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WASHINGTON, DC

Assessing the Association Between Autism Incidence and DEHP Phthalate Exposure: A Systematic Review

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Introduction:

- Autism Spectrum Disorder (ASD) is a developmental disorder that is expected to affect 1 in 54 children in the United States
- The etiologic agent for autism is unknown but scientists suspect that environmental factors and genetics play a role.
- DEHP is a phthalate that is commonly used as a plasticizer in PVC to make everyday consumer goods such as raingear, shower curtains, and medical tubing more flexible.
- DEHP is an endocrine disrupting compound (EDC). EDC's are chemicals that interfere with the metabolic activities and natural hormones in the body which are responsible for homeostasis, reproduction, or development.

Objective

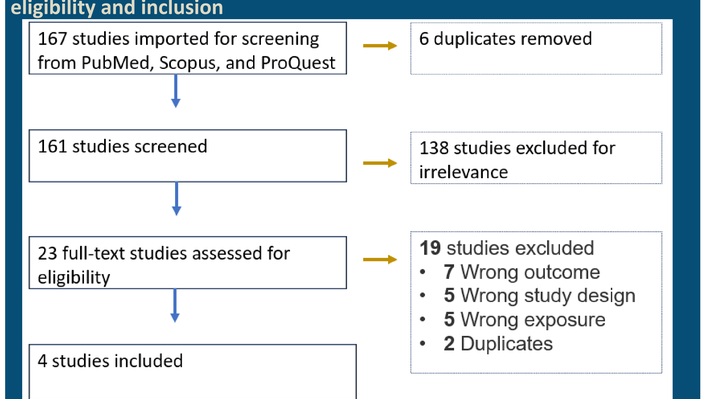
- To systematically review the literature published since 2014 to identify if there is an association between gestational and/or early childhood DEHP exposure and Autism incidence.

Participants: Children from 3-12 years old
Exposure: Children with high gestational or early childhood exposure to the DEHP phthalate
Comparator: Children with low gestational or early childhood DEHP phthalate exposure
Outcomes: Autism Spectrum Disorder

Methods

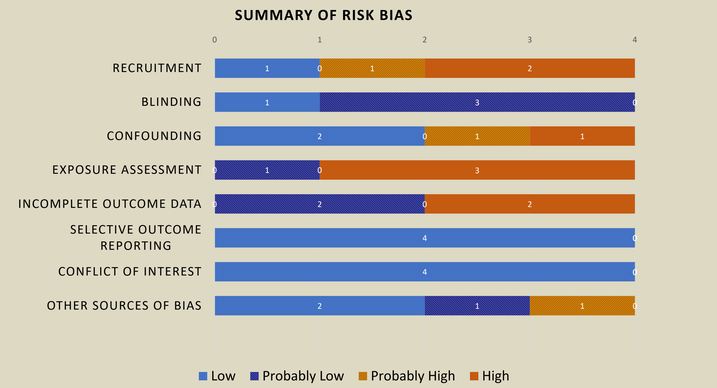
- Followed the navigation guide methodology to screen studies and assess them for risk of bias and quality

Figure 1. Prisma Graphic showing study identification, screening, eligibility and inclusion



Risk of Bias Assessment

Study	Recruitment Strategy	Blinding	Confounding	Exposure Assessment	Incomplete Outcome Data	Selective Outcome Reporting	Conflict of Interest	Other Sources of Bias	Quality Rating
Rahbar et al., 2017	High	Probably Low	High	High	High	Low	Low	N/A	Low Quality
Shin et al., 2018	High	Probably Low	Low	Probably High	Probably Low	Low	Low	Low	High Quality
Ponsonby et al., 2020	High	Probably Low	Probably High	High	High	Low	Low	Low	Low Quality
Oulhote et al., 2020	Probably high	Low	Low	High	Probably low	Low	Low	Probably Low	Moderate



Quality Assessment

Quality Factor	Rating	Basis
Downgrade		
Risk of Bias Across Studies	-1	There was a high risk of bias across studies, specifically in the exposure assessment
Indirectness	0	The studies assessed the outcome, population, and exposure of interest.
Inconsistency	-1	There was variability in the results; one study showed a potential protective effect of DEHP on ASD, one showed no association, and the other showed moderate risk for adverse neurological outcomes.
Imprecision	0	All evaluated studies had an adequate sample size. Before stratification by sex. The confidence intervals were wide or straddled the null.
Publication Bias	0	There was no reason to suspect publication bias
Upgrade		
Large Magnitude of Effect	0	Studies either show no effect or a protective effect, will not upgrade
Dose Response	0	Evidence is not compelling enough to offer an upgrade
Confounding minimizes effect	1	Two studies suggested that supplements during pregnancy were potentially protective factors
Overall Quality of Evidence	0	Overall, the evidence does not support upgrading
Summary of Qualitative Findings	LOW	The overall quality of evidence is low. Only one study was deemed to be of high quality and all studies did a poor job at assessing exposure.

References:

- ATSDR. (2019). *Toxicological Profile for Di(2-Ethylhexyl)Phthalate (DEHP)* (United States, US Department of Health and Human Services, Agency for Toxic Substances and Disease Registry). Atlanta, GA
- CDC 2020: https://www.cdc.gov/ncbddd/autism/data.html
- Oulhote et al., 2020: doi:10.1289/EHP5621
- Ponsonby et al., 2020: doi:10.1016/j.neuro.2020.05.006
- Rahbar et al., 2017: doi: http://dx.doi.org.proxygw.wrlc.org/10.3390/ijerph14111425
- Shin et al., 2018: doi:10.1186/s12940-018-0428-4
- Zota et al., 2014 : https://doi.org/10.1289/ehp.1306681

Results

- Most studies did not take a sufficient number of urine samples to adequately assess exposure
- There was downgrading due to inconsistency in results across studies while the other two studies showed no statistically significant effect.
- All the evaluated studies suggested that prenatal supplements or folic acid intake during pregnancy potentially have an attenuating effect on social behavioral outcomes from DEHP exposure.

Study	Study Type	Results
Shin et al. (2018)	Cohort	No increased risk for ASD with higher exposure to DEHP; There was a sex dependent association between high phthalate concentrations and non-typical development in males.
Oulhote et al. (2020)	Cohort	No observed association between gestational DEHP exposure and higher SRS scores, which are correlated with non-typical development.
Ponsonby et al. (2020)	Cohort	They found that infants with high phthalate levels, including DEHP, were at moderate risk for an adverse neurological outcome but that the risk was substantially elevated if infants had a high gene score for oxidative stress and high phthalate exposure.
The Rahbar et al. (2017)	Case-Control	Not-evaluated due to extremely low-quality study

Conclusion and Recommendations

Following an extensive review of the literature I found four studies that examined the potential influence of DEHP during gestation and early childhood on Autism incidence

- Risk of bias of included studies was moderate
- This review shows potential evidence of DEHP exposure influencing ASD incidence.
- Due to the different statistics used for summarizing results and a lack of homogeneity between studies a meta-analysis could not be performed.
- There was low quality of evidence found across studies and a low number of studies included in review.
- The low-quality rating was driven primarily by poor exposure assessments; specifically, most studies used an insufficient number of urine samples to assess exposure which are likely only reflective of the last 6-12 hours of exposure to DEHP.
- Future cohort studies need to account for the potential variability in exposure across pregnancy and early childhood by taking many urine samples and pooling.