Prenatal Exposure to Phthalates and Cord Blood Mononuclear Cell DNA Methylation

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Introduction

• Phthalates are ubiquitous industrial plasticizers. Routes for human exposure include diet, inhalation, and dermal exposure.

• Prenatal exposure to phthalates may affect DNA methylation levels and lead to adverse developmental outcomes in children.

• This study investigated the association between prenatal phthalates exposure and cord blood mononuclear cell (CMBC) methylation in infants.

Methods

• We used data from 12 mother-newborn dyads in a Center for Environmental Genetics pilot project that enrolled pregnant women at delivery in the University of Cincinnati Medical Center.

• We included 13 metabolites of phthalates and phthalate alternatives: mBP, mBzP, mCNP, MCOCH, mCOP, mCPP, MECPTP, MEHHTP, mEP, MHiNCH, miBP, mNP, MONP measured in maternal urine samples except DEHP metabolites that were deemed too high due to potential tube-related exposure in the delivery unit (Table).

• We associated phthalate metabolites with cord blood DNA methylation (Illumina 450K Methylation Beadchip) to identify differentially methylated regions (DMR) for each creatinine-standardized phthalate metabolite.

• We adjusted for maternal age, race, smoking status, gestational age, and infant sex.

• We selected the top 10 significant DMRs for each phthalate metabolite, with a false discovery rate of 0.1.
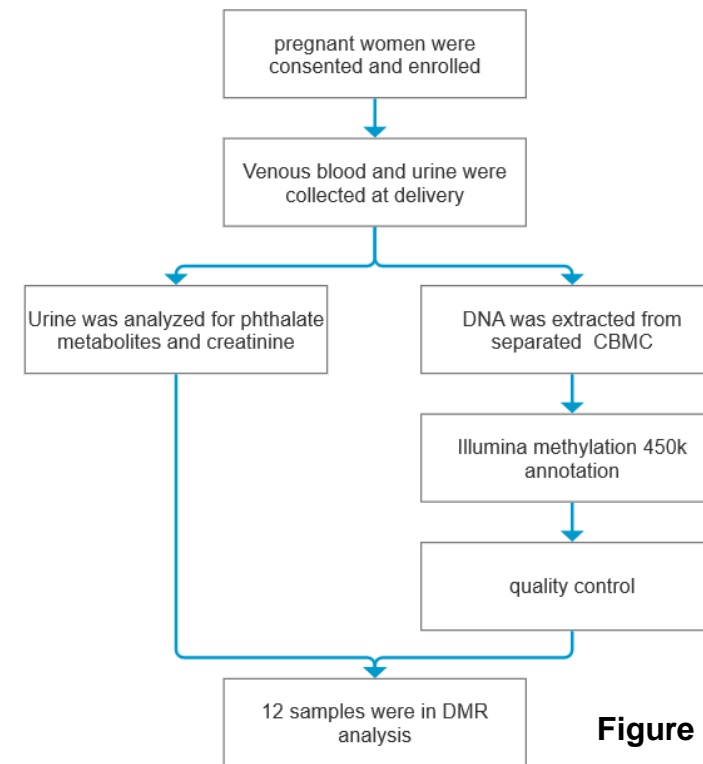

Figure 1. Flow chart for the study

| Parent compound	Metabolite
Di-n-octyl phthalate (DOP)	Mono (3-carboxypropyl) phthalate (mCPP)
Di-n-butyl phthalate (DBP)	
Di-n-butyl phthalate (DBP)	Mono-butyl phthalate (mBP)
Butyl benzyl phthalate (BBP)	Mono-benzyl phthalate (mBzP)
	Mono-butyl phthalate (mBP, minor)
Di-isobutyl phthalate (DiBP)	Mono-isobutyl phthalate (MiBP)
1,2-Cyclohexane dicarboxylic acid, diisononyl ester (DINCH)	Cyclohexane-1,2-dicarboxylic acid mono(hydroxy-isononyl) ester (MHiNCH)
	cyclohexane-1,2-dicarboxylic acid monocarboxyisooctyl ester (MCOCH)
Di-isononyl phthalate (DiNP)	Mono-carboxy-iso-octyl phthalate (MCOP)
	Mono-isononyl phthalate (mNP)
	Mono-oxoisononyl phthalate (MONP)
Di-isodecyl phthalate (DiDP)	Mono-carboxy-iso-nonyl phthalate (MCNP)
Diethyl phthalate (DEP)	Mono-ethyl phthalate (mEP)
Di-2-ethylhexyl terephthalate (DEHTP)	Mono-2-ethylhydroxyhexyl terephthalate (MEHHTP)
	Mono-2-ethyl-5-carboxypentyl terephthalate (MECPTP)

Acknowledgement
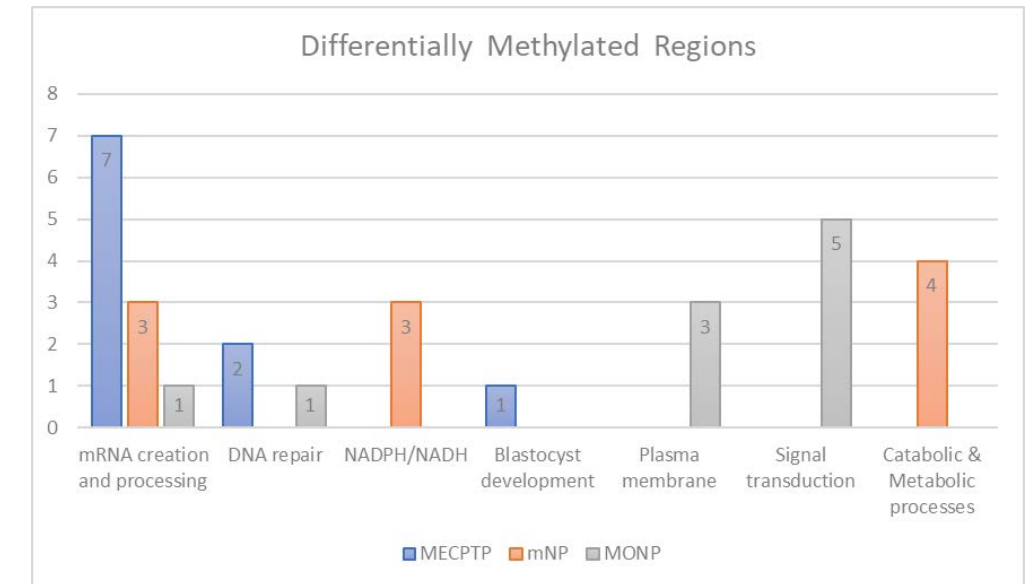
Figure 2. Differentially methylated regions associated with phthalate metabolites.

Results

• Three phthalate metabolites: MECPTP, mNP, and MONP were associated with DNA methylation, for a total of 30 function regions.

• We classified 30 function regions to seven classes: mRNA creation and processing, DNA repair, NADPH/NADH, Blastocyst development, Plasma membrane, Signal transduction, Catabolic & Metabolic processes.

• mRNA creation and processing was the most frequently noted functional class with 11 hits. All three phthalate metabolites were associated with this class.

Discussion

• We found an association between prenatal phthalate exposure and cord blood mononuclear cell DNA methylation, with relation to several biological functions.

• One limitation was the small simple size (n=12).