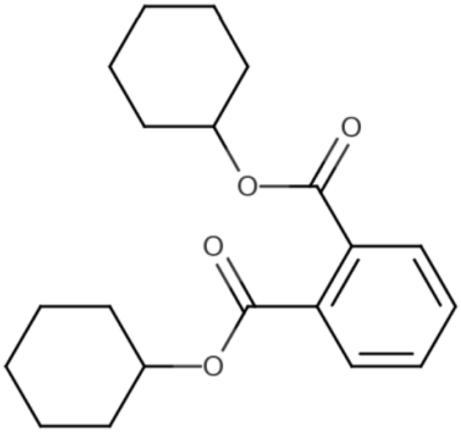
United States
Environmental Protection Agency

December 2024
Office of Chemical Safety and
Pollution Prevention

Draft Data Quality Evaluation Information for Human Health Hazard Epidemiology for Dicyclohexyl Phthalate (DCHP) (1,2- Benzenedicarboxylic acid, 1,2-dicyclohexyl ester)

Systematic Review Support Document for the Draft Risk Evaluation

CASRN: 84-61-7



December 2024

This supplemental file contains the data quality evaluation results for epidemiology data sources that met the PECO screening criteria and further filtering criteria for the *Draft Human Health Hazard Assessment for Dicyclohexyl Phthalate (DCHP)*. EPA conducted data quality evaluation based on author-reported descriptions and results; additional analyses (*e.g.*, statistical analyses performed during data integration into the risk evaluation) potentially conducted by EPA are not contained in this supplemental file. EPA used the TSCA systematic review process described in the *Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances* (also referred to as '2021 Draft Systematic Review Protocol'). Any updated steps in the systematic review process since the publication of the 2021 Draft Systematic Review Protocol are described in the *Draft Risk Evaluation for Dicyclohexyl Phthalate (DCHP) – Systematic Review Protocol*.

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Study Citation:	Fernandez, Moreira, M. A., Cardeal, Z. L., Carneiro, M. M., André, L. C. (2019). Study of possible association between endometriosis and phthalate and bisphenol A by biomarkers analysis. Journal of Pharmaceutical and Biomedical Analysis 172:238-242.
Health Outcome(s) Assessed:	Reproductive/Developmental- Endometriosis, Non-cancer
Chemical:	Dicyclohexyl Phthalate- Metabolite: Monocyclohexyl phthalate (MCHP)
HERO ID:	5432788

Domain	Metric		Rating	Comments
Domain 1: Study Participation				
	Metric 1A:	Participant Selection	Low	This case-control study evaluated the association between phthalate metabolites and endometriosis. Participants were aged 18-45 years. Diagnosis or the absence of disease was confirmed at the Endometriosis Center of the Hospital School of the Federal University of Minas Gerais, Brazil. 30 endometriosis cases and 22 controls without endometriosis were recruited in Brazil. No information was provided on the recruitment process, participation rates, inclusion/exclusion criteria, or on the underlying population(s) from which the cases and controls arose. The potential for selection bias cannot be ruled out.
Domain 2: Exposure Characterization				
	Metric 2A:	Exposure Measurement	Medium	Phthalate metabolites were measured in urine samples using an Agilent 7890 "GC system...coupled to a MS equipped with a quadrupole mass analyser." Details on the analytic method were previously published (Fernandez et al 2016, HEROID 3466575). Concentrations were adjusted for creatinine. Measured metabolites included MiNP, MiBP, MBP, MCHP, MBzP, and MEHP. Limits of quantification (LOQ) ranged from 2.91 ug/L for MBzP to 38.9 ug/L for MiBP. Values below the LOQ were replaced with 0. The proportion of participants above LOQ was typically <50%. Of 30 cases and 22 controls, case/control Ns above LOQ were: MiNP 9/6, MiBP 18/7, MBP 8/3, MCHP 10/3, MBzP 2/0, and MEHP 10/6. The authors' stated that metabolites were categorized at the median for analysis, or effectively as any vs no detectable amounts. No information on the details or timing of urine sample collection was provided (e.g., spot urine sample vs. first morning void). Given the case control design, samples were collected after diagnosis. However, timing of diagnosis relative to enrollment (e.g., inclusion of incident vs. prevalent cases) was not discussed. As such, there is uncertainty as to whether the exposure represents the etiologically relevant time period. However, there is no direct evidence of bias (e.g. post-diagnosis behavior changes or treatments that affected exposure).
Domain 3: Outcome Assessment				
	Metric 3A:	Outcome Ascertainment	Medium	Presence or absence of endometriosis was confirmed in cases and controls using "videolaparoscopy surgery with visual inspection of the pelvis and biopsy of suspected lesions" for most participants. For three participants, diagnosis was done via MRI. Though the rationale for the use of a different method for these three participants was not provided, both methods are valid, and the different approaches may be medically justified. The authors did not discuss whether cases were incident diagnosis or had prevalent disease. There was no discussion of the stage of disease. The authors did not discuss whether controls were patients who had been examined in relation to ongoing medical concerns (e.g. pelvic pain, infertility) to exclude a diagnosis of endometriosis.

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Domain	Metric		Rating	Comments
	Metric 3B:	Selective Reporting	Medium	The authors described their primary and secondary analyses in the methods section and results were reported for all primary and secondary analyses.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Low	No potential confounders accounted for either by design or adjustment. Descriptive data indicated differences in cases and controls in variables including BMI (24.7 vs 27.6 kg/m2), family history of endometriosis (16.7% vs 9.1%), oral contraceptive use (43.3 vs. 31.8%), and frequent intake of microwaved food (36.6 vs 45.4%); there was no significance testing. Associations between potential risk factors for endometriosis and phthalate metabolites were not shown. Though residual confounding is likely, there is no direct evidence of substantial bias.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	The association between creatinine adjusted phthalate metabolites and endometriosis was assessed using a chi-square test and via calculation of an odds ratio and 95% confidence interval. Phthalate metabolite concentrations were dichotomized at the median for analysis. Only bivariate analyses were conducted. No sensitivity analyses were conducted to assess robustness of findings.
	Metric 5B:	Sensitivity	Low	The overall sample size was relatively small (n=52). In addition to a small number of cases (n=30) this study did not increase the number of controls (n=22) to enhance statistical power. Few participants had urinary concentrations of phthalate metabolites above LOQ. For example, only 15 participants (9 cases, 6 controls) had quantifiable MiNP. However, among participants with detectable amounts, there was variability in exposure (e.g., MiNP median 21.8 ug/L, range 8.4 to 249 among cases). The unclear timing of outcome diagnosis vs. exposure ascertainment and the use of a single urine sample to characterize exposure may have contributed to misclassification that would further reduce statistical power.

Additional Comments: This case-control study of women in Brazil evaluated the association between phthalate metabolites and endometriosis. The sample included 30 cases and 22 controls. An important concern was the potential for residual confounding, as no potential confounders were controlled for by design or by adjustment. Descriptive data indicated that cases and controls differed in several characteristics, including BMI. Additional concerns include the lack of information on the participant recruitment process, and whether cases were incident diagnoses vs. women with prevalent disease. It was also unclear whether controls were screened laparoscopically for endometriosis because they were patients being attended at the same hospital center with other unnamed gynecologic or reproductive disorders.

Overall Quality Determination — Low

Study Citation:	Strassle, P. D., Smit, M., L.A., Hoppin, J. A. (2018). Endotoxin enhances respiratory effects of phthalates in adults: Results from NHANES 2005-6. Environmental Research 162:280-286.
Health Outcome(s) Assessed:	Lung/Respiratory- Asthma, wheeze, hay fever, rhinitis (symptoms in the past 12 months), Non-cancer
Chemical:	Dicyclohexyl Phthalate- Metabolite: Monocyclohexyl phthalate (MCHP)
HERO ID:	4728797

Domain	Metric	Rating	Comments
Domain 1: Study Participation			
	Metric 1A: Participant Selection	Medium	This study utilized the publicly available NHANES 2005-2006 data, designed to represent the US population. These data are the only recent NHANES that include information on respiratory and allergic symptoms and endotoxin measurements. The analysis sample included adults aged >= 18 years who had complete information on urinary phthalates, dust endotoxin levels, and potential confounders, and had not moved between the clinic visit and dust collection (n=1,091). NHANES methods including participation rates are documented (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/overview.aspx?BeginYear=2005). The authors described the proportion of participants with complete data as about one third of NHANES participants with urinary phthalate measures. The sample analyzed in this study was similar to that in a previous study by these authors examining main effects of phthalates on these respiratory outcomes; the sample in this study was reduced as fewer participants had valid endotoxin measures. The authors noted some differences in the significance of main effects of some phthalates in this study vs their prior analysis (Hoppin et al., 2013 HEROID 1987636). Nonetheless, there is no direct evidence that inclusion in this sample was selective.
Domain 2: Exposure Characterization			
	Metric 2A: Exposure Measurement	Medium	Phthalate metabolites were analyzed in spot urine samples collected during the NHANES clinic visit using high performance liquid chromatography-mass spectrometry. Concentrations below limits of detection (LOD) were imputed as the LOD divided by the square root of 2. Urine dilution was addressed by including creatinine as a covariate in regression models. Phthalate concentrations were log10 transformed for analysis. Any phthalates present in ≥50% of the sample were included. MCHP was excluded from analyses as the LOD was reported as 2%. A primary aim was to examine whether endotoxin levels in the home modified associations between phthalates and respiratory symptoms. Endotoxin was measured in combined dust from the participants bed and bedroom floor within 7 days of the clinic visit. Limitations of exposure measurement include the use of a single spot urine to quantify exposure and the cross-sectional design. Given the relatively short half-life of phthalate metabolites in urine, exposure may be misclassified by a single sample. Reverse causation in a cross-sectional study cannot be ruled out, should some individuals experiencing respiratory and/or allergic symptoms adjust behaviors in ways that influence phthalates exposure. However, there is no evidence of such bias.
Domain 3: Outcome Assessment			

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Health Outcome(s) Assessed: Lung/Respiratory- Asthma, wheeze, hay fever, rhinitis (symptoms in the past 12 months), Non-cancer

Chemical: Dicyclohexyl Phthalate- Metabolite: Monocyclohexyl phthalate (MCHP)

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Domain	Metric		Rating	Comments
	Metric 3A:	Outcome Ascertainment	Medium	The outcomes analyzed in this study were defined based on self-reported symptoms of asthma, hay fever, rhinitis, and wheeze during the past 12 months. Current asthma was defined based on both a doctor diagnosis of asthma and symptoms in the past year. Wheeze was defined as any episode of wheezing or whistling in the chest in the past year.
	Metric 3B:	Selective Reporting	Medium	The authors described their primary (and secondary) analyses in the methods section and results were reported for all primary analyses. Associations with hay fever and current rhinitis were described as null in the main manuscript and included in supplemental materials not available at the time of this assessment.
Domain 4: Potential Confounding / Variability Control				
	Metric 4A:	Potential Confounding	Medium	Models adjusted for variables included in a previous study on phthalates and allergy in NHANES 2005-2006 by these authors which did not analyze endotoxin interactions (Hoppin et al., 2013 HEROID 1987636). Covariates were selected a priori based on the literature, and included age, gender, race/ethnicity, BMI, urinary creatinine, and cotinine. Poverty-income ratio was excluded in the previous study as it did not confound associations and inclusion would have reduced sample size. To examine effect modification, endotoxin levels in dust were categorized in approximate tertiles (low: $<$ 10 endotoxin units [EU]/mg, medium: 10–25 EU/mg, and high: $\geq$25 EU/mg). Potential co-exposure confounding was not discussed.
Domain 5: Analysis				
	Metric 5A:	Analysis	Medium	Multivariable logistic regression was used to analyze the association between phthalates and respiratory and allergic outcomes, potentially modified by endotoxin. Each phthalate was analyzed individually using log10 transformed variables. Results were reported as adjusted odds ratios for the main effects of phthalates alone and for effects stratified by endotoxin tertile. Phthalates-endotoxin interaction p-values were reported based on Wald tests for overall differences in slope across tertiles. Results were also presented graphically. As a sensitivity analysis, the authors analyzed interactions between phthalates and total dust weight to provide evidence that any interactions were due to the endotoxin content of dust vs. the dust itself. Gender interactions were not discussed in either study.
	Metric 5B:	Sensitivity	Uninformative	The study included phthalates that were detected in $\geq$50% of the study population in the analyses. The study sample included more than 1,000 adults, but the DCHP metabolite mono-cyclohexyl phthalate (MCHP) was found above the limit of detection in only 22 participants, which is only 2% of participants. Therefore, MCHP was excluded from the analyses. The limit of detection for MCHP was 0.6 ng/mL and the geometric mean detected in participants was only 0.44 ng/mL. Thus, the study was unable to detect an association if it exists between the interaction between MCHP and endotoxin and respiratory and allergic outcomes.

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Domain	Metric	Rating	Comments
Additional Comments:	This study used NHANES 2005-2006 data to analyze whether dust endotoxin levels modified the association between phthalate exposures and respiratory symptoms in the past year, including symptoms of asthma (among doctor-diagnosed participants) and wheeze. The study utilized a sample (n = 1,091) of nearly 1/3 of the NHANES sample size due to exclusions of participants with missing data such as lacking spot urine samples, home endotoxin measures, or confounding factors. However, MCHP was excluded from the analyses because MCHP was found above the limit of detection (LOD) in only 2% of participants. Although this study includes quality data on other phthalates, it is uninformative for DCHP due to lack of data.		

Overall Quality Determination Uninformative