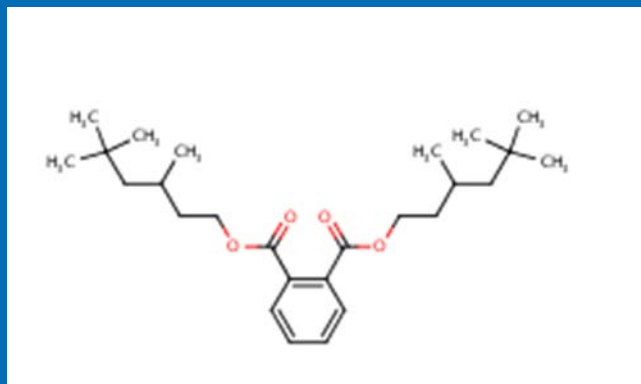


# Preliminary Materials for the IRIS Assessment of Diisononyl Phthalate

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## General Information

- DINP is used in the production of plastics, mostly polyvinyl chloride products (PVC), to increase flexibility
  - Flooring, roofing, wall coverings, hoses, tubing, wires, cables, footwear, car undercoatings, toys, and food contact plastics
- Formulations of DINP are typically a mixture of isomers with an average side chain length of nine carbons
- DINP is currently being used as a substitute for di-2-ethyl hexyl phthalate (DEHP)

## General Information

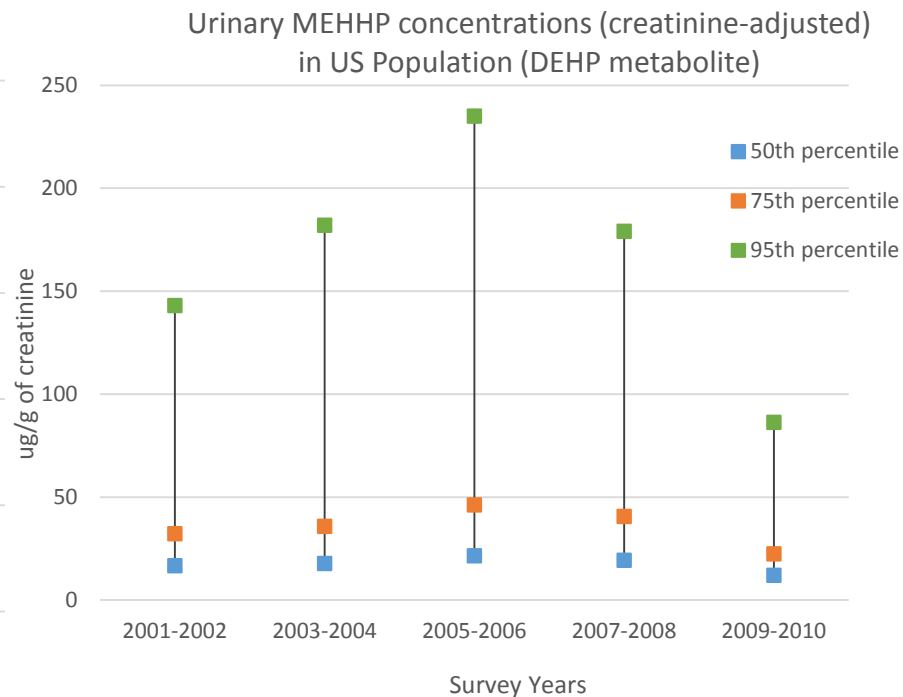
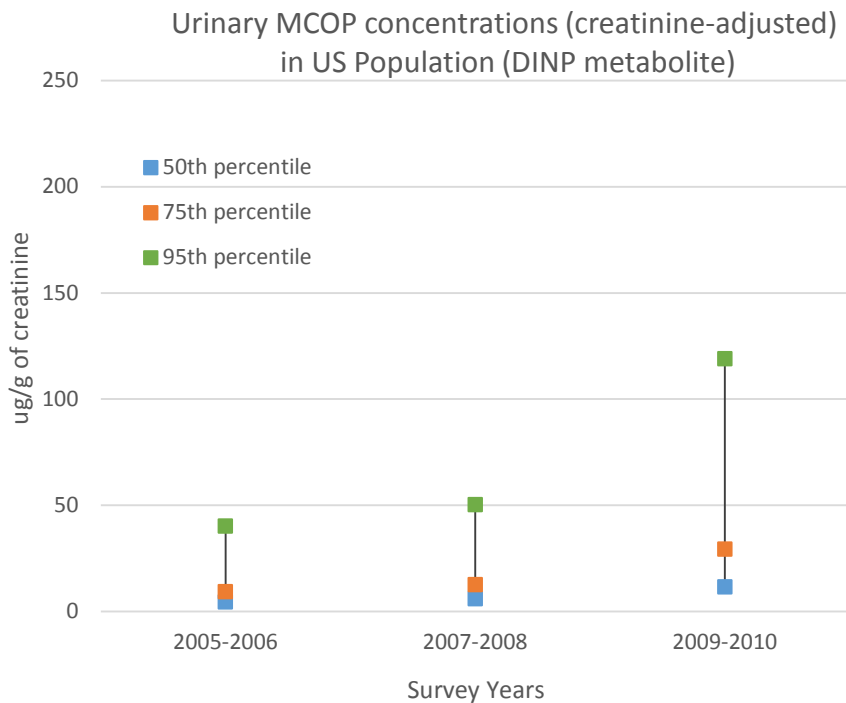
- Multiple entities have evaluated the health effects associated with exposure to DINP, including:
  - 2014, Consumer Product Safety Commission (CPSC) Chronic Hazard Advisory Panel (CHAP) on Phthalates and Phthalate Alternatives report
  - 2013, European Chemicals Agency
  - 2003, European Union
  - 2003, NIH/NIEHS/Center for the Evaluation of Risks to Human Reproduction
  - 2001, CPSC CHAP on DINP

## Exposure

- Exposure to DINP occurs primarily through the oral route, and to a lesser extent, through inhalation and dermal routes
  - Phthalate metabolites have been detected in saliva, urine, amniotic fluid, and breast milk in humans
  - Metabolism: first to MINP and then to secondary metabolites
- NHANES data indicates that DINP metabolite concentrations are increasing in US population, paralleling the decline in DEHP metabolites in the population



# Trends in DINP and DEHP Metabolite Concentrations in Humans



## **The evidence tables present data for the following potential hazards:**

- Reproductive and developmental effects
- Thyroid effects
- Immune effects
- Obesity effects
- Liver effects
- Kidney effects
- Hematopoietic effects

# DINP Science Issues for the October IRIS Bimonthly Meeting

- Liver effects, including spongiosis hepatitis
- Male reproductive effects
- Human relevance of testicular xenograft studies
- Human relevance of mononuclear cell leukemia
- Transparency and utility of mechanistic data

# Science Question 1: Liver effects, including spongiosis hepatitis

- Oral exposure to DINP results in increases in liver weight, serum liver enzyme levels, and histopathological effects
- A dose-dependent increase in the incidence of spongiosis hepatitis, also described as cystic degeneration (Lington et al., 1997; Covance, 1998b; Bio/Dynamics, 1986)
- The classification of spongiosis hepatitis/cystic degeneration as either a preneoplastic or neoplastic change has been the subject of scientific debate (Bannasch, 2003; Karbe and Kerlin, 2002)

**EPA is seeking public discussion of DINP-induced spongiosis hepatitis and other liver effects.**





## Science Question 2: Male reproductive effects

- Various experimental studies report evidence for DINP-induced phthalate syndrome effects in rats
- However, some malformations included in the phthalate syndrome (e.g., hypospadias and cryptorchidism) have not been observed

**EPA is seeking public comment on the evidence for DINP-induced male reproductive toxicity.**

# Related Science Question 2: Male reproductive effects

Related question suggested by Douglass Weed, (DLW Consulting Services, LLC.), on behalf of the American Chemistry Council High Phthalates Panel:

- A phthalate syndrome response is not consistently identified in rats exposed to phthalates versus human epidemiology studies
- How can the results from two epidemiological studies that focus on DINP (Joensen et al., 2013; Jurewicz et al., 2013) be used to understand the significance of the DINP induced male rat reproductive effects and their human relevance?

# Science Question 3: Human relevance of testicular xenograft studies

- Studies using human testicular tissue xenografts and ex-vivo tissue culture preparations have raised questions about the human relevance of some of the testes-specific endpoints measured in rodents exposed to phthalates
- Recent reviews have suggested limitations in these studies, including:
  - Variability in the human population
  - Sample size
  - Gestational age of the human tissues

**EPA is seeking public discussion of the relevance of the xenograft and ex-vivo tissue studies.**



# Science Question 4: Human relevance of mononuclear cell leukemia

- Experimental studies have reported that DINP exposure is associated with increased incidences of mononuclear cell leukemia (MNCL) in rats
- The human relevance of MNCLs observed in animals has been a topic of scientific debate

**EPA is seeking public discussion of the human relevance of MNCL in rats following exposure to DINP.**

# Science Question 5: Transparency and utility of mechanistic data

- The preliminary materials include an inventory of mechanistic data intended to facilitate subsequent identification of potential mode(s) of action and development of adverse outcome pathways for the health effects of DINP

**EPA is seeking public discussion on the following:**

- **Transparency and utility of the presentation of mechanistic data**
- **How mechanistic data can inform the hazard identification and dose-response analysis for each hazard?**