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Review

Systematic review and meta-analysis of early life exposure to di(2-ethylhexyl) phthalate and obesity related outcomes in rodents

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HIGHLIGHTS

- Early life exposure to DEHP was significantly associated with increased fat weight.
- A non-significant negative association was estimated for body weight.
- There was substantial heterogeneity across studies.
- Reported information was insufficient to assess the risk of bias for most studies.
- More data is necessary to strengthen the evidence base of the obesogenic effects.

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ABSTRACT

Background: It has been suggested that the plasticizer di(2-ethylhexyl) phthalate (DEHP) exerts obesogenic effects after pre- or perinatal exposure.
Objective: A systematic review with meta-analyses was conducted of early life exposure to DEHP, or its biologically active metabolite mono(2-ethylhexyl) phthalate (MEHP), on the obesity related outcome measures body weight, fat (pad) weight, triglycerides, free fatty acids and leptin in experimental rodent studies.
Methods: The applied methodology was pre-specified in a rigorous protocol. Relevant articles were identified using PubMed and EMBASE and meta-analyses were performed using mean differences (MD) and random effects model when at least five studies could be included per outcome measure. Risk of bias and the quality of evidence was assessed using established methodologies.
Results: Overall, 31 studies could be included and meta-analyses could be performed for body weight and fat weight. Early life exposure to DEHP was significantly associated with increased fat weight (MD = 0.02; 95% CI: 0.00, 0.03), while a non-significant association was estimated for body weight (MD = −0.14; 95% CI: −0.32, 0.04). There was substantial heterogeneity across studies and the information was insufficient to assess the risk of bias for most studies. No meta-analyses could be conducted for other outcome measures, because too few studies were available.
Conclusions: The results of this systematic review indicate that early life exposure to DEHP is potentially associated with increased adiposity in rodents. More data is needed to strengthen the evidence base.

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1. Introduction

Di(2-ethylhexyl) phthalate (DEHP) is used in many plastic products as plasticizer, including in packaging material, flooring, cables and medical products (ECHA, 2009). Its use has been subject of discussion as DEHP is ubiquitous in the environment (Erythropel et al., 2014) and has been identified as a substances with reproductive toxicity properties (ECHA, 2008; NTP, 2006). In addition, within Europe, DEHP has also been identified as endocrine disrupting chemical (EDC) in humans and the environment, and its use has been restricted in many products (ECHA, 2017, 2014).

In addition to the effects of DEHP on reproductive endpoints, DEHP has putative obesogenic properties. Obesogens are chemicals that can inappropriately regulate lipid metabolism via hormonal pathways, and thereby stimulate lipid accumulation and adipogenesis or could result in higher susceptibility to develop obesity (Grün and Blumberg, 2006). Early life exposure has been suggested to be the critical exposure period for the occurrence of these obesogenic effects, and is of concern as DEHP is found in urine samples of children in the US and EU (Casas et al., 2013; DEMOCOPHES, 2013; Zota et al., 2014), and is identified in maternal blood, cord blood and meconium of mother-newborn pairs (Li et al., 2013). Obesogenic effects of DEHP have been demonstrated in multiple studies including in *in vitro* and animal experiments as well as in epidemiological studies (Gore et al., 2015). It has been suggested that DEHP exerts its endocrine disrupting effects mainly via its primary metabolite mono(2-ethylhexyl) phthalate (MEHP), through activation of the nuclear peroxisome proliferator-activated receptors (PPAR) as well as PPAR mediated anti-androgenic effects (Desvergne et al., 2009; Kim and Park, 2014). Of these receptors, PPARα and $-\gamma$ play a pivotal role in fatty acid and lipid metabolism and adipogenesis (Desvergne et al., 2009). In addition, potential thyroid and estrogenic disrupting have been suggested as a mode of action of DEHP (ECHA, 2014; Kim and Park, 2014).

In order to provide a more rigorous evaluation of the existing evidence we conducted a systematic review on the effects of DEHP exposure on obesity development. In this review, we investigated the effects of pre- or perinatal exposure of rodents to DEHP and MEHP on the following obesity related outcome measures: body weight, fat (pad) weight, triglycerides, free fatty acids (FFA), and leptin (Table 1). We determined the quality of the studies, rated the confidence of the evidence using established methodologies and, where possible, conducted meta-analyses.

2. Methods

The methodology of this systematic review was pre-specified in a protocol, following guidelines of the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE; de Vries et al., 2015). This protocol has been published on the SYRCLE Website in 2015 and is provided in the Appendix. The applied methodology is similar to the methodology as described by Wassenaar et al. (In Press).

2.1. Search strategy and selection of papers

A comprehensive search strategy was applied on September 21, 2015 in order to identify relevant articles in the databases MEDLINE via PubMed and EMBASE (Table A.1). In addition, the reference lists of the included articles and of relevant reviews were screened manually in order to identify potentially relevant new articles.

Study selection consisted of two screening phases, including a title and abstract screening and a full text screening. Studies were selected for full text screening when they met all the inclusion criteria: 1) original full paper which presented unique data; 2) exposure to DEHP or MEHP; 3) obesity related article or at least one of the outcome measures was examined (body weight, fat pad weights, triglyceride levels, FFA levels or leptin levels); 4)

Table 1
PECO statement (Population, Exposure, Comparator and Outcomes).

Population	Experimental rodent studies
Exposure	Early life exposure to di(2-ethylhexyl) phthalate or mono(2-ethylhexyl) phthalate (during gestation and/or lactation up to postnatal day 21)
Comparator	Animals exposed to vehicle-only treatment
Outcomes	Body weight, fat (pad) weights, triglyceride levels, free fatty acids levels and leptin levels