exposure, and treatments with DEHP 10 mg/kg/day during pregnancy reportedly induced fetal effects in rats. Thus, precautions should be taken to prevent the reproductive toxicity of this substance even if exposure levels are at or below the current OEL-M.

References

- 1) Toft G, Jönsson BA, Lindh CH, et al. Association between pregnancy loss and urinary phthalate levels around the time of conception. *Environ Health Perspect* 2012; 120: 458-63.
- 2) Ferguson KK, McElrath TF, Meeker JD. Environmental phthalate exposure and preterm birth. *JAMA Pediatr* 2014; 168: 61-7.
- 3) Ferguson KK, McElrath TF, Ko YA, Mukherjee B, Meeker JD. Variability in urinary phthalate metabolite levels across pregnancy and sensitive windows of exposure for the risk of preterm birth. *Environ Int* 2014; 70: 118-24.
- 4) Latini G, De Felice C, Presta G et al. In utero exposure to di-(2-ethylhexyl)phthalate and duration of human pregnancy. *Environ Health Perspect* 2003; 111: 1783-5.
- 5) Meeker JD, Hu H, Cantonwine DE, et al. Urinary phthalate metabolites in relation to preterm birth in Mexico city. *Environ Health Perspect* 2009; 117: 1587-92.
- 6) Whyatt RM, Adibi JJ, Calafat AM et al. Prenatal di(2-ethylhexyl)phthalate exposure and length of gestation among an inner-city cohort. *Pediatrics* 2009; 124: e1213-20.
- 7) Huang Y, Li J, Garcia JM et al. Phthalate levels in cord blood are associated with preterm delivery and fetal growth parameters in Chinese women. *PLoS One* 2014; 9: e87430.
- 8) Swan SH, Liu F, Hines M, et al. Prenatal phthalate exposure and reduced masculine play in boys. *Int J Androl* 2010; 33: 259-69.
- 9) Yolton K, Xu Y, Strauss D, Altaye M, Calafat AM, Khoury J. Prenatal exposure to bisphenol A and phthalates and infant neurobehavior. *Neurotoxicol Teratol* 2011; 33: 558-66.
- 10) Engel SM, Zhu C, Berkowitz GS, et al. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. *Neurotoxicology* 2009; 30: 522-8.
- 11) Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ Health Perspect* 2010; 118: 565-71.
- 12) Kim Y, Ha EH, Kim EJ, et al. Prenatal exposure to phthalates and infant development at 6 months: prospective Mothers and Children's Environmental Health (MOCEH) study. *Environ Health Perspect* 2011; 119: 1495-500.
- 13) Polanska K, Ligocka D, Sobala W, Hanke W. Phthalate exposure and child development: The Polish Mother and Child Cohort Study. *Early Hum Dev* 2014; 90: 477-85.
- 14) Téllez-Rojo MM, Cantoral A, Cantonwine DE et al. Prenatal urinary phthalate metabolites levels and neurodevelopment in children at two and three years of age. *Sci Total Environ* 2013; 461-2: 386-90.
- 15) Huang LP, Lee CC, Hsu PC, Shih TS. The association between semen quality in workers and the concentration of di(2-ethylhexyl) phthalate in polyvinyl chloride pellet plant air. *Fertil Steril* 2011; 96: 90-4.
- 16) Huang LP, Lee CC, Fan JP, Kuo PH, Shih TS, Hsu PC. Urinary metabolites of di(2-ethylhexyl) phthalate relation to sperm motility, reactive oxygen species generation, and apoptosis in polyvinyl chloride workers. *Int Arch Occup Environ Health* 2014; 87: 635-46.
- 17) Pan G, Hanaoka T, Yoshimura M et al. Decreased serum free testosterone in workers exposed to high levels of di-n-butyl phthalate (DBP) and di-2-ethylhexyl phthalate (DEHP): a cross-sectional study in China. *Environ Health Perspect* 2006; 114: 1643-8.
- 18) Specht IO, Toft G, Hougaard KS, et al. Associations between serum phthalates and biomarkers of reproductive function in 589 adult men. *Environ Int* 2014; 66: 146-56.
- 19) Jurewicz J, Radwan M, Sobala W, et al. Human urinary phthalate metabolites level and main semen parameters, sperm chromatin structure, sperm aneuploidy and reproductive hormones. *Reprod Toxicol* 2013; 42: 232-41.
- 20) Joensen UN, Frederiksen H, Jensen MB et al. Phthalate excretion pattern and testicular function: a study of 881 healthy Danish men. *Environ Health*

- Perspect 2012; 120: 1397–403.
- 21) Han X, Cui Z, Zhou N, et al. Urinary phthalate metabolites and male reproductive function parameters in Chongqing general population, China. *Int J Hyg Environ Health* 2014; 217: 271–8.
 - 22) Liu L, Bao H, Liu F, Zhang J, Shen H. Phthalates exposure of Chinese reproductive age couples and its effect on male semen quality, a primary study. *Environ Int* 2012; 42: 78–83.
 - 23) Gangolli SD. Testicular effects of phthalate esters. *Environ Health Perspect* 1982; 45: 77–84.
 - 24) Akingbemi BT, Ge R, Klinefelter GR, Zirkin BR, Hardy MP. Phthalate-induced Leydig cell hyperplasia is associated with multiple endocrine disturbances. *Proc Natl Acad Sci USA* 2004; 101: 775–80.
 - 25) Shiota K, Nishimura H. Teratogenicity of di(2-ethylhexyl) phthalate (DEHP) and di-n-butyl phthalate (DBP) in mice. *Environ Health Perspect* 1982; 45: 65–70.
 - 26) Lamb JC 4th, Chapin RE, Teague J, Lawton AD, Reel JR. Reproductive effects of four phthalic acid esters in the mouse. *Toxicol Appl Pharmacol* 1987; 88: 255–69.
 - 27) Christiansen S, Boberg J, Axelstad M, et al. Low-dose perinatal exposure to di(2-ethylhexyl) phthalate induces anti-androgenic effects in male rats. *Reprod Toxicol* 2010; 30: 313–21.
 - 28) Hayashi Y, Ito Y, Yamagishi N et al. Hepatic peroxisome proliferator-activated receptor α may have an important role in the toxic effects of di(2-ethylhexyl)phthalate on offspring of mice. *Toxicology* 2011; 289: 1–10.