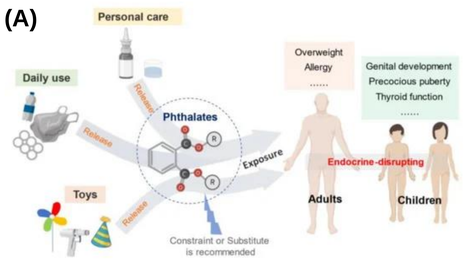
Sex-Specific Expression of Phthalate-Metabolizing Enzymes in the Livers of CD-1 Mice Following DEHP Exposure

Ashley Parker[1,3], Dustin Rehnke[1,3], Maile McSwain[3], and Estela J. Jauregui[2,3]
Arizona College of Osteopathic Medicine[1], Department of Physiology[2], Midwestern University[3], Glendale, AZ.

Introduction

- Di-2-ethylhexyl phthalate (DEHP) is a phthalate family member known for its potent endocrine-disrupting properties.
- DEHP is commonly added to plastics to make them flexible and is found in many consumer products, including medical devices, food packaging, and personal care products.
- Exposure to DEHP can occur through inhalation, ingestion, or dermal contact with DEHP-containing products.
- Chronic exposure has been linked to a range of adverse health outcomes, particularly affecting reproductive and developmental health.
- Being lipophilic, DEHP persists in the environment, leading to prolonged effects even at low-level exposures.
- This study highlights potential sex differences in susceptibility to toxic effects from DEHP exposure.

(A)



(B)

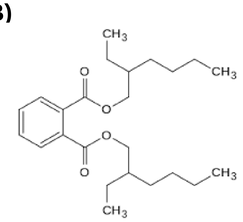


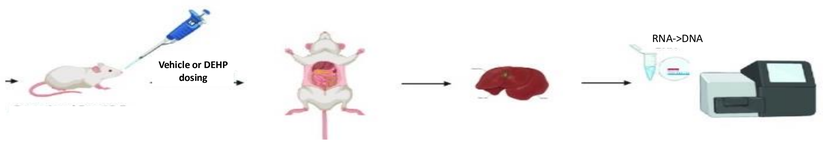
Figure 1: Di-2-ethylhexyl phthalate (DEHP) is commonly found in a wide range of consumer products, with exposure linked to significant health impacts, particularly concerning reproductive and developmental outcomes (A). The chemical structure of Di-2-ethylhexyl phthalate (DEHP) is illustrated in panel (B).

Objective

Investigate sex differences in DEHP metabolism in the livers of male and female CD-1 mice.

Methods

- 60-day-old CD-1 mice were administered corn oil (vehicle control) or DEHP at doses of 20 µg/kg/day, 200 µg/kg/day, or 1000 mg/kg/day via mouth pipetting for 12 days in males and 10-14 consecutive days in females.
- Two hours after the final treatment, liver tissues were dissected and snap-frozen for further analysis.
- Hepatic mRNA was then isolated from the frozen liver samples and converted into complementary DNA for subsequent analysis.
- Quantitative PCR (qPCR) was performed to examine key genes involved in DEHP metabolism, specifically *Adh1*, *Aldh1a1*, *Iah1, and Tbp (housekeeping gene).*



Results

Female vs. Male

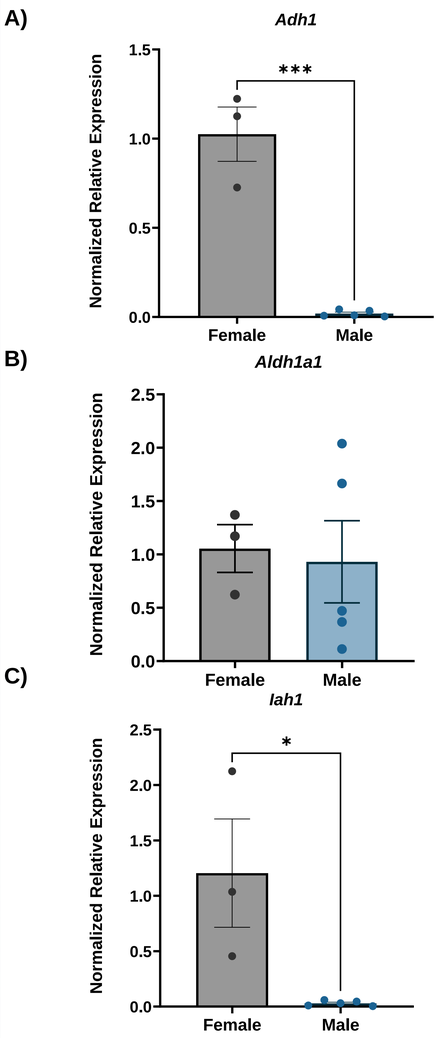


Figure 2: Differences in the expression of key phthalate-metabolizing enzymes, *Aldh1a1* **(A)**, *Adh1* **(B)**, and *Iah1* **(C),** normalized to *Tbp* in male and female mice under vehicle control conditions, as measured by qPCR. Significant increases in hepatic expression ($p < 0.05$) are indicated by an asterisk (*).

Female Liver

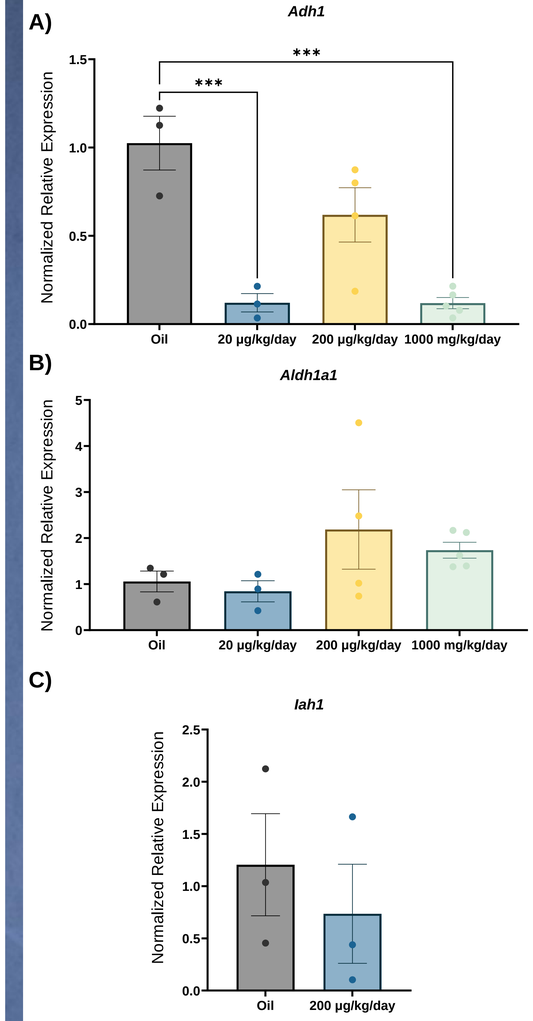


Figure 3: Differences in the expression of key phthalate-metabolizing enzymes, *Adh1* **(A),** *Aldh1a1* **(B),** and *Iah1* **(C)**, normalized to *Tbp* in female mice after receiving either vehicle (corn oil) or DEHP at doses of 20 µg/kg/day, 200 µg/kg/day, or 1000 mg/kg/day, as measured by qPCR. Significant changes ($p < 0.05$) are indicated by an asterisk (*).

Male Liver

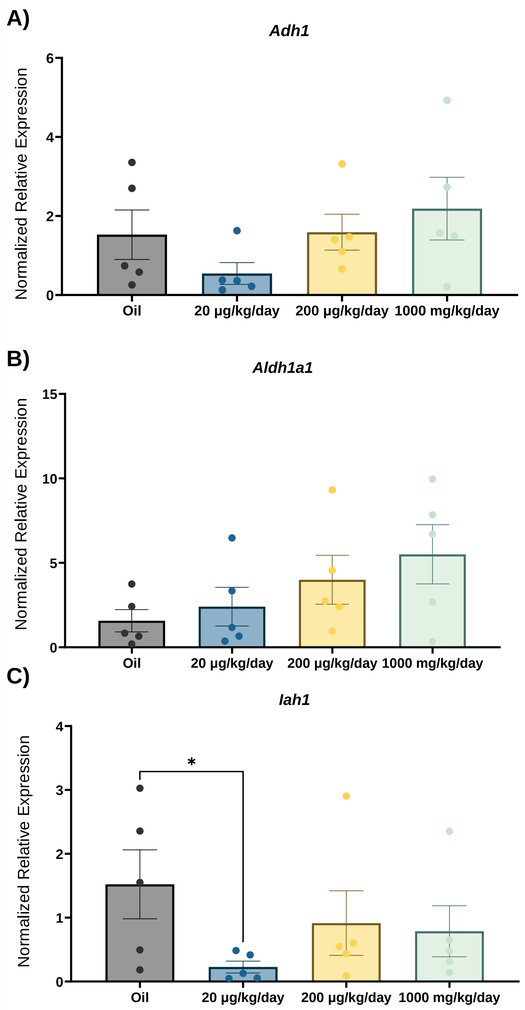


Figure 4: Differences in the expression of phthalate-metabolizing enzymes, *Iah1* **(A),** *Aldh1a1* **(B),** and *Adh1* **(C),** normalized to *Tbp* in male mice after receiving either vehicle (corn oil) or DEHP at doses of 20 µg/kg/day, 200 µg/kg/day, or 1000 mg/kg/day, as measured by qPCR. Significant changes ($p < 0.05$) are indicated by an asterisk (*).

Conclusions

- There were differences in the gene expression of liver enzymes involved in phthalate metabolism between female and male mice.
- Higher expression of *Adh1* and *Iah1* in female mice may increase their susceptibility to adverse health effects from DEHP exposure, including menstrual cycle dysregulation, fertility issues, hormone-dependent cancers, and overall well-being concerns due to these enzymes' key roles in DEHP metabolism.
- Potential adverse health effects for both sexes include liver damage and endocrine disruption.
- Understanding these sex differences is crucial for accurate risk assessment and the development of tailored public health strategies to reduce exposure and safeguard overall health.

Acknowledgements

Midwestern University Startup Funding (EJ).

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