DIISONONYL PHTHALATE (DINP)

Diisononyl phthalate (DINP) is a mixture of isomeric compounds that are branched alkyl di-ester phthalates of 1,2-benzenedicarboxylic acid, in which the alkyl ester moieties contain a total of nine carbons. DINP is used as a plasticizer, especially in the production of polyvinyl chloride (PVC). It is not bound to the PVC plastic, and is released over time into the environment. DINP is used in a broad range of consumer products, including coated fabrics, electrical insulation, vinyl flooring, wood veneer, carpet backing, artificial leather, shoes, sealants, gloves, tubing, garden hoses, pool liners, and tarps. Workers are exposed during the manufacture of DINP and the manufacture and processing of DINP-containing products. The general population is exposed through the use of products containing DINP, and through environmental exposures.

DINP passed the animal data screen, underwent a preliminary toxicological evaluation, and is being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

No cancer epidemiology studies were identified.

Animal carcinogenicity data

- Long-term diet studies of DINP in rats
  - Two-year studies in male and female Fischer 344 rats: Moore (1998a) / Covance, as described in CPSC (2001, pp. 67-70) and Babich *et al*. (2004, pp. 156-157)
  - Two-year studies in male and female Fischer 344 rats: Lington *et al*. (1997), also described in CPSC (2001, pp. 70-71) and Babich *et al*. (2004, pp. 156- 157)

- Long-term diet studies of DINP in mice
  - Two-year studies in male and female B6C3F_1 mice: Moore (1998b) / Covance, as described in CPSC (2001, pp. 72-73) and Babich *et al*. (2004, pp. 156-157)

- Long-term diet studies of Saniticizer 900 (a 99.9% pure mixture of dinonyl phthalates)
  - Two-year studies in male and female Sprague-Dawley CD rats: Bio/dynamics (1986), as described in CPSC (2001, pp. 74-77)

Other relevant data

- Genotoxicity
  - Review: Babitch *et al*. (2004, p. 154)

- Effects on testosterone synthesis: Borch *et al.* (2004); Babich *et al*. (2004, p. 158)

- Structure activity considerations
  - DINP is similar in structure, metabolism, anti-androgen activity in fetal male rats, and tumor induction to the Proposition 65 carcinogen di-(2-ethylhexyl)phthalate (DEHP): CPSC (2001, pp. 77-78)
  - Similar in structure, metabolism, and tumor induction with other phthalates: CPSC (2001, pp. 77-78)

- Mechanisms
  - Testicular dysgenesis syndrome: Borch *et al*. (2004)
  - Peroxisome proliferator-activated receptor α (PPARα) agonism: Ito *et al*. (2007), Takashima *et al.* (2008), Yang *et al.* (2007), Babich *et al*. (2004), Kaufmann *et al*. (2002), Valles *et al*. (2003)

Reviews

- Fed Reg (2000)

- CPSC (2001)

- Babich *et al*. (2004)

References[1]

Babich MA, Chen SB, Greene MA, Kiss CT, Porter WK, Smith TP, Wind ML, Zamula WW (2004). Risk assessment of oral exposure to diisononyl phthalate from children's products. *Regul Toxicol Pharmacol* **40**:151-67.

Borch J, Ladefoged O, Hass U, Vinggaard AM (2004). Steroidogenesis in fetal male rats is reduced by DEHP and DINP, but endocrine effects of DEHP are not modulated by DEHA in fetal, prepubertal and adult male rats. *Reprod Toxicol* **18**:53-61.

Consumer Product Safety Commission (CPSC, 2001). Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Diisononyl

[1] Copies of these listed references, as either the abstract, the relevant sections of the publication, or the complete publication, have been provided to members of the Carcinogen Identification Committee. These references have been provided in the order in which they are discussed in this document.

Phthalate (DINP). June 2001. U.S. CPSC, Directorate for Health Sciences, Bethesda, Maryland.

Federal Register (Fed Reg, 2000). Addition of Diisononyl Phthalate Category; Community Right-to-Know Toxic Chemical Release Reporting. Environmental Protection Agency. Proposed Rule. Vol. 65, No. 172:53681-89. September 5, 2000.

Ito Y, Yamanoshita O, Asaeda N, Tagawa Y, Lee C-H, Aoyama T, Ichihara G, Furuhashi K, Kamijima M, Gonzalez FJ, Nakajima T (2007). Di(2-ethylhexyl)phthalate induces hepatic tumorigenesis through a peroxisome proliferator-activated receptor α-independent pathway. *J Occup Health* **49**:172-182.

Kaufmann W, Deckardt K, McKee RH, Butala JH, Bahnemann R (2002). Tumor induction in mouse liver: di-isononyl phthalate acts via peroxisome proliferation. *Regul Toxicol Pharmacol* **36**:175-83.

Lington AW, Bird MG, Plutnick RT, Stubblefield WA, Scala RA (1997). Chronic toxicity and carcinogenic evaluation of diisononyl phthalate in rats. *Fund Appl Toxicol* **36**:79-89.

Takashima K, Ito Y, Gonzalez FJ, Nakajima T (2008). Different mechanisms of DEHP-induced hepatocellular adenoma tumorigenesis in wild-type and *Pparα*-null mice. *J Occup Health* **50**:169-80.

Valles EG, Laughter AR, Dunn CS, Cannelle S, Swanson CL, Cattley RC, Corton JC (2003). Role of the peroxisome proliferator-activated receptor alpha in responses to diisononyl phthalate. *Toxicology* **191**:211-25.

Yang Q, Ito S, Gonzalez FJ (2007). Hepatocyte-restricted constitutive activation of PPARα induces hepatoproliferation but not hepatocarcinogenesis. *Carcinogenesis* **28**:1171-1177.