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Plasticizers in the Neonatal Intensive Care Unit: A review on exposure sources and health hazards

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49 **List of abbreviations**

ATBC	Acetyl tributyl citrate
BBzP	Butyl-benzyl phthalate
CPB	Cardiopulmonary bypass
CMR	Carcinogenic, mutagenic or toxic for reproduction
D	Day
DEHA	Di-(2-ethylhexyl) adipate
DEHP	Di-(2-ethylhexyl) phthalate
DEHT	Di-(2-ethylhexyl) terephthalate
DiBP	Di-iso-butyl phthalate
DINCH	Diisononyl cyclohexane-1,2-dicarboxylate
DINP	Diisononyl phthalate
DNEL	Derived no-effect level
EDC	Endocrine disrupting chemical
EDI	Estimated daily intake
ELBW	Extremely low birth weight
EPA	Environmental Protection Agency
ETT	Endotracheal tube
EVA	Ethylene-vinyl acetate
EU	European Union
GA	Gestational Age
h	hour
IV	Intravenous
kg	Kilogram
LBW	Low birth weight
MDR	Medical Devices Regulation
MEHHP	Mono-(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	Mono-(2-ethylhexyl) phthalate
MEOHP	Mono-(2-ethyl-5-oxohexyl) phthalate
mg	milligram
ml	milliliter
MMCHP	Mono-(2-carboxymethyl-hexyl) phthalate
NGT	Nasogastric tube
NICU	Neonatal intensive care unit
NOAEL	No Observed Adverse Effects Level
PN	Parenteral Nutrition
PET	Polyethylene Terephthalate
PP	Polypropylene

PPAR	Peroxisome proliferator-activated receptor
PVC	Polyvinyl chloride
RBCC	Red blood cell concentrate
SCENIHR	Scientific Committee on Emerging and Newly Identified Health Risks
SCHEER	Scientific Committee on Health, Environmental and Emerging Risks
TDI	Tolerable daily intake
TOTM	Tris-(2-ethylhexyl) trimellitate
VLBW	Very low birth weight
µg	microgram

Plasticizers in the Neonatal Intensive Care Unit: A review on exposure sources and health hazards

Abstract

Plasticizers, used to increase the flexibility of plastic materials, can leach into the environment and the human body. Various adverse health effects are attributed to exposure to plasticizers, particularly phthalates. Premature newborns admitted to a neonatal intensive care unit (NICU) are exposed to many indwelling plastic devices containing plasticizers while in a developmentally vulnerable period. This is the first comprehensive review of its kind, providing an overview of DEHP and alternative plasticizers (APs), their sources and degree of exposure in the NICU, and the resulting health risks in (premature) infants. Despite the 2017 EU Medical Devices Regulation (2017/745), di-(2-ethylhexyl) phthalate (DEHP) is still a commonly present plasticizer in plastic medical devices in the NICU, with current labelling being insufficient to guarantee absence. Estimated NICU exposures remain elevated above the tolerable daily intake. Medical procedures leading to the highest exposure of phthalates and APs, are extracorporeal membrane oxygenation, blood transfusion, parenteral nutrition and respiratory support. As traditional matrices, such as blood and urine, are not always readily available in neonates, the accumulation of plasticizers in alternative matrices, such as hair and nails, provides an opportunity to study long-term accumulation of toxic chemicals. Impaired respiratory and neurodevelopment correlate with phthalate exposure at both biological and epidemiological levels in childhood, yet knowledge gaps about the effects in neonates prevail. Some APs provide interesting opportunities to reduce toxicity, but human data regarding health effects remain limited. Although toxicologists and regulators have addressed the problem for some time, awareness is lacking mainly among healthcare professionals.

Keywords

Plasticizers; medical devices; premature neonates; neonatal intensive care unit; neurodevelopment; lung development

Introduction

Plasticizers are chemical compounds added to rigid plastics, such as polyvinyl chloride (PVC), to make them more flexible, softer and extend their lifetime. Phthalates are the best-known and most widespread group of plasticizers. Human exposure to these phthalates is ubiquitous and occurs from various environmental sources, including food, dust, pharmaceuticals and household products (Wallner et al., 2016). Another route of exposure is through plastic medical devices, which for a long time have been mainly plasticized with di-(2-ethylhexyl) phthalate (DEHP). Due to low cost, enhanced flexibility, elasticity and physical stability, DEHP is incorporated in many (invasive) medical devices, such as intravenous (IV) infusion sets, IV storage bags, endotracheal tubes, nasogastric tubes and blood bags (Lai & Bearer, 2008; Malarvannan et al., 2019). However, phthalates, such as DEHP, have been reported to leach from plastic products into the environment and the human body due to their lipophilic nature and noncovalent binding to PVC. Once the parent compound enters the body (see Figure 1), hydrolysis will occur, producing mono-ester metabolites (*e.g.,* mono-(2-ethylhexyl) phthalate (MEHP) from the initial di-ester DEHP). This process is catalyzed by lipases and esterases (Bui et al., 2016; Wang et al., 2019). MEHP undergoes further phase I metabolism into secondary oxidative or hydroxylated metabolites. Phase II metabolism involves the conjugation of all metabolites through glucuronidation (via UDP-glucuronyl-transferase) and enhances urinary excretion (Wang et al., 2019).

Various adverse health effects have been attributed to phthalates and their metabolites, with DEHP being the most extensively studied (Zarean et al., 2016). Most phthalates are known endocrine-disrupting chemicals that can interact (as agonist or antagonist) with the ligand-binding domain of different nuclear transcription factors (*e.g.,* peroxisome proliferator-activated receptor-alpha, estrogen and progesterone receptors), exerting an effect on various target tissues (Benjamin et al., 2017). Both animal and epidemiological studies have shown strong correlations between phthalate exposure and different adverse outcomes, such as type 2 diabetes, insulin resistance, obesity, testicular toxicity, carcinogenicity and reproductive effects in men and women (Benjamin et al., 2017; Radke et al., 2019; Rowdhwal & Chen, 2018; Zarean et al., 2016). Concerning reproductive and developmental toxicity, the EU Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) referred to

102 several phthalates, including DEHP, classified as carcinogenic, mutagenic or toxic for reproduction
103 (CMR 1B) and as endocrine disrupting chemicals (EDCs) (Testai et al., 2016). Moreover, the SCENIHR
104 presented a tolerable daily intake (TDI) of 48 µg/kg/d for DEHP (Testai et al., 2016). In 2009, the EU
105 prohibited the use of and banned DEHP, di-iso-butyl phthalate (DiBP) and butyl-benzyl phthalate
106 (BBzP) in toys, childcare articles and cosmetics (EU, 2009). In May 2017, the EU adopted the Medical
107 Devices Regulation (MDR 2017/745) (EU, 2017), declaring that CMR 1A/1B and/or EDC substances
108 in medical devices above a concentration of 0.1 weight percent is subject to justification and labelling.
109 A three-year transition period was established to increase compliance from manufacturers, with
110 certificates approved before implementation being authorized for up to 3 more years. Unfortunately, due
111 to the COVID-19 pandemic, on 23 April 2020, the MDR was postponed another year and entered
112 application on 26 May 2021 (EU, 2020).

113 The classification of DEHP as a reproductive toxicant and the imposed concentration limit of
114 the MDR has forced manufacturers to 'quickly' search for alternatives. Different alternative plasticizers
115 (APs) have been developed to replace DEHP (see Table 1), including di-(2-ethylhexyl) terephthalate
116 (DEHT), tris-(2-ethylhexyl) trimellitate (TOTM), diisononyl cyclohexane-1,2-dicarboxylate (DINCH),
117 di-(2-ethylhexyl) adipate (DEHA) and diisononyl phthalate (DINP) (Den Braver-Sewradj et al., 2020).
118 Although novel strict regulations are currently in place and plasticizer use is constantly evolving,
119 reference to guide manufacturers and an overview of the prevailing exposure levels to DEHP or its
120 alternatives in the NICU are still missing.

121 In recent decades, survival rates in the Neonatal Intensive Care Unit (NICU) have improved
122 significantly. Nevertheless, surviving neonates are still challenged with long-term consequences,
123 especially respiratory (Jensen & Schmidt, 2014; Jobe & Bancalari, 2001) and neurodevelopmental
124 impairments (Fawke, 2007), which can be partially explained by early complications of prematurity.
125 Neonatal intensive care relies on several indwelling plastic medical devices with a crucial and
126 fundamental role in respiratory support, IV catheterization, and nutrition. Intensive and continuous
127 exposure to these invasive medical devices, while being in a critical developmental period (Raybaud et
128 al., 2013; Woods, 2016) with immature renal function (Gubhaju et al., 2014) and low body weight,
129 makes premature neonates more susceptible to DEHP and APs potential toxicity (Lai & Bearer, 2008).

130 Appropriately, the SCENIHR claimed these premature neonates to be at risk of exposure to plasticizers
131 (Testai et al., 2016). It is of the utmost importance that adequate information is gathered on the safety
132 of medical devices employed in the NICU to fill the remaining knowledge gaps on exposure and health
133 effects of plasticizers in the NICU. This review provides a comprehensive overview of DEHP and APs
134 on the sources of exposure in the NICU, the evolution and total exposure in the NICU and the resultant
135 health risk in (premature) infants and children (Figure 2).
136

137 Review strategy

138 An in-depth literature study was performed by means of PubMed and EMBASE databases. Initial
139 keywords were combined to generate different key concepts, such as plasticizers (phthalates OR DEHP
140 OR plasticizers OR "alternative plasticizers"), neonates (newborn OR "premature neonate" OR infant
141 OR premature OR preterm), NICU ("neonatal intensive care unit" OR NICU OR "Intensive Care" OR
142 "neonatal intensive care"), medical devices ("medical device" OR "gastric tube" OR "catheterization"
143 OR "infusion line" OR "infusion" OR "invasive medical device" OR "respiratory support") and health
144 effects ("respiratory development" OR "lung development" OR "asthma" OR "neurocognitive
145 development"). Publications from 1988 up to March 2021 were extracted. Papers were considered
146 relevant if one of the topics studied was at least a phthalate or an alternative plasticizer. It assessed either
147 human biomonitoring, its exposure in the NICU or its health effects in children. Out of 642 papers, 141
148 were finally included after a detailed review.
149

150 Sources of plasticizers in the NICU: Medical devices

151 According to the manufacturers, out of 21 NICU medical devices inventoried by Van Vliet et
152 al. (2011), 50 % were DEHP-free. However, Genay et al. (2011) found that 70% of the PVC infusion
153 lines, labelled as "DEHP-free", still contained a certain DEHP concentration. Moreover, Fischer
154 Fumeaux et al. (2015) identified the sources of plasticizer exposure to DEHP in a level III NICU in
155 Lausanne, Switzerland. Ten percent of the medical devices were labelled as containing DEHP, and

156 approximately 7% were labelled as DEHP-free. It should be noted that particularly devices destined for
157 respiratory support contained DEHP (about 71%), while this group represents only 28% of all reviewed
158 devices (Fischer Fumeaux et al., 2015). In 2016, Bourdeaux et al. (2016) tested the presence of
159 plasticizers in 32 medical devices in a NICU. They identified that TOTM (45%) was the most frequently
160 used plasticizer, followed by DEHP (29%), DINCH (16%), DINP (7%), acetyl tributyl citrate (ATBC;
161 3%) and DEHA (3%). TOTM was the most prevalent plasticizer in extension lines and infusion sets,
162 and DEHP was the major plasticizer in extracorporeal membrane oxygenation (ECMO) and blood
163 transfusion sets. All medical devices with TOTM contained a trace of DEHT and DEHP, albeit less than
164 0.1 mass percent. Malarvannan et al. (2019) identified the presence of plasticizers in 97 invasive plastic
165 medical devices used in two pediatric intensive care units (PICUs). DEHP was found to be
166 predominantly present as a plasticizer in 60 out of 97 samples (62%), even when indicated to be DEHP-
167 free. DEHP presence in the devices is a consequence of DEHP use with other plasticizers or as an
168 impurity of TOTM technical mixture used in several devices. This contribution was higher than that of
169 DEHA, DEHT or TOTM.

170 *Ex vivo experiments* are used to estimate exposure, as the mere presence of a certain plasticizer
171 in a medical device is not fully informative of migration to a patient. Experimental study results must
172 be interpreted critically since extraction is defined as removing compounds under laboratory conditions,
173 while leaching is releasing compounds from devices under clinical conditions (Cuadros-Rodriguez et
174 al., 2020). Estimated exposures from invasive medical devices or procedures in the NICU are
175 summarized in Table 2.

176

177 ***Parameters influencing extraction/leaching***

178 Temperature: Loff *et al*. conducted their simulation experiments first at 24°C and then at 33°C,
179 showing that a higher ambient temperature increased DEHP extraction by 28% (Loff et al., 2002; Loff
180 et al., 2000). Several studies confirmed that DEHP release increases linearly and significantly with
181 temperature (Bourdeaux et al., 2004)·(Rose et al., 2012). DEHP extraction experiments performed at a
182 lower temperature could underestimate neonatal exposure, since premature neonates reside most of the
183 time in an incubator at 37°C with high humidity.

184 Flow rate: Bernard, Cueff, Chagnon, et al. (2015) demonstrated that the slower the infusion rate of
185 a solution, the greater the amount of DEHP released per volume, while Kambia et al. (2003) found that
186 leaching was higher when increasing the flow rate. IV administration rates vary from less than 1 mL/h
187 for PN to 300 mL/h for medicinal infusions, so appropriate flow rates need to be used when estimating
188 patient exposure.

189 Contact time: The rate of plasticizer migration was reported to change depending on exposure time,
190 albeit not linearly as the first hour of exposure was observed to contribute the most (Bernard, Cueff,
191 Chagnon, et al., 2015; Bourdeaux et al., 2016). After the first hour, the release rate decreased and reached
192 a plateau after 8 hours (Bourdeaux et al., 2016).

193 Nature of the infused solution: Leachability increases with higher lipid content of the infused
194 solution (Kambia et al., 2003; Loff et al., 2000; Welle et al., 2005). This is particularly important for
195 PN consisting of both lipid and a crystalloid solution. Bagel et al. (2011) assessed the influence of the
196 lipid type on DEHP leaching from infusion lines into PN, albeit in static conditions. After 24 h contact
197 exposure, far higher amounts of DEHP were found in olive- (Clinoleic) and soybean-based solutions
198 (Intralipid, Structolipid) than in coconut and cod liver (Omegaven) oil-based solutions. The effect of pH
199 is not well documented, but based on preliminary tests, a higher release was suggested with an acidic
200 pH (Bernard, Cueff, Chagnon, et al., 2015).

201 Plasticizer's intrinsic migration potential: After 24 hours of immersion of samples cut from infusion
202 lines in an ethanol/water simulant at 40°C, DEHP and DINCH were extracted similarly, but 3 to 20
203 times more than DEHT and TOTM (Bernard, Cueff, Breysse, et al., 2015), respectively. Other studies
204 showed the migration ability of TOTM to be more than 100 times lower than that of DEHA (Bourdeaux
205 et al., 2016) and over 200-fold lower than that of DEHP (Münch et al., 2018). Welle et al. (2005)
206 confirmed considerably lower migration of DINCH and TOTM from PVC tubes into enteral feeding
207 solutions compared to DEHP, while ATBC showed by far the highest migration. Marcilla et al. (2004)
208 demonstrated an inversive correlation between molecular weight (MW) and migration capacity within
209 plasticizer classes. Irrespective of MW, they confirmed the higher migration capacity of citrates (*e.g.,*
210 ATBC) than phthalates (*e.g.,* DEHP) (Marcilla et al., 2004).

211 Coating of the contact surface: The coating of the inner surface of infusion lines has been
212 hypothesized to reduce plasticizer leaching, but it does not prevent DEHP extraction in lipid emulsions
213 (Loff et al., 2004). The latter is also confirmed by a study from Bourdeaux et al. (2004) that reported
214 multilayer infusion tubing as an inefficient barrier to DEHP diffusion from its outer PVC layers. The
215 results of Münch et al. (2018) even indicate that phospholipid coating rather enhances the migration of
216 plasticizers from PVC tubing into streaming blood.

217 Infusion bags containing solutions also need to be considered. Haned et al. (2018) determined the
218 migration potential of plasticizers from PVC/DEHP infusion bags. It was determined that outdated loads
219 massively increased plasticizer migration, with a 3-year shelf life increasing DEHP levels 10 times.

220 In-line filters (0.2 µm for nonlipid and 1.2 µm for lipid solutions) are currently used in infusion
221 circuits to prevent air and particles from entering the systemic circulation (Foster et al., 2015). Still,
222 their effect on plasticizer leaching has not been assessed yet.

223

224 ***Intravenous exposure***

225 *Parenteral nutrition*

226 Dynamic models are used to simulate solutions running through plastic infusion circuits. Exposure
227 of plasticizers to parenteral nutrition (PN) can be calculated by multiplying the plasticizer concentration
228 in the infused solution by the total administered volume in one day. Loff et al. (2000) analyzed DEHP
229 concentrations in lipid emulsions before and after infusion through NICU infusion lines. They calculated
230 that neonates receiving PN are exposed to up to 10 mg/kg/d of DEHP, 200 times higher than the TDI.
231 In 2017, Faessler et al. (2017) showed that leaching of DEHP from DEHP-plasticized lines into lipid
232 emulsions reached up to 1000 µg/kg/d, still 20 times higher than the TDI.

233

234 *Blood products*

235 Although administered IV, blood products deserve a distinctive discussion. The MDR
236 2007/47/EC of the European Parliament does not apply to blood bank services, while it does apply to
237 empty blood bags, since the use of DEHP has some benefits in storing red blood cells (Sampson & de

238 Korte, 2011). According to the Scientific Committee on Health, Environmental and Emerging Risks
239 (SCHEER) (Marschner, 2019), DEHP increases the membrane stability of red blood cells (RBCs) and
240 helps prevent hemolysis by leaching from blood bag systems into blood products and intercalating into
241 their lipid layer. Alternative blood bags should thus preserve adequate storage time to avoid waste and
242 to provide sufficient stock at all times. DINCH (in 2015) and DEHT (in 2020) were proposed as
243 promising candidates to replace DEHP in blood product collection and storage but are still not widely
244 used in practice. PVC blood bags plasticized with DINCH significantly outperformed DEHP bags, with
245 better adenosine triphosphate (ATP) levels, until the maximum shelf life of 43 days (Lagerberg et al.,
246 2015; Serrano et al., 2016). Recently, Larsson et al. (2020) compared PVC-DEHT to PVC-DEHP blood
247 bags, with DEHT providing adequate blood component quality for the entire storage time.

248 The contribution of blood products to DEHP exposure should be interpreted with caution.
249 Firstly, DEHP continues to leach from blood bags into blood products during storage, making the DEHP
250 content highly dependent on the shelf life of the blood product (Rael et al., 2009; Sampson & de Korte,
251 2011). Sampson and de Korte (2011) showed that transfusion of fresh (< 24 hours old) red blood cell
252 concentrate (RBCC) exposes a patient to 164 µg of DEHP per unit (20 mL), while the use of RBCC
253 stored for 35 days increases DEHP exposure to almost 500 µg per transfusion. Secondly, up to 30% of
254 DEHP can be bound to RBCs, yet most studies only analyze the fluid fraction (Rael et al., 2009;
255 Sampson & de Korte, 2011) and underestimate real exposure. Lastly, not all studies consider the
256 involvement of the plastic infusion circuit used for administrating the blood products, while DEHP
257 remains the predominant plasticizer in these blood transfusion sets, although currently changing
258 (Bourdeaux et al., 2016).

259

260 *Extracorporeal Membrane Oxygenation (ECMO) and cardiopulmonary bypass (CPB)*

261 Historically, DEHP exposure of infants receiving ECMO has been calculated to be extremely
262 high. Shneider et al. (1989) and Karle et al. (1997) calculated DEHP cumulative exposure over 3-10
263 days in a 4 kg infant, respectively 42-140 mg/kg and 10-35 mg/kg. In 2016, Eckert et al. (2016) also
264 assessed the migration of DEHP from a PVC circuit into sheep blood. They calculated an estimated
265 daily intake for 2-6 hours cardiopulmonary bypass (CPB) to be 1-2 mg/kg, based on 400 mL blood

266 volume for a 5 kg infant. Strikingly, *ex vivo* treatments of 24 h and more (ECMO) showed that the TDI
267 could be exceeded by 390-fold (Münch et al., 2018). Eckert et al. (2020) showed that infant cardiac
268 surgery using DEHP-free CPB tubing and blood products stored in DEHP plasticized blood bags
269 resulted in a median exposure of 670 µg/kg, exceeding the TDI 6-25 times.
270

271 ***Enteral nutrition***

272 Subotic et al. (2007) analyzed the extraction of DEHP from PVC nasogastric tubes (NGTs) by
273 immersing 5 cm pieces at 37°C in either gastric juice (collected in the PICU) or typical feeding solutions.
274 Remarkably, the extraction of DEHP into gastric juice was significantly higher than that in feeding
275 solution. Mean daily DEHP exposure over 4 weeks was estimated to be 38 µg/d for feeding solutions
276 and 121 µg/d for gastric juice (Subotic et al., 2007). Takatori et al. (2008) estimated exposure from
277 enteral nutrition in the NICU by irrigating an orogastric tube with commercially available food
278 administered 7 times per day. Worst-case daily exposure to DEHP was calculated to be 148 µg/kg/d,
279 based on a daily nutrition volume of 392 mL, a bodyweight of 3 kg and a DEHP concentration after
280 perfusion of 1130 ng/mL (Takatori et al., 2008). Welle et al. (2005) estimated DEHP exposure from
281 enteral nutrition via PVC tubes to be 726 µg/kg/d for a 2 kg neonate, while using DINCH-plasticized
282 tubes resulted in 94 µg/kg/d DINCH.
283

284 ***Respiratory support***

285 In 1988, Roth et al. (1988) indicated DEHP leaching from PVC respiratory tubing systems by
286 analyzing the condensate collected from water traps in inspiratory- and expiratory tubes of premature
287 neonates ventilated *via* an endotracheal tube (ETT), and found DEHP concentrations reaching up to
288 4100 µg/mL. A decade later, Latini and Avery (1999) compared clinically used and virgin ETTs and
289 observed a 6-12% DEHP loss in previously used tubes. The effective discharge of DEHP from these
290 tubes was proclaimed to occur almost entirely within the first 24 hours of application (Chiellini et al.,
291 2011). Another study executed by Morton et al. (2013) quantified the exact phthalate extraction by
292 immersing ETTs in ultrapure water and reported an increase in DEHP concentration from 6.7 to 149

293 µg/L over 5 days. Importantly, it should be kept in mind that *in vivo* concentrations might be even
294 higher, as plasticizer release is affected by several additional factors, which occur after endotracheal
295 intubation, including airflow, temperature and pH.

296 Recently, Bouattour et al. (2020) developed an *ex vivo* model simulating support *via* a PVC
297 oxygen cannula. Specific cartridges were designed to capture air samples before and after the ventilation
298 circuit to assess the DEHP concentration in these samples. The operator settings included a temperature
299 of 23°C, a flow rate of 2-4 L/min and a duration of 6 days. Concentrations were the highest in samples
300 taken on day 1 of simulation. Inhalation of DEHP was estimated to be 10.6 µg/d (Bouattour et al., 2020).
301 Other parameters than humidity and flow rate (2 L/min), such as temperature, air composition and
302 oxygen content, were not studied. Moreover, oxygen therapy *via* an oxygen cannula does not accurately
303 represent the most invasive and non-invasive respiratory equipment used in a NICU (Wheeler &
304 Smallwood, 2020).

305

306 Despite changing regulations, DEHP is still present in neonatal intensive care medical devices,
307 and labelling is insufficient to guarantee its absence (Fischer Fumeaux et al., 2015; Malarvannan et al.,
308 2019). TOTM, the predominant alternative plasticizer used in medical devices, has a low migration
309 potential (Bourdeaux et al., 2016; Kambia et al., 2001; Münch et al., 2018), but its use involves the risk
310 of DEHP impurity (Bourdeaux et al., 2016; Genay et al., 2011; Gimeno et al., 2014; Welle et al., 2005).
311 TOTM and other frequently used alternatives as DEHT and DINP are not subject to labelling (EU,
312 2008). Leaching experiments showed that medical devices expose premature neonates in the NICU to
313 high levels of DEHP. ECMO (Eckert et al., 2016; Münch et al., 2018), blood transfusion (Bourdeaux et
314 al., 2016; Sampson & de Korte, 2011) and PN (Faessler et al., 2017) are estimated to exceed the TDI
315 the most. Exposure from (non-) invasive respiratory support equipment remains challenging to quantify
316 (Bouattour et al., 2020). Given that different clinical parameters influence leaching, care needs to be
317 taken to match experimental conditions to the clinical situation as much as possible.

318

Assessment of NICU exposure to plasticizers using biomonitoring

The estimated daily intake of plasticizers based on solely *ex vivo* experiments have several limitations. Firstly, caring for a premature neonate in the NICU usually means using multiple medical devices or procedures simultaneously rather than only one device mimicked in an *ex vivo* analysis. Moreover, a "single procedure" may also encompass several devices, exemplified by different serial infusion lines for PN administration. Altogether, this may lead to an underestimation of real *in vivo* exposure.

Current and future biomonitoring strategies in neonates

To quantify whole-body exposure, plasticizers' metabolites are used as biomarkers instead of their parent compounds. These metabolites can be measured in different human matrices (Wang et al., 2019), such as urine, hair and nails.

Urine enables a fast screening, is easy to sample and remains relatively stable in time. As such, urine is the matrix of choice to study exposure in the NICU (Alves, Covaci, et al., 2016; Koch et al., 2017). All phthalate metabolites have been quantified in neonatal urine and could be compared against a reference dose obtained from biomonitoring studies in general populations ((CDC), 2019). Concentrations of these urinary phthalate metabolites can be used to estimate daily exposure to their parent compound when other parameters, like the fractional urinary excretion factor (F_{UE}), creatinine clearance and molar weights of the metabolite and parent compound, are taken into account (Koch et al., 2003). Unfortunately, the use of urine samples has several drawbacks since urinary concentrations are highly dependent on urinary dilution and should be adjusted for creatinine content or specific gravity (Gaynor et al., 2019; Pearson et al., 2009). It is important to note that urinary creatinine concentrations in neonates are highly dependent on gestational age, postnatal age and body weight (Rios et al., 2021). Additionally, only recent exposure can be reflected accurately in urine biomarkers due to a urinary elimination half-life of 6-12 h (Alves, Covaci, et al., 2016). On the other hand, the half-life in premature infants is presumably longer than in adults due to the immature liver and kidney function, characterized by immature glucuronidation and a low glomerular filtration (Gubhaju et al., 2014).

346 Plasma samples have also been used to screen for exposure biomarkers of (alternative)
347 plasticizers (Been et al., 2019). High plasma levels (sometimes exceeding one μM) of DEHP metabolites
348 found in adults (Huygh et al., 2015) and children (Verstraete et al., 2016) hospitalized in the ICU are
349 proof of high and continuous levels of plasticizer exposure during a period with intensive plastic medical
350 device use while being undetectable in plasma of healthy controls (Verstraete et al., 2016). It is tentative
351 to speculate that high plasma levels of DEHP metabolites and/or APs can be detected in neonates.
352 Obtaining plasma to monitor exposure to plasticizers might be associated with some constraints, one of
353 them being hydrolytic enzymes, ubiquitous in blood, which can rapidly hydrolyze parent compounds
354 into primary metabolites and artificially elevate their levels *ex vivo* (Calafat et al., 2013). Much lower
355 levels in blood compared to urine increase the risk of contamination that can obscure true exposure
356 (Calafat et al., 2013). Furthermore, the half-life in plasma is even shorter than in urine (Verstraete et al.,
357 2016).

358 Given the difficulties of obtaining plasma in neonates and the drawbacks in the detection method
359 and interpretation, we can speculate that alternative matrices (including scalp hair and nails) will soon
360 be available to monitor exposure to plasticizers in neonates. We hope and anticipate that the advantages
361 and availability of these alternative matrices will initiate further discussion/debate on this topic in the
362 future.

363 Scalp hair is well known for the assessment of drug (ab)use. Sampling is noninvasive and easy
364 to collect and store. Chemicals are considered to be incorporated in hair *via* passive diffusion during the
365 anagen growing phase (Kirschbaum et al., 2009), characterized by increased metabolic activity and cell
366 division (Paus et al., 2014). This alternative matrix reflects short- and long-term exposure. Scalp hair
367 starts growing during the 3rd trimester of pregnancy and can be tested until three months after birth,
368 providing a broad detection window. In 2019, phthalate and AP metabolites were measured in hair to
369 monitor human exposure (Yin et al., 2019). A disadvantage with this type of detection method is the
370 absence of epidemiological studies as a reference.

371 Nails could also be a valuable alternative noninvasive matrix for estimating long-term human
372 exposure to DEHP and other phthalates. Phthalate metabolites have been quantified in nail samples, yet

373 metabolization characteristics and factors influencing migration from blood or different body
374 compartments into nails require further investigation (Alves, Koppen, et al., 2016).

375 Meconium, amniotic fluid and breast milk: Detection of metabolites in meconium has been
376 suggested for measuring *in utero* exposure to phthalates (Arbuckle et al., 2016; Guo et al., 2020).
377 Advantages are that its collection is non-invasive, and that meconium accumulates from the 12th week,
378 representing cumulative exposure throughout pregnancy. Urine samples should be analyzed
379 simultaneously to correct for urinary contamination. DEHP metabolites were also determined in
380 amniotic fluid of pregnant women undergoing amniocentesis (Katsikantami et al., 2020). Still, since
381 both amniotic fluid and meconium reflect prenatal exposure, they are of limited value to assess exposure
382 in the NICU. Some studies have reported phthalate metabolites in breast milk (An et al., 2020; Arbuckle
383 et al., 2016). However, there is no information about the half-life of metabolites in this matrix, and
384 esterases in milk could hydrolyze diesters to primary metabolites (Arbuckle et al., 2016; Katsikantami
385 et al., 2020).

386

387 ***Total NICU exposure assessed by biomonitoring***

388 Table 3 summarizes all studies, from 2000 until 2020, assessing NICU exposure to plasticizers
389 based on urinary concentrations of their metabolites. The latter was achieved by collecting urine *via* a
390 cotton gauze placed in the infants' diapers.

391

392 Calafat et al. (2004) prospectively collected urine samples from premature neonates born at less
393 than 26 weeks gestational age (GA) and determined urinary concentrations of both primary (MEHP)
394 and secondary, mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl)
395 phthalate (MEOHP), metabolites. Median urinary concentrations of the secondary metabolites, the most
396 valuable biomarkers immune to external contamination, were several folds higher than in the general
397 population ((CDC), 2019; Frederiksen et al., 2020). In another level III NICU, they analyzed neonatal
398 urine samples and registered DEHP-exposure categories based on treatment with (invasive) medical
399 devices for three days before urine sampling (Calafat et al., 2009; Green et al., 2005; Weuve et al.,
400 2006). The intensity of DEHP-containing product use was linearly correlated with urinary levels of all

401 metabolites. Based on the formula defined by Koch et al. (2003), which used the urinary concentrations
402 of MEHHP and MEOHP with an assumed creatinine clearance rate of 9.8 mg/kg/d, an estimated daily
403 intake (EDI) of 352 µg/kg/d DEHP was calculated in the highest exposure group (Weuve et al., 2006).
404 Additionally, Koch et al. (2006) determined MECCP and MMCHP as two extra secondary metabolites
405 since they are expected to reflect a broader window of exposure. The mean and maximum EDI of DEHP
406 were 42 and 2300 µg/kg/d, respectively (Koch et al., 2006). EDI calculations need to be interpreted
407 cautiously since urinary excretion fractions of metabolites are derived from adult studies, and average
408 creatinine excretion is often used instead of individual concentrations. In addition, immature metabolism
409 and glucuronidation pathways should be considered as they may also lead to underestimating exposure
410 levels.

411 A Taiwanese study took urine samples weekly from premature and term (control) neonates (Su
412 et al., 2012). Median levels of DEHP-metabolites were significantly higher in neonates treated with an
413 endotracheal or a gastric tub. In contrast, concentrations of DEHP-metabolites were substantially lower
414 in samples from control neonates. Frederiksen et al. (2014) compared concentrations of different
415 phthalate metabolites in urine samples from full-term and preterm Finnish infants in the neonatal period
416 and consecutive infant period. The concentration of DEHP metabolites were 50 times higher in preterm
417 infants than in full-term infants after already one week. Children with relatively high exposure to at least
418 one phthalate were also highly exposed to other phthalates, and as a result, may exceed the 'safe
419 thresholds' even more. Remarkably, the relative proportion of carboxylated metabolites decreased and
420 that of oxidized metabolites, on the other hand, increased by postmenstrual age, defined as the sum of
421 gestational age and postnatal age (Frederiksen et al., 2014). As such, the influence of prematurity on
422 metabolization patterns needs to be kept in mind, even though information about a potential protective
423 or harmful effect is still missing. Finally, birth weight might be of importance since concentrations of
424 both primary and secondary phthalate metabolites (*e.g.,* MEHHP) were significantly higher in the first
425 urine samples of extremely low birth weight (ELBW, < 1000 g) neonates relative to those in very low
426 birth weight (VLBW, 1000-1500 g) neonates (Demirel et al., 2016).

427 In 2016, Strommen et al. (2016) measured phthalate metabolites in urine samples from VLBW
428 infants. Significantly higher phthalate metabolites were found in infants with lower birth weight, late-

429 onset sepsis or bronchopulmonary dysplasia (BPD). In addition, there was a significant positive
430 correlation between duration of respiratory support (invasive and noninvasive) and urinary
431 concentration of DEHP metabolites. The NICU-HEALTH, a prospective project set up by Stroustrup
432 *et al*. (Stroustrup, Bragg, Andra, et al., 2018; Stroustrup, Bragg, Busgang, et al., 2018) in a level III
433 NICU in New York, collects urine samples and assesses medical equipment exposure in premature
434 neonates with birth weight less than 1500 g. Phase I of this study confirmed that exposure to more
435 invasive medical equipment and respiratory support equipment are still associated with higher urinary
436 concentrations of DEHP metabolites. In 2019, Jenkins et al. (2019) detected an association between
437 urinary DEHP metabolites and prior use of IV lines and respiratory support equipment labelled
438 containing DEHP. A more extensive IV and respiratory DEHP exposure in hypertensive patients also
439 noted an association between increased blood pressure and postnatal DEHP exposure. Gaynor et al.
440 (2019) showed that in neonates undergoing cardiac surgery, concentrations of urinary DEHP
441 metabolites rose significantly postoperatively, rising 100 times higher than the reference levels.
442 The ARMED project by Pinguet et al. (2019) was the first to add urinary metabolites of APs to
443 DEHP metabolites in NICU-admitted newborns. DEHP metabolite concentrations were consistent with
444 other NICU studies assessed between 2010 and 2020 (see Table 3). Secondary metabolites were the
445 major metabolites, and MEHP the minor metabolite. Pinguet et al. (2019) also observed a decrease
446 compared to Calafat et al. (2004). DEHP metabolites were 100- to 2000-fold more concentrated than
447 alternative plasticizer' metabolites.
448
449 Up to this date, urine is the sole matrix studied for plasticizer exposure in the NICU. Scalp hair
450 and plasma are promising alternative matrices to assess long term accumulation and recent short time
451 exposure, respectively, though reference values are still largely missing. Although decreasing over the
452 previous two decades, urinary phthalate metabolite concentrations of neonates being cared for in the
453 NICU are still several folds higher than in the general population and the TDI. Except for Pinguet et al.
454 (2019), no clinical studies analyzed metabolites of APs in neonatal samples. Lower birth weight and
455 lower gestational age (markers of prematurity) are related to higher phthalate metabolites, explained by
456 increased use of plastic devices. Intensity of DEHP-containing medical product use is linearly associated

457 with urinary levels of all DEHP metabolites (Calafat et al., 2009; Green et al., 2005; Weuve et al., 2006).
458 Exposure to (invasive and noninvasive) respiratory support is significantly positively correlated with
459 higher urinary concentrations of DEHP metabolites (Strommen et al., 2016; Stroustrup, Bragg, Andra,
460 et al., 2018; Stroustrup, Bragg, Busgang, et al., 2018; Su et al., 2012). Other important sources are IV
461 lines used for PN, gastric tubes and cardiac surgery.

462

463 **Health effects of plasticizers on (premature) infant development**

464 The reproductive and endocrine-disrupting toxicity of phthalate exposure has been well
465 documented (Benjamin et al., 2017; Radke et al., 2019; Rowdhwal & Chen, 2018; Zarean et al., 2016).
466 Still, much less is known about its effects on lung and brain development, the two typical long-term
467 challenges for premature neonates.

468

469 ***Phthalates and respiratory development***

470 Experimental studies in *in vitro* models and *in vivo* animal models indicate some mechanisms
471 of action presenting adverse effects of phthalates on respiratory development in neonates. On a
472 subcellular level, DEHP and its metabolites showed to alter the activation of airway epithelial cell
473 peroxisome proliferator-activated receptor (PPAR) (Casals-Casas et al., 2008; Manteiga & Lee, 2017;
474 Wu et al., 2011), which is essential for normal lung structure and function (Simon et al., 2006). In
475 rodents, phthalates in the form of dust or vapours were reported to lead to airway inflammation (Alfardan
476 et al., 2018) and airway hyperresponsiveness (Guo et al., 2012), aggravated by oxidative-stress-
477 mediated pathways (Zhou et al., 2020). Observational studies showed a strong positive association
478 between prenatal or early childhood DEHP exposure and later asthma development, confirmed by two
479 recent systematic reviews and meta-analyses (Li et al., 2017; Wu et al., 2020).

480 Interestingly, DEHP can also modify lung parenchyma both at structural and functional levels.
481 Perinatal DEHP exposure in rats leads to changes in lung alveolar development, characterized by a
482 decreased number of parenchymal airspaces, decreased alveolar septation, reduced gas exchange surface
483 and increased collagen deposition (Atia & Abdel-Gawad, 2019; Camacho et al., 2020; Chen et al., 2010;

484 Guo et al., 2012; Liang et al., 2018; Magliozzi et al., 2003; Rosicarelli & Stefanini, 2009). Since these
485 alterations are similar to the pathology observed in infants with BPD (Bancalari & Jain, 2019), different
486 authors hypothesized that DEHP exposure could exacerbate BPD in the NICU (Atia & Abdel-Gawad,
487 2019; Camacho et al., 2020; Liang et al., 2018; Magliozzi et al., 2003; Rosicarelli & Stefanini, 2009).
488 DEHP exposed rat pups showed a delayed differentiation of type II pneumocytes into flat
489 epithelial type I pneumocytes (Magliozzi et al., 2003; Rosicarelli & Stefanini, 2009). However, the
490 morphology of type II pneumocytes was also altered, with a decreased amount of lung surfactant (Atia
491 & Abdel-Gawad, 2019; Rafael-Vazquez et al., 2018). Resulting in a reduced gas exchange area and
492 inadequate surfactant production, perinatal DEHP exposure might aggravate neonatal respiratory
493 distress syndrome (RDS), an important cause of morbidity and mortality in premature neonates (Yadav
494 et al., 2021).
495
496 ***Phthalates and neurodevelopment***
497 Proposed mechanisms in how perinatal phthalate exposure affects neurodevelopment include
498 androgen-dependent brain differentiation, impact on neurotransmitter systems, and inference with
499 myelination and neurogenesis processes (Engel et al., 2021; Lee et al., 2018). Boys are expected to be
500 more vulnerable to phthalate exposure than girls since phthalates act as androgen receptor antagonists
501 (Berghuis et al., 2015). Similarly, DEHP exposure negatively impacted hippocampal development in
502 males but not in female rats (Smith et al., 2011). Postnatally DEHP-exposed mice showed a reduction
503 in neural progenitor cell proliferation and differentiation in the dentate gyrus (Komada et al., 2020), an
504 essential structure within the hippocampus, critical in consolidating information from short- to long-
505 term memory. Moreover, additional studies in rodents also showed prenatal DEHP exposure to influence
506 the cortical regions by reducing the neocortical proliferation and neurogenesis (Komada et al., 2016),
507 resulting in a reduction in neuron and synapse numbers and reduced size of the prefrontal cortex
508 (Kougias et al., 2018).
509 Multiple birth cohort studies combining maternal urine during gestation and longitudinal
510 follow-up data showed a connection between urine phthalate metabolite levels and autism spectrum
511 disorder (Jeddi et al., 2016; Schug et al., 2015), and attention deficit hyperactivity disorder in their

512 children (Ejaredar et al., 2015; Engel et al., 2021; Ponsonby et al., 2020; Schug et al., 2015). Maternal
513 urinary DEHP metabolites were associated with higher delinquent behavior and externalizing problem
514 scores in adolescence (Huang et al., 2019). Further, there is a significant association between prenatal
515 DEHP exposure, diminished psychomotor function (Lee et al., 2018) and reduced communication skills
516 (Ejaredar et al., 2015) during childhood. In addition to impaired behavioral development, different birth
517 cohorts showed that prenatal phthalate exposure is associated with adverse cognitive outcomes in
518 offspring (Dzwilewski et al., 2021; Ejaredar et al., 2015; Zhang et al., 2019), more pronounced in male
519 infants (Merced-Nieves et al., 2021). A systematic review by Radke et al. (2020) observed that the
520 results among the different epidemiological studies are not entirely consistent, mainly when focusing
521 on cognitive development. The latter could be explained by the exposure effects of phthalate mixtures
522 (and the temporal changes in the contribution of specific phthalates), periods of increased susceptibility
523 (late pregnancy, early infancy, adolescence) and sex-specific effects (Engel et al., 2021; Radke et al.,
524 2020). Sex-specific effects were not only identified on cognitive development, but an impact is also
525 observed on psychomotor and behavioral development in boys (Zhang et al., 2019).

526 In children treated in the pediatric intensive care unit (PICU), plasma levels of DEHP
527 metabolites were independently and robustly associated with vital attention deficit four years after
528 critical illness (Verstraete et al., 2016). Stroustrup, Bragg, Andra, et al. (2018) implemented the NICU
529 Network Neurobehavioral Scale before discharging premature newborns (birth weight <1500 g) and
530 discovered a positive association between NICU-based exposure to phthalate mixtures and improved
531 attention and social response. This suggests that the impact of phthalate exposure on neurodevelopment
532 in neonates may follow a non-linear trajectory and could potentially even accelerate specific neural
533 networks' development.

534

535 ***Health effects of alternative plasticizers***

536 Alternative plasticizers have been used for over a decade, but data regarding human exposure
537 and health effects are limited (Bui et al., 2016). After *in vitro* toxicity screening of chemically engineered
538 alternatives, acute toxicity *in vivo* studies have been used to identify presumably safer plasticizers
539 (Albert et al., 2018). Alternative plasticizer use in medical devices is constantly evolving as there is no

540 reference to guide manufacturers in the choice and amount to be integrated into their products (Bernard
541 et al., 2014).
542 DEHT is a structural isomer to DEHP, with the para- compared to orthoposition of the benzene-
543 group assumed to allow DEHT for complete metabolism and therefore a less toxic profile (Wirnitzer et
544 al., 2011). Nevertheless, Kambia et al. (2019) observed hormonal activities of DEHT-derived
545 metabolites, by stimulating human estrogen and androgen receptors. DINCH was developed as a non-
546 aromatic analogue of DINP and has been evaluated to preserve whole blood (David et al., 2015). DEHA
547 is a liquid of low volatility, usually blended with other plasticizers, mostly used in devices for
548 hemodialysis and transfusion (Bernard et al., 2014). TOTM and ATBC are expected to result in less
549 toxicity due to their metabolic breakdown. TOTM shows weaker hepatotoxicity than DEHP due to its
550 slow metabolic transformation capacity, with a low urinary excretion rate (Hollerer et al., 2018) and up
551 to 75% of the oral dose eliminated in the feces, primarily as an unchanged parent compound (Bernard
552 et al., 2014). Despite its rapid absorption and excretion, ATBC is still a concern due to its high intrinsic
553 migration potential (Bernard et al., 2014).
554
555 A limited number of risk assessment reports are available. Table 4 summarizes the critical
556 endpoints of the most common APs by introducing the no observed adverse effect levels of (NOAELs)
557 each compound derived from rat models, published by SCENIHR (Testai et al., 2016) and the Danish
558 Environmental Protection Agency (EPA, 2014). Derived no-effect levels (DNEL) are used as a TDI
559 substitute for the general population.
560 Even when assuming similar leaching rates, the margin of safety associated with the critical
561 toxicity outcome of APs exceeds that of DEHP from 3 (DINP) up to 8 (DINCH, DEHA) and even more
562 than 20 (TOTM, DEHT, ATBC) times (Testai et al., 2016). However, TOTM, DINCH and DEHT are
563 poorly absorbed after oral administration explaining at least in part the relatively low toxicity observed
564 in oral toxicity studies (Testai et al., 2016). Therefore, repeat dose toxicity studies after IV exposure are
565 more relevant for the parenteral route of exposure leaching from medical devices (meaning 100%
566 bioavailability). As shown in Table 4, studies assessing toxicity after IV exposure (Cammack et al.,
567 2003; David et al., 2015; Wirnitzer et al., 2011; Xu et al., 2019) show that the safety margin of APs

568 exceeds that of DEHP less than after oral exposure, DEHT 6 compared to more than 20 times, and
569 DINCH 5 compared to 8 times. Despite being used in different medical devices used for infusion and
570 transfusion, the toxicity of DINP, DEHA and ATBC has not been assessed after IV exposure.
571 Unfortunately, data gaps remain regarding non-standard toxicological endpoints (Bui et al.,
572 2016), no studies were found on human health effects of these APs.
573
574 ***Effects of cumulative exposure***
575 Even though different phthalates show to be associated with children's adverse health outcomes,
576 few studies examined the effect of mixtures of these compounds. Since NICU neonates are
577 simultaneously exposed to different plastic medical devices or procedures, the possible risk of
578 cumulative exposure to multiple plasticizers is important to be considered. Exposure to a mixture of
579 contaminants may be associated with adverse health endpoints, even though associations are not found
580 with exposure levels of individual compounds below regulatory doses (Stroustrup et al., 2019).
581 Cumulative risk to different phthalates and APs can be assessed by estimating a hazard index
582 (HI), defined as the sum of multiple hazard quotients (HQ), *i.e*. the ratio of (estimated) exposure over
583 the reference dose (TDI or NOAEL), derived from exposure to different compounds (Frederiksen et al.,
584 2014). Concerning non-classic toxicological endpoints, traditional methods (*e.g.,* ordinary or logistic
585 regression) for effect assessment of environmental mixtures on health outcomes induce analytical
586 difficulties when correlations occur between different chemicals within (phthalates) or between
587 (phthalates and APs) classes of contaminants (Carrico et al., 2015; Stroustrup et al., 2019). However,
588 Weighted Quantile Sum (WQS) regression offers a statistical strategy for objective consideration of
589 multiple concurrent exposures by empirical construction of weighted indices as an estimation of the
590 mixture exposure and can be used in regression models (Adgent et al., 2020; Carrico et al., 2015;
591 Stroustrup et al., 2019).
592
593 Experimental and human epidemiological studies show that impaired respiratory development
594 might be an adverse health outcome associated with perinatal phthalate exposure. To date, no studies

595 have assessed the association between phthalate exposure in the NICU and respiratory function in later
596 life. For impaired neurodevelopment, studies of perinatal phthalate exposure in animal models are
597 generally consistent with birth cohort studies, pointing at internalizing and externalizing behaviors,
598 attention deficit, cognitive and psychomotor impairments as the most observed effects. The long-term
599 neurodevelopmental impact of iatrogenic exposure to phthalates during NICU remains largely unknown.
600 The health risk of APs measured on classical toxicological endpoints is less critical than DEHP. Still,
601 no clinical endpoints have been studied because of insufficient human exposure data.

602

603 **The NICU population is at high risk for exposure to plasticizers**

604 In recent decades, despite evolving regulation, overall urinary DEHP metabolites have
605 decreased but remain elevated above the TDI (Pinguet et al., 2019), especially in the extremely
606 premature group (Frederiksen et al., 2014).

607 Medical procedures leading to the highest exposure are ECMO (Eckert et al., 2016; Münch et
608 al., 2018), blood transfusion (Bourdeaux et al., 2016; Sampson & de Korte, 2011) and PN (Faessler et
609 al., 2017). A major part of NICU exposure is IV exposure with a bioavailability of 100%, which is
610 higher than through oral exposure on which most toxicity data are based (Testai et al., 2016). The
611 contribution of respiratory support equipment remains challenging to quantify, even though this group
612 of medical devices is still the most plasticized by DEHP. Their use is highly correlated with higher
613 levels of DEHP urinary metabolites.

614 Premature neonates are especially vulnerable to exogenous toxicants since the perinatal period
615 is a critical window for lung (Woods, 2016) and brain (Raybaud et al., 2013) maturation, specifically
616 alveolarization, the latest stage of lung development. Indeed, inhaled phthalates, leaching from
617 respiratory support systems, could act directly at these vulnerable peripheral airways.

618 Neonates with lower gestational age or birth weight are at increased risk of developing
619 complications, such as sepsis and bronchopulmonary dysplasia treated with plastic medical devices,
620 exposing them to even more plasticizers (Strommen et al., 2016). Moreover, urinary concentrations of
621 metabolites of different phthalates showed strong correlations in a NICU population, indicating that

622 neonates are presumably exposed to various toxicants simultaneously (Frederiksen et al., 2014). In
623 addition, exposure of premature neonates to plasticizers is relatively higher than in children or adults
624 due to their low body weight and immature renal and liver metabolism (Gubhaju et al., 2014).

625 Although phthalates were generally not considered pneumo- or neurotoxic pollutants,
626 respiratory diseases and impaired neurodevelopment are essential health outcomes correlated with
627 phthalate exposure at biological and epidemiological levels in childhood, albeit studies combining
628 biomonitoring of plasticizers in the NICU and respiratory or neurodevelopmental assessment afterwards
629 are scarce to non-existing. Moreover, for some APs, data gaps remain regarding non-standard
630 toxicological endpoints of APs, making their risk assessment insufficient (Bui et al., 2016). Lastly,
631 NICU neonates are simultaneously exposed to different plasticizers, without sufficient knowledge on
632 the effect of cumulative exposure.

633 Conclusions and Perspectives

634 There is an urgent need to generate adequate information relevant to assessing current exposure
635 levels of plasticizers in the NICU. This could be achieved by extending biomonitoring with non-invasive
636 matrices, like hair and nails, to monitor the cumulative exposure of metabolites of phthalates and
637 alternative plasticizers. The limited human risk assessment of AP exposure remains another important
638 knowledge gap. Additionally, investigators should consider combining exposure assessment in the
639 NICU with a standardized respiratory and neurocognitive follow-up since both are significant
640 contributors to morbidity later in life.

641 The lower migration potentials of TOTM, DINCH and DEHT provide opportunities to reduce
642 exposure, but improving leaching experiments concerning real-life clinical conditions is warranted. *Ex*
643 *vivo* experiments should start from a clinical, theoretical assumption approaching the NICU
644 environment as much as possible to determine applicable acceptable migration limits. In addition, a
645 clinically relevant *ex vivo* model assessing exposure from (non-)invasive respiratory support should be
646 developed as well.

647 Even though the MDR entered into application on 26 May 2021, we cannot depend on
648 legislation to change plasticizer use in this vulnerable population. Awareness about the potential risks

649 of plasticizer exposure in the NICU is lacking mainly among healthcare professionals, even those
650 providing neonatal intensive care (Bickle-Graz et al., 2020). (Environmental) toxicologists and
651 manufacturers have addressed the problem of plasticizer exposure for some time. Still, the production
652 of safe alternatively plasticized medical devices (*e.g.,* blood bags) also relies on physicians and hospitals
653 asking for DEHP-free products. As such, clinicians can and should help in determining alternative
654 strategies. When evaluating the benefit-risk ratio of alternatives, health hazards need to be compared to
655 those of phthalates; none withstanding the impact of using alternatives on the functionality and
656 performance of medical devices is equally important and should be evaluated by clinicians (Den Braver-
657 Sewradj et al., 2020). Finally, appropriate labelling of medical devices indicating the presence of any
658 plasticizer remains the priority and has to be executed in cooperation with nurses and physicians.
659

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664

665 **Disclosure statement**

666 The authors report no competing interests.
667

668 **Informed Consent Statement**

669 Not applicable.

Tables

Table 1: Overview of phthalates and alternative plasticizers, and their major metabolites; MW: molecular weight (g/mol); n/a: not available

Parent compounds				**Metabolites**		
Name	**Abbreviation**	**Formula**	**MW**	**Name**	**Abbreviation**	**MW**
Di-(2-ethylhexyl) phthalate	DEHP	$C_{24}H_{38}O_4$	390.6	Mono-2-ethylhexyl phthalate	MEHP	278.3
				Mono-(2-ethyl-5-hydroxyhexyl) phthalate	MEHHP / 5-OH-MEHP	294.3
				Mono-(2-ethyl-5-oxohexyl) phthalate	MEOHP / 5-oxo-MEHP	292.3
				Mono-(2-ethyl-5-carboxypentyl) phthalate	MECPP / 5-cx-MEPP	308.3
				Mono-(2-carboxymethyl-hexyl) phthalate	MMCHP / 2-cx-MMHP	308.3
Diethyl phthalate	DEP	$C_{12}H_{14}O_4$	222.2	Mono-ethyl phthalate	MEP	222.2
Di-n-butyl phthalate	DnBP	$C_{16}H_{22}O_4$	278.3	Mono-*n*-butyl phthalate	MnBP	222.2
Diisobutyl phthalate	DiBP	$C_{16}H_{22}O_4$	278.3	Mono-isobutyl phthalate	MiBP	222.2
Benzylbutyl phthalate	BzBP	$C_{19}H_{20}O_4$	312.4	Mono-benzyl phthalate	MBzP	256.3
Diisononyl phthalate	DINP	$C_{26}H_{42}O_4$	418.6	Monoisononyl phthalate	MINP	292.4
				Mono (carboxyisooctyl) phtalate	OH-MINP	322.4
				Monoisononyl phthalate	cx-MINP	292.4
Di-(2-ethylhexyl) terephthalate	DEHTP	$C_{24}H_{38}O_4$	390.6	Mono(2-ethylhexyl) terephthalate	MEHTP	278.3
				Mono(2-ethyl-5-hydroxyhexyl) terephthalate	OH-MEHTP	294.3
				Mono(2-ethyl-5-carboxypentyl) terephthalate	5-cx-MEPTP	308.3
Tris-(2-ethylhexyl) trimellitate	TOTM	$C_{33}H_{54}O_6$	546.8	1,4-di-(2-ethylhexyl) trimellitate	1,4-DEHTM	434.6
				2,4-di-(2-ethylhexyl) trimellitate	2,4-DEHTM	434.6
Diisononyl cyclohexane-1,2-dicarboxylate	DINCH	$C_{26}H_{48}O_4$	424.7	Cyclohexane-1,2-dicarboxylic mono isononyl ester	MINCH	302.4
				Cyclohexane-1,2-dicarboxylic mono hydroxyisononyl ester	OH-MINCH	314.4
				Cyclohexane-1,2-dicarboxylic mono carboxyisooctyl ester	cx-MINCH	328.4
Di-(2-ethylhexyl) adipate	DEHA	$C_{22}H_{42}O_4$	370.6	Mono(2-ethylhexyl) adipate	MEHA	258.4
				Mono(2-ethyl-5-hydroxyhexyl) adipate	OH-MEHA	274.4
				Mono-5-carboxy-2-ethylpentyl adipate	5-cx-MEPA	274.4
Acetyl tributyl citrate	ATBC	$C_{20}H_{34}O_8$	402.5	n/a	n/a	n/a

Table 2: Estimated DEHP exposure from different sources in the NICU

Medical Device	Simulant	Experimental setup	Estimated DEHP Exposure	Reference
Infusion line		Dynamic, 24 h, 27 °C	*2 kg neonate*	Loff et al. (2000)
	20 % lipid emulsion	24 ml	10186 µg/d	
	Midazolam	24 ml	26 µg / infusion	
	Fentanyl	28.8 ml	132 µg / infusion	
	Propofol	10 ml	6561 µg / infusion	
Perfusion line	20 % lipid emulsion	24 ml, 1 ml/h, 24 h, 23-25 °C	*1 kg neonate*	Faessler et al. (2017)
			1116 µg/kg/d	
Blood bag	Plasma	Fresh	312 µg / 20 ml	Sampson and de Korte (2011)
		5-day storage – 4 °C	1362 µg / 20 ml	
	RBC concentrate	Fresh	164 µg / 20 ml	
		35-day storage – 4 °C	498 µg / 20 ml	
	PC in plasma	Fresh	300 µg / 20 ml	
		7-day storage – 22 °C	606 µg / 20 ml	
	Exchange transfusion	Fresh	6640 µg / 800 ml	
		24-hour storage – 4 °C	10640 µg / 800 ml	
PVC tubing used for CPB/ECMO	Sheep blood	320 ml, 400 mL/min, 24 h, 37 °C	*5 kg infant (400 ml blood volume)*	Eckert et al. (2016)
	CPB (2 h)		1200 µg/kg	
	CPB (6 h)		2600 µg/kg	
	ECMO (24 h)		6000 µg/kg	
Gastric tube	Enteral nutrition (20 % lipid emulsion)	60 mL, 5 mL/h, 25 °C	726 µg/kg/d (2 kg neonate)	Welle et al. (2005)
	Enteral nutrition	Immersion of 5 cm NGT, 4 weeks, 37 °C	38 µg/d (*per 5 cm)*	Subotic et al. (2007)
	Gastric juice		121 µg/d (*per 5 cm)*	
	Enteral nutrition (20 % lipid emulsion)	7 x 56 mL over 15 min, 25 °C	148 µg/kg/d *(3 kg neonate)*	Takatori et al. (2008)
Oxygen canula	Medical air	2 L/min, humidified	11 µg/d	Bouattour et al. (2020)

Table 3: Studies (n=11) assessing NICU exposure to plasticizers using biomonitoring (urinary metabolite concentrations, median ng/mL, not corrected for urinary dilution unless stated otherwise)

Study population	**Exposure assessment**	**Subgroup analysis**	**MEHP**	**MEHHP**	**MEOHP**	**MECPP**	**Sum DEHP$_m$**	**Mean EDI of DEHP (µg/kg/d)**	**Reference**
Extreme premature neonates >2 w IV infusion (n=6) - GA 23-26 w - BW 440-880 g	Urine sample - Day 4-discharge - Metabolites of DEHP	n/a	129	2 221	1697	n/a	n/a	n/a	Calafat et al. (2004) **New Jersy, USA**
Level III NICU > 3 d (n=54)	Medical device exposure category for 1-3 days - Low: bottle and/or gavage feedings - Medium: IV hyperalimentation, nCPAP - High: continuous UVC, ETT, CVC Urine sample - At the end of the observation period - Metabolites of DEHP	*Overall* *Low* *Medium* *High*	22 4 28 86	267 27 307 555	256 29 286 598	n/a	n/a	352[c]	Calafat et al. (2009); Green et al. (2005); Weuve et al. (2006) **Boston, USA**
Neonates undergoing a medical procedure with risk of high DEHP exposure (n=45) - GA 25-40 w - BW 490-4200 g	Urine sample - Metabolites of DEHP	n/a	n/a	n/a	n/a	n/a	n/a	42[d]	Koch et al. (2006) **Erlangen, Germany**
Premature neonates (n=32) - GA <37 w - VLBW <1500 g (n=20) - LBW <2500 g (n=10) Control neonates (n=31)	Medical device exposure category - Respiratory tract - Gastrointestinal tract - Cardiovascular tract - Chest tube Urine sample - Day 0-discharge - Metabolites of DEHP	*ETT +* *GT+ ETT-* *ETT/GT-* *Ctrl - IV* *Control*	332 294 164 101 73	1 335 1 175 406 71 63	1 093 971 377 87 50	n/a	2 924 2 581 947 354 155	n/a	Su et al. (2012) **Chung Shan, Taiwan**
Full-term infants (n=58) Preterm infants (n=67) - GA 24.7-36.6 w	Urine sample - Day 1-7 - Month 1-14 (PMA) - Metabolites of DEHP, DEP, DiBP, DnBP, BBzP & DiNP	*PT (all)* *FT (all)* *PT (D7)* *FT (D7)* *PT (M2)* *FT (M2)*	0.99 0.44	8.6 5.01	6.1 3.9	18 11	45 8.8 1 000 20	243[e] 4.34 7.2 7.0	Frederiksen et al. (2014) **Kuopio, Finland**
Premature infants (n=36) - GA <32 w and/or BW <1500 g - NICU > 2 w	Medical device exposure category - Only feeding tube after 2 weeks - Extra medical devices after 2 weeks Urine sample - Day 1-discharge - Metabolites of DEHP	*Overall* *Low (W4)* *High (W4)*	n/a	84 66 255	48	n/a	n/a	n/a	Demirel et al. (2016) **Istanbul, Turkey**

VLBW infants (n=46) - BW <1500 g - GA 24-33 w	Urine sample - Week 1, 3 & 5 - Metabolites of DEHP, DEP, BBzP, DiBP, DnBP, DiNP	*Week 1* *Week 3* *Week 5*	57 8.0 7.5	122 96 72	68 59 48	1 215 837 917	1 441 1 017 1 105	n/a	Strommen et al. (2016) **Oslo, Norway**
Premature infants (n=64) - BW <1500 g - 81 patients, 64 survived	Medical device exposure category - Low: no respiratory support, enterally fed - Medium: non-invasive respiratory support - High: invasive respiratory support, IV hyperalimentation, gastric decompression Urine sample - Metabolites of DEHP, DEP, BBzP, DiBP, DnBP	*Overall* *Low* *Medium* *High*	7.1	12	12	50	 68[a] 76[a] 134[a]	n/a	Stroustrup, Bragg, Andra, et al. (2018); Stroustrup, Bragg, Busgang, et al. (2018) **New York City, USA**
Premature infants (n=18) - GA < 37 w	Medical devices exposure (based on product labelling) - Volume of IV fluid from DEHP-containing bags - Number of days connected to respiratory tubing containing DEHP Urine sample - Metabolites of DEHP	n/a	n/a	n/a	n/a	n/a	n/a	n/a	Jenkins et al. (2019) **Boise, USA**
Neonates undergoing cardiac surgery (n=18)	Urine samples - Pre- and post-operatively - Metabolites of DEHP	*Pre-op* *Post-op*	1.7 27	11 229	7.2[b] 149	56 1 166	n/a	n/a	Gaynor et al. (2019) **Philadelphia, USA**
NICU newborns (n=104) ARMED project	Urine sample - After 24 h of exposure to medical device - Metabolites of DEHP, DEHT, DEHA, DINP, DINCH, TOTM	n/a	38	50	36	n/a	n/a	n/a	Pinguet et al. (2019) **Clermont-Ferrand & Lille, France**

a) Specific gravity adjusted concentration
b) Geometric mean concentration
c) EDI based on concentrations of MEHHP & MEOHP
d) EDI based on concentrations of MEHHP, MEOHP, MECPP & MMCHP
e) EDI based on concentrations of MEHP, MEHHP, MEOHP & MECPP
f) n/a: not determined or not published by the authors

Table 4: Comparison of toxicological endpoints of DEHP with alternative plasticizers, and their respective TDI (only for DEHP and DINP) or derived no-effect levels (DNEL) (based on the SCENIHR (Testai et al., 2016) and the Danish EPA (EPA, 2014))

Compound	Lowest NOAEL in mg/kg/d (critical endpoints)	DNEL (general population)	NO(A)EL in mg/kg/d after IV exposure (critical endpoints)
DEHP	4.8 (reproductive toxicity) (Testai et al., 2016)	0.048 mg/kg/d (Testai et al., 2016) (TDI)	60 (reproductive toxicity and lung alveolar development) (Cammack et al., 2003)
DINP	15 (hepatotoxicity and kidney toxicity) (EPA, 2014)	0.15 mg/kg/d (EPA, 2014) (TDI)	n/a
DEHT	100 (body weight, hematological effects) (EPA, 2014)	3.95 mg/kg/d (EPA, 2014)	381.6 (reproductive toxicity, hepatotoxicity and kidney toxicity) (Wirnitzer et al., 2011)
TOTM	100 (reproduction) (EPA, 2014) 100 (reproductive toxicity, hepatotoxicity) (Testai et al., 2016)	1.13 mg/kg/d (EPA, 2014)	n/a
DINCH	40 (liver/kidney weight) (EPA, 2014) 40 (kidney, thyroid follicular cell hyperplasia and adenomas) (Testai et al., 2016)	2 mg/kg/d (EPA, 2014)	300 (behavior, organ weight and serum chemistry) (David et al., 2015)
DEHA	40 (kidney weight reduction) (EPA, 2014; Testai et al., 2016)	n/a	200 (decreased body weight, increased liver weight) (Xu et al., 2019)
ATBC	100 (decreased BW, hematological and biochemical changes, increased liver weight) (EPA, 2014; Testai et al., 2016)	1 mg/kg/d (EPA, 2014)	n/a

Figures

Figure 1: Typical metabolism pathways for plasticizers in the human body (DEHP is given here as example)

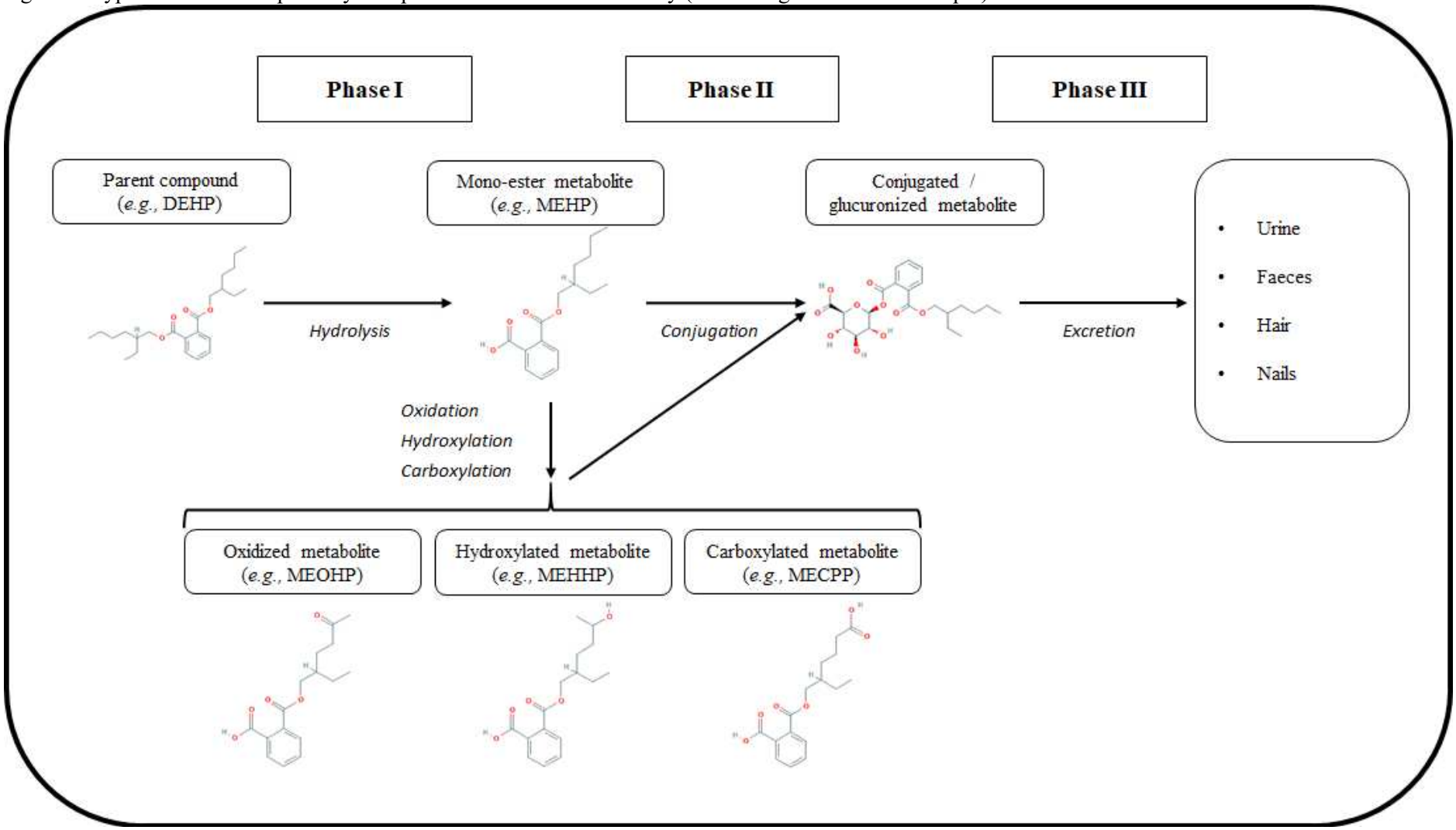
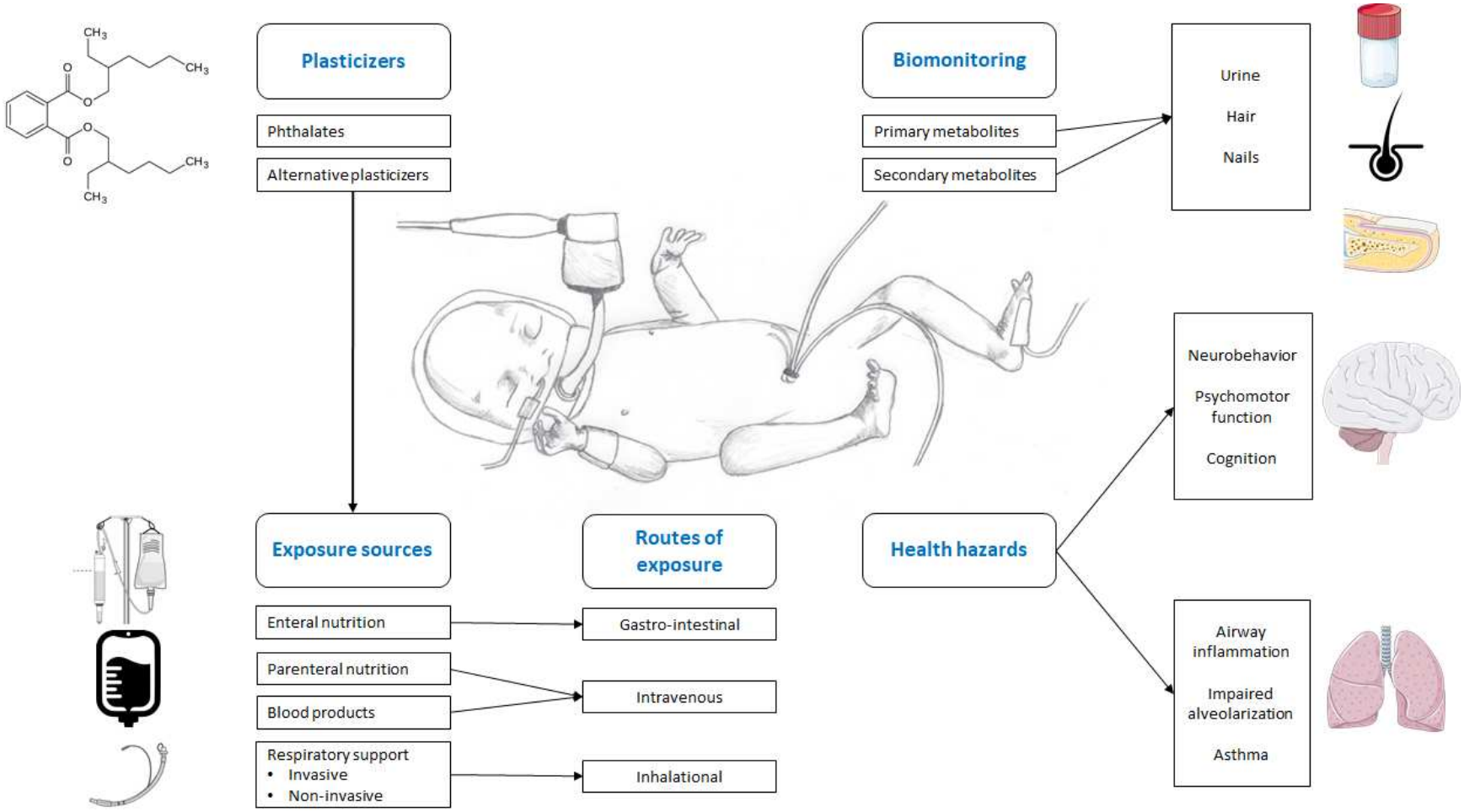


Figure 2. Premature neonates in the neonatal intensive care unit are exposed to high amounts of phtahaltes and alternative plasticizers through various invasive medical devices. Major sources are parenteral nutrition, blood product administration and respiratory support. Metabolites of these plasticizers can be measured in urine and emerging alternative matrices as hair and nails. Impaired respiratory and neurodevelopment are correlated with phthalate exposure at both biological and epidemiological levels.



References

(CDC), C. f. D. C. a. P. (2019). *Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019*.

Adgent, M. A., Carroll, K. N., Hazlehurst, M. F., Loftus, C. T., Szpiro, A. A., Karr, C. J., Barrett, E. S., LeWinn, K. Z., Bush, N. R., Tylavsky, F. A., Kannan, K., & Sathyanarayana, S. (2020, Jul 30). A combined cohort analysis of prenatal exposure to phthalate mixtures and childhood asthma. *Environ Int, 143*, 105970. https://doi.org/10.1016/j.envint.2020.105970

Albert, O., Nardelli, T. C., Hales, B. F., & Robaire, B. (2018, Feb 1). Identifying Greener and Safer Plasticizers: A 4-Step Approach. *Toxicol Sci, 161*(2), 266-275. https://doi.org/10.1093/toxsci/kfx156

Alfardan, A. S., Nadeem, A., Ahmad, S. F., Al-Harbi, N. O., Al-Harbi, M. M., & AlSharari, S. D. (2018, Jul). Plasticizer, di(2-ethylhexyl)phthalate (DEHP) enhances cockroach allergen extract-driven airway inflammation by enhancing pulmonary Th2 as well as Th17 immune responses in mice. *Environ Res, 164*, 327-339. https://doi.org/10.1016/j.envres.2018.02.039

Alves, A., Covaci, A., & Voorspoels, S. (2016, Nov). Are nails a valuable non-invasive alternative for estimating human exposure to phthalate esters? *Environ Res, 151*, 184-194. https://doi.org/10.1016/j.envres.2016.07.023

Alves, A., Koppen, G., Vanermen, G., Covaci, A., & Voorspoels, S. (2016, Nov 15). Long-term exposure assessment to phthalates: How do nail analyses compare to commonly used measurements in urine. *J Chromatogr B Analyt Technol Biomed Life Sci, 1036-1037*, 124-135. https://doi.org/10.1016/j.jchromb.2016.09.039

An, J., Kim, Y. Y., Cho, H. D., Kim, J., Lee, J. Y., Lee, Y., Jo, E., Lee, J., Cha, S., & Han, S. B. (2020, Mar 20). Development and investigation of a QuEChERS-based method for determination of phthalate metabolites in human milk. *J Pharm Biomed Anal, 181*, 113092. https://doi.org/10.1016/j.jpba.2019.113092

Arbuckle, T. E., Fisher, M., MacPherson, S., Lang, C., Provencher, G., LeBlanc, A., Hauser, R., Feeley, M., Ayotte, P., Neisa, A., Ramsay, T., & Tawagi, G. (2016, May 1). Maternal and early life exposure to phthalates: The Plastics and Personal-care Products use in Pregnancy (P4) study. *Sci Total Environ, 551-552*, 344-356. https://doi.org/10.1016/j.scitotenv.2016.02.022

Atia, T., & Abdel-Gawad, S. (2019, Aug - Aug). Pulmonary toxicity induced by exposure to phthalates, an experimental study. *Inhal Toxicol, 31*(9-10), 376-383. https://doi.org/10.1080/08958378.2019.1695025

Bagel, S., Dessaigne, B., Bourdeaux, D., Boyer, A., Bouteloup, C., Bazin, J. E., Chopineau, J., & Sautou, V. (2011, Nov). Influence of lipid type on bis (2-ethylhexyl)phthalate (DEHP) leaching from infusion line sets in parenteral nutrition. *JPEN J Parenter Enteral Nutr, 35*(6), 770-775. https://doi.org/10.1177/0148607111414021

Bancalari, E., & Jain, D. (2019). Bronchopulmonary Dysplasia: 50 Years after the Original Description. *Neonatology, 115*(4), 384-391. https://doi.org/10.1159/000497422

Been, F., Malarvannan, G., Bastiaensen, M., Yin, S., van Nuijs, A. L. N., & Covaci, A. (2019, Jun 1). Development and validation of a bioanalytical assay based on liquid chromatography-tandem mass spectrometry for measuring biomarkers of exposure of alternative plasticizers in human urine and serum. *Talanta, 198*, 230-236. https://doi.org/10.1016/j.talanta.2019.02.024

Benjamin, S., Masai, E., Kamimura, N., Takahashi, K., Anderson, R. C., & Faisal, P. A. (2017, Oct 15). Phthalates impact human health: Epidemiological evidences and plausible mechanism of action. *J Hazard Mater, 340*, 360-383. https://doi.org/10.1016/j.jhazmat.2017.06.036

Berghuis, S. A., Bos, A. F., Sauer, P. J., & Roze, E. (2015, May). Developmental neurotoxicity of persistent organic pollutants: an update on childhood outcome. *Arch Toxicol, 89*(5), 687-709. https://doi.org/10.1007/s00204-015-1463-3

Bernard, L., Cueff, R., Breysse, C., Decaudin, B., Sautou, V., & Armed Study, G. (2015, May 15). Migrability of PVC plasticizers from medical devices into a simulant of infused solutions. *Int J Pharm, 485*(1-2), 341-347. https://doi.org/10.1016/j.ijpharm.2015.03.030

Bernard, L., Cueff, R., Chagnon, M., Abdoulouhab, F., Decaudin, B., Breysse, C., Kauffmann, S., Cosserant, B., Souweine, B., Sautou, V., & group, A. s. (2015, Oct 15). Migration of plasticizers from PVC medical devices: Development of an infusion model. *Int J Pharm, 494*(1), 136-145. https://doi.org/10.1016/j.ijpharm.2015.08.033

Bernard, L., Decaudin, B., Lecoeur, M., Richard, D., Bourdeaux, D., Cueff, R., Sautou, V., & Armed Study, G. (2014, Nov). Analytical methods for the determination of DEHP plasticizer alternatives present in medical devices: a review. *Talanta, 129*, 39-54. https://doi.org/10.1016/j.talanta.2014.04.069

Bickle-Graz, M., Tolsa, J. F., & Fischer Fumeaux, C. J. (2020, Jan). Phthalates in the NICU: a survey. *Arch Dis Child Fetal Neonatal Ed, 105*(1), 110-111. https://doi.org/10.1136/archdischild-2019-317582

Bouattour, Y., Wasiak, M., Bernard, L., Pinguet, J., Richard, D., Le Rouzo-Greves, M., Dhifallah, I., Lambert, C., Pereira, B., Chennell, P., & Sautou, V. (2020, Sep). Quantification of bis(2-ethylhexyl) phthalate released by medical devices during respiratory assistance and estimation of patient exposure. *Chemosphere, 255*, 126978. https://doi.org/10.1016/j.chemosphere.2020.126978

Bourdeaux, D., Sautou-Miranda, V., Bagel-Boithias, S., Boyer, A., & Chopineau, J. (2004, Apr 1). Analysis by liquid chromatography and infrared spectrometry of di(2-ethylhexyl)phthalate released by multilayer infusion tubing. *J Pharm Biomed Anal, 35*(1), 57-64. https://doi.org/10.1016/j.jpba.2003.12.018

Bourdeaux, D., Yessaad, M., Chennell, P., Larbre, V., Eljezi, T., Bernard, L., & Sautou, V. (2016, Jan 25). Analysis of PVC plasticizers in medical devices and infused solutions by GC-MS. *J Pharm Biomed Anal, 118*, 206-213. https://doi.org/10.1016/j.jpba.2015.10.034

Bui, T. T., Giovanoulis, G., Cousins, A. P., Magner, J., Cousins, I. T., & de Wit, C. A. (2016, Jan 15). Human exposure, hazard and risk of alternative plasticizers to phthalate esters. *Sci Total Environ, 541*, 451-467. https://doi.org/10.1016/j.scitotenv.2015.09.036

Calafat, A. M., Koch, H. M., Swan, S. H., Hauser, R., Goldman, L. R., Lanphear, B. P., Longnecker, M. P., Rudel, R. A., Teitelbaum, S. L., Whyatt, R. M., & Wolff, M. S. (2013). Misuse of blood serum to assess exposure to bisphenol A and phthalates. *Breast Cancer Res, 15*(5), 403. https://doi.org/10.1186/bcr3494

Calafat, A. M., Needham, L. L., Silva, M. J., & Lambert, G. (2004, May). Exposure to di-(2-ethylhexyl) phthalate among premature neonates in a neonatal intensive care unit. *Pediatrics, 113*(5), e429-434.

Calafat, A. M., Weuve, J., Ye, X., Jia, L. T., Hu, H., Ringer, S., Huttner, K., & Hauser, R. (2009, Apr). Exposure to bisphenol A and other phenols in neonatal intensive care unit premature infants. *Environ Health Perspect, 117*(4), 639-644. https://doi.org/10.1289/ehp.0800265

Camacho, L., Latendresse, J. R., Muskhelishvili, L., Law, C. D., & Delclos, K. B. (2020, Oct). Effects of intravenous and oral di(2-ethylhexyl) phthalate (DEHP) and 20% Intralipid vehicle on neonatal rat testis, lung, liver, and kidney. *Food Chem Toxicol, 144*, 111497. https://doi.org/10.1016/j.fct.2020.111497

Cammack, J. N., White, R. D., Gordon, D., Gass, J., Hecker, L., Conine, D., Bruen, U. S., Friedman, M., Echols, C., Yeh, T. Y., & Wilson, D. M. (2003, May-Jun). Evaluation of reproductive development following intravenous and oral exposure to DEHP in male neonatal rats. *Int J Toxicol, 22*(3), 159-174. https://doi.org/10.1080/10915810305098

Carrico, C., Gennings, C., Wheeler, D. C., & Factor-Litvak, P. (2015, Mar). Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. *J Agric Biol Environ Stat, 20*(1), 100-120. https://doi.org/10.1007/s13253-014-0180-3

Casals-Casas, C., Feige, J. N., & Desvergne, B. (2008, Dec). Interference of pollutants with PPARs: endocrine disruption meets metabolism. *Int J Obes (Lond), 32 Suppl 6*, S53-61. https://doi.org/10.1038/ijo.2008.207

Chen, S. Q., Chen, J. N., Cai, X. H., Chen, G. R., Gao, Y., Ge, R. S., Wu, H. S., Lin, Z. L., & Lin, J. (2010, Sep). Perinatal exposure to di-(2-ethylhexyl) phthalate leads to restricted growth and delayed lung maturation in newborn rats. *J Perinat Med, 38*(5), 515-521. https://doi.org/10.1515/JPM.2010.083

Chiellini, F., Ferri, M., & Latini, G. (2011, May 16). Physical-chemical assessment of di-(2-ethylhexyl)-phthalate leakage from poly(vinyl chloride) endotracheal tubes after application in high risk newborns. *Int J Pharm, 409*(1-2), 57-61. https://doi.org/10.1016/j.ijpharm.2011.02.024

Cuadros-Rodriguez, L., Lazuen-Muros, M., Ruiz-Samblas, C., & Navas-Iglesias, N. (2020, Jun 15). Leachables from plastic materials in contact with drugs. State of the art and review of current analytical approaches. *Int J Pharm, 583*, 119332. https://doi.org/10.1016/j.ijpharm.2020.119332

David, R. M., White, R. D., Larson, M. J., Herman, J. K., & Otter, R. (2015, Oct 14). Toxicity of Hexamoll((R)) DINCH((R)) following intravenous administration. *Toxicol Lett, 238*(2), 100-109. https://doi.org/10.1016/j.toxlet.2015.07.013

Demirel, A., Coban, A., Yildirim, S., Dogan, C., Sanci, R., & Ince, Z. (2016, Sep 1). Hidden Toxicity in Neonatal Intensive Care Units: Phthalate Exposure in Very Low Birth Weight Infants. *J Clin Res Pediatr Endocrinol, 8*(3), 298-304. https://doi.org/10.4274/jcrpe.3027

Den Braver-Sewradj, S. P., Piersma, A., & Hessel, E. V. S. (2020, Sep). An update on the hazard of and exposure to diethyl hexyl phthalate (DEHP) alternatives used in medical devices. *Crit Rev Toxicol, 50*(8), 650-672. https://doi.org/10.1080/10408444.2020.1816896

Dzwilewski, K. L. C., Woodbury, M. L., Aguiar, A., Shoaff, J., Merced-Nieves, F., Korrick, S. A., & Schantz, S. L. (2021, Mar 8). Associations of prenatal exposure to phthalates with measures of cognition in 7.5-month-old infants. *Neurotoxicology, 84*, 84-95. https://doi.org/10.1016/j.neuro.2021.03.001

Eckert, E., Muller, J., Hollerer, C., Purbojo, A., Cesnjevar, R., Goen, T., & Munch, F. (2020, May 6). Plasticizer exposure of infants during cardiac surgery. *Toxicol Lett, 330*, 7-13. https://doi.org/10.1016/j.toxlet.2020.04.004

Eckert, E., Munch, F., Goen, T., Purbojo, A., Muller, J., & Cesnjevar, R. (2016, Feb). Comparative study on the migration of di-2-ethylhexyl phthalate (DEHP) and tri-2-ethylhexyl trimellitate (TOTM) into blood from PVC tubing material of a heart-lung machine. *Chemosphere, 145*, 10-16. https://doi.org/10.1016/j.chemosphere.2015.11.067

Ejaredar, M., Nyanza, E. C., Ten Eycke, K., & Dewey, D. (2015, Oct). Phthalate exposure and childrens neurodevelopment: A systematic review. *Environ Res, 142*, 51-60. https://doi.org/10.1016/j.envres.2015.06.014

Engel, S. M., Patisaul, H. B., Brody, C., Hauser, R., Zota, A. R., Bennet, D. H., Swanson, M., & Whyatt, R. M. (2021, Apr). Neurotoxicity of Ortho-Phthalates: Recommendations for Critical Policy Reforms to Protect Brain Development in Children. *Am J Public Health, 111*(4), 687-695. https://doi.org/10.2105/AJPH.2020.306014

EPA DK. Alternatives to classified phthalates in medical devices. Environmental Project No. 1557: The Danish Environmental Protection Agency, (2014).

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives

67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 (1), (2008). https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ:L:2008:353:TOC

REGULATION (EC) No 1223/2009 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 30 November 2009 on cosmetic products, (2009). https://ec.europa.eu/health/sites/default/files/endocrine_disruptors/docs/cosmetic_1223_2009_regulation_en.pdf

Regulation (EU) 2017/745 of the European Parliament and of the council of 5 April 2017, (2017).

Regulation (EU) 2020/561 amending Regulation (EU) 2017/745 on medical devices, as regards the dats of application of certain of its provisions, (2020).

Faessler, D., McCombie, G., Biedermann, M., Felder, F., & Subotic, U. (2017, Mar 30). Leaching of plasticizers from polyvinylchloride perfusion lines by different lipid emulsions for premature infants under clinical conditions. *Int J Pharm, 520*(1-2), 119-125. https://doi.org/10.1016/j.ijpharm.2017.01.046

Fawke, J. (2007, Oct). Neurological outcomes following preterm birth. *Semin Fetal Neonatal Med, 12*(5), 374-382. https://doi.org/10.1016/j.siny.2007.06.002

Fischer Fumeaux, C. J., Stadelmann Diaw, C., Palmero, D., M'Madi, F., & Tolsa, J. F. (2015, Feb). [Phthalate exposure in the neonatal intensive care unit]. *Arch Pediatr, 22*(2), 203-210. https://doi.org/10.1016/j.arcped.2014.10.026 (Sources d'exposition aux phtalates dans une unite de soins neonatals.)

Foster, J. P., Richards, R., Showell, M. G., & Jones, L. J. (2015, Aug 6). Intravenous in-line filters for preventing morbidity and mortality in neonates. *Cochrane Database Syst Rev*(8), CD005248. https://doi.org/10.1002/14651858.CD005248.pub3

Frederiksen, H., Kuiri-Hanninen, T., Main, K. M., Dunkel, L., & Sankilampi, U. (2014, Sep). A longitudinal study of urinary phthalate excretion in 58 full-term and 67 preterm infants from birth through 14 months. *Environ Health Perspect, 122*(9), 998-1005. https://doi.org/10.1289/ehp.1307569

Frederiksen, H., Nielsen, O., Koch, H. M., Skakkebaek, N. E., Juul, A., Jorgensen, N., & Andersson, A. M. (2020, Jan). Changes in urinary excretion of phthalates, phthalate substitutes, bisphenols and other polychlorinated and phenolic substances in young Danish men; 2009-2017. *Int J Hyg Environ Health, 223*(1), 93-105. https://doi.org/10.1016/j.ijheh.2019.10.002

Gaynor, J. W., Ittenbach, R. F., Calafat, A. M., Burnham, N. B., Bradman, A., Bellinger, D. C., Henretig, F. M., Wehrung, E. E., Ward, J. L., Russell, W. W., & Spray, T. L. (2019, Feb). Perioperative Exposure to Suspect Neurotoxicants From Medical Devices in Newborns With Congenital Heart Defects. *Ann Thorac Surg, 107*(2), 567-572. https://doi.org/10.1016/j.athoracsur.2018.06.035

Genay, S., Luciani, C., Decaudin, B., Kambia, N., Dine, T., Azaroual, N., Di Martino, P., Barthelemy, C., & Odou, P. (2011, Jun 30). Experimental study on infusion devices containing polyvinyl chloride: to what extent are they di(2-ethylhexyl)phthalate-free? *Int J Pharm, 412*(1-2), 47-51. https://doi.org/10.1016/j.ijpharm.2011.03.060

Gimeno, P., Thomas, S., Bousquet, C., Maggio, A. F., Civade, C., Brenier, C., & Bonnet, P. A. (2014, Feb 15). Identification and quantification of 14 phthalates and 5 non-phthalate plasticizers in PVC medical devices by GC-MS. *J Chromatogr B Analyt Technol Biomed Life Sci, 949-950*, 99-108. https://doi.org/10.1016/j.jchromb.2013.12.037

Green, R., Hauser, R., Calafat, A. M., Weuve, J., Schettler, T., Ringer, S., Huttner, K., & Hu, H. (2005, Sep). Use of di(2-ethylhexyl) phthalate-containing medical products and urinary levels of mono(2-ethylhexyl) phthalate in neonatal intensive care unit infants. *Environ Health Perspect, 113*(9), 1222-1225. https://doi.org/10.1289/ehp.7932

Gubhaju, L., Sutherland, M. R., Horne, R. S., Medhurst, A., Kent, A. L., Ramsden, A., Moore, L., Singh, G., Hoy, W. E., & Black, M. J. (2014, Jul 15). Assessment of renal functional maturation and injury in

preterm neonates during the first month of life. *Am J Physiol Renal Physiol, 307*(2), F149-158. https://doi.org/10.1152/ajprenal.00439.2013

Guo, J., Han, B., Qin, L., Li, B., You, H., Yang, J., Liu, D., Wei, C., Nanberg, E., Bornehag, C. G., & Yang, X. (2012). Pulmonary toxicity and adjuvant effect of di-(2-exylhexyl) phthalate in ovalbumin-immunized BALB/c mice. *PLoS One, 7*(6), e39008. https://doi.org/10.1371/journal.pone.0039008

Guo, J., Wu, M., Gao, X., Chen, J., Li, S., Chen, B., & Dong, R. (2020, Oct 22). Meconium Exposure to Phthalates, Sex and Thyroid Hormones, Birth Size and Pregnancy Outcomes in 251 Mother-Infant Pairs from Shanghai. *Int J Environ Res Public Health, 17*(21). https://doi.org/10.3390/ijerph17217711

Haned, Z., Moulay, S., & Lacorte, S. (2018, Jul 15). Migration of plasticizers from poly(vinyl chloride) and multilayer infusion bags using selective extraction and GC-MS. *J Pharm Biomed Anal, 156*, 80-87. https://doi.org/10.1016/j.jpba.2018.04.011

Hollerer, C., Becker, G., Goen, T., & Eckert, E. (2018, Sep). Human metabolism and kinetics of tri-(2-ethylhexyl) trimellitate (TEHTM) after oral administration. *Arch Toxicol, 92*(9), 2793-2807. https://doi.org/10.1007/s00204-018-2264-2

Huang, H. B., Kuo, P. H., Su, P. H., Sun, C. W., Chen, W. J., & Wang, S. L. (2019, May). Prenatal and childhood exposure to phthalate diesters and neurobehavioral development in a 15-year follow-up birth cohort study. *Environ Res, 172*, 569-577. https://doi.org/10.1016/j.envres.2019.02.029

Huygh, J., Clotman, K., Malarvannan, G., Covaci, A., Schepens, T., Verbrugghe, W., Dirinck, E., Van Gaal, L., & Jorens, P. G. (2015, Aug). Considerable exposure to the endocrine disrupting chemicals phthalates and bisphenol-A in intensive care unit (ICU) patients. *Environ Int, 81*, 64-72. https://doi.org/10.1016/j.envint.2015.04.008

Jeddi, M. Z., Janani, L., Memari, A. H., Akhondzadeh, S., & Yunesian, M. (2016, Nov). The role of phthalate esters in autism development: A systematic review. *Environ Res, 151*, 493-504. https://doi.org/10.1016/j.envres.2016.08.021

Jenkins, R., Tackitt, S., Gievers, L., Iragorri, S., Sage, K., Cornwall, T., O'Riordan, D., Merchant, J., & Rozansky, D. (2019, Aug). Phthalate-associated hypertension in premature infants: a prospective mechanistic cohort study. *Pediatr Nephrol, 34*(8), 1413-1424. https://doi.org/10.1007/s00467-019-04244-4

Jensen, E. A., & Schmidt, B. (2014, Mar). Epidemiology of bronchopulmonary dysplasia. *Birth Defects Res A Clin Mol Teratol, 100*(3), 145-157. https://doi.org/10.1002/bdra.23235

Jobe, A. H., & Bancalari, E. (2001, Jun). Bronchopulmonary dysplasia. *Am J Respir Crit Care Med, 163*(7), 1723-1729. https://doi.org/10.1164/ajrccm.163.7.2011060

Kambia, K., Dine, T., Azar, R., Gressier, B., Luyckx, M., & Brunet, C. (2001, Oct 23). Comparative study of the leachability of di(2-ethylhexyl) phthalate and tri(2-ethylhexyl) trimellitate from haemodialysis tubing. *Int J Pharm, 229*(1-2), 139-146. https://doi.org/10.1016/s0378-5173(01)00840-7

Kambia, K., Dine, T., Gressier, B., Bah, S., Germe, A. F., Luyckx, M., Brunet, C., Michaud, L., & Gottrand, F. (2003, Aug 27). Evaluation of childhood exposure to di(2-ethylhexyl) phthalate from perfusion kits during long-term parenteral nutrition. *Int J Pharm, 262*(1-2), 83-91. https://doi.org/10.1016/s0378-5173(03)00335-1

Kambia, N. K., Severin, I., Farce, A., Moreau, E., Dahbi, L., Duval, C., Dine, T., Sautou, V., & Chagnon, M. C. (2019, Jul). In vitro and in silico hormonal activity studies of di-(2-ethylhexyl)terephthalate, a di-(2-ethylhexyl)phthalate substitute used in medical devices, and its metabolites. *J Appl Toxicol, 39*(7), 1043-1056. https://doi.org/10.1002/jat.3792

Karle, V. A., Short, B. L., Martin, G. R., Bulas, D. I., Getson, P. R., Luban, N. L., O'Brien, A. M., & Rubin, R. J. (1997, Apr). Extracorporeal membrane oxygenation exposes infants to the plasticizer, di(2-

ethylhexyl)phthalate. *Crit Care Med, 25*(4), 696-703. https://doi.org/10.1097/00003246-199704000-00023

Katsikantami, I., Tzatzarakis, M. N., Alegakis, A. K., Karzi, V., Hatzidaki, E., Stavroulaki, A., Vakonaki, E., Xezonaki, P., Sifakis, S., Rizos, A. K., & Tsatsakis, A. M. (2020). Phthalate metabolites concentrations in amniotic fluid and maternal urine: Cumulative exposure and risk assessment. *Toxicol Rep, 7*, 529-538. https://doi.org/10.1016/j.toxrep.2020.04.008

Kirschbaum, C., Tietze, A., Skoluda, N., & Dettenborn, L. (2009, Jan). Hair as a retrospective calendar of cortisol production-Increased cortisol incorporation into hair in the third trimester of pregnancy. *Psychoneuroendocrinology, 34*(1), 32-37. https://doi.org/10.1016/j.psyneuen.2008.08.024

Koch, H. M., Drexler, H., & Angerer, J. (2003, Mar). An estimation of the daily intake of di(2-ethylhexyl)phthalate (DEHP) and other phthalates in the general population. *Int J Hyg Environ Health, 206*(2), 77-83. https://doi.org/10.1078/1438-4639-00205

Koch, H. M., Preuss, R., & Angerer, J. (2006, Feb). Di(2-ethylhexyl)phthalate (DEHP): human metabolism and internal exposure-- an update and latest results. *Int J Androl, 29*(1), 155-165; discussion 181-155. https://doi.org/10.1111/j.1365-2605.2005.00607.x

Koch, H. M., Ruther, M., Schutze, A., Conrad, A., Palmke, C., Apel, P., Bruning, T., & Kolossa-Gehring, M. (2017, Mar). Phthalate metabolites in 24-h urine samples of the German Environmental Specimen Bank (ESB) from 1988 to 2015 and a comparison with US NHANES data from 1999 to 2012. *Int J Hyg Environ Health, 220*(2 Pt A), 130-141. https://doi.org/10.1016/j.ijheh.2016.11.003

Komada, M., Gendai, Y., Kagawa, N., & Nagao, T. (2016, Sep 30). Prenatal exposure to di(2-ethylhexyl) phthalate impairs development of the mouse neocortex. *Toxicol Lett, 259*, 69-79. https://doi.org/10.1016/j.toxlet.2016.07.019

Komada, M., Nagao, T., & Kagawa, N. (2020, Jul 7). Postnatal di-2-ethylhexyl phthalate exposure affects hippocampal dentate gyrus morphogenesis. *J Appl Toxicol*. https://doi.org/10.1002/jat.4027

Kougias, D. G., Sellinger, E. P., Willing, J., & Juraska, J. M. (2018, Aug 1). Perinatal Exposure to an Environmentally Relevant Mixture of Phthalates Results in a Lower Number of Neurons and Synapses in the Medial Prefrontal Cortex and Decreased Cognitive Flexibility in Adult Male and Female Rats. *J Neurosci, 38*(31), 6864-6872. https://doi.org/10.1523/JNEUROSCI.0607-18.2018

Lagerberg, J. W., Gouwerok, E., Vlaar, R., Go, M., & de Korte, D. (2015, Mar). In vitro evaluation of the quality of blood products collected and stored in systems completely free of di(2-ethylhexyl)phthalate-plasticized materials. *Transfusion, 55*(3), 522-531. https://doi.org/10.1111/trf.12870

Lai, T. T., & Bearer, C. F. (2008, Mar). Iatrogenic environmental hazards in the neonatal intensive care unit. *Clin Perinatol, 35*(1), 163-181, ix. https://doi.org/10.1016/j.clp.2007.11.003

Larsson, L., Sandgren, P., Ohlsson, S., Derving, J., Friis-Christensen, T., Daggert, F., Frizi, N., Reichenberg, S., Chatellier, S., Diedrich, B., Antovic, J., Larsson, S., & Uhlin, M. (2020, Sep 12). Non-phthalate plasticizer DEHT preserves adequate blood component quality during storage in PVC blood bags. *Vox Sang*. https://doi.org/10.1111/vox.12982

Latini, G., & Avery, G. B. (1999, Oct). Materials degradation in endotracheal tubes: a potential contributor to bronchopulmonary dysplasia. *Acta Paediatr, 88*(10), 1174-1175. https://doi.org/10.1080/08035259950168333

Lee, D. W., Kim, M. S., Lim, Y. H., Lee, N., & Hong, Y. C. (2018, Aug 18). Prenatal and postnatal exposure to di-(2-ethylhexyl) phthalate and neurodevelopmental outcomes: A systematic review and meta-analysis. *Environ Res, 167*, 558-566. https://doi.org/10.1016/j.envres.2018.08.023

Li, M. C., Chen, C. H., & Guo, Y. L. (2017, Oct). Phthalate esters and childhood asthma: A systematic review and congener-specific meta-analysis. *Environ Pollut, 229*, 655-660. https://doi.org/10.1016/j.envpol.2017.06.083

Liang, Z. J., Wu, Q. P., Chen, B. T., Lin, Z. L., Lin, J., & Chen, S. Q. (2018, Feb). Postnatal hyperoxia or DEHP exposure leads to growth restriction and delayed lung development in newborn rats. *Pediatr Neonatol, 59*(1), 24-30. https://doi.org/10.1016/j.pedneo.2016.11.002

Loff, S., Kabs, F., Subotic, U., Schaible, T., Reinecke, F., & Langbein, M. (2002, Sep-Oct). Kinetics of diethylhexyl-phthalate extraction From polyvinylchloride-infusion lines. *JPEN J Parenter Enteral Nutr, 26*(5), 305-309. https://doi.org/10.1177/0148607102026005305

Loff, S., Kabs, F., Witt, K., Sartoris, J., Mandl, B., Niessen, K. H., & Waag, K. L. (2000, Dec). Polyvinylchloride infusion lines expose infants to large amounts of toxic plasticizers. *J Pediatr Surg, 35*(12), 1775-1781. https://doi.org/10.1053/jpsu.2000.19249

Loff, S., Subotic, U., Reinicke, F., Wischmann, H., & Brade, J. (2004, Oct). Extraction of di-ethylhexyl-phthalate from perfusion lines of various material, length and brand by lipid emulsions. *J Pediatr Gastroenterol Nutr, 39*(4), 341-345.

Magliozzi, R., Nardacci, R., Scarsella, G., Di Carlo, V., & Stefanini, S. (2003, Jul). Effects of the plasticiser DEHP on lung of newborn rats: catalase immunocytochemistry and morphometric analysis. *Histochem Cell Biol, 120*(1), 41-49. https://doi.org/10.1007/s00418-003-0543-2

Malarvannan, G., Onghena, M., Verstraete, S., van Puffelen, E., Jacobs, A., Vanhorebeek, I., Verbruggen, S., Joosten, K. F. M., Van den Berghe, G., Jorens, P. G., & Covaci, A. (2019, Feb 5). Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units. *J Hazard Mater, 363*, 64-72. https://doi.org/10.1016/j.jhazmat.2018.09.087

Manteiga, S., & Lee, K. (2017, Apr). Monoethylhexyl Phthalate Elicits an Inflammatory Response in Adipocytes Characterized by Alterations in Lipid and Cytokine Pathways. *Environ Health Perspect, 125*(4), 615-622. https://doi.org/10.1289/EHP464

Marcilla, A., Garia, S., & Garcia-Quesada, J. C. (2004, Jun). Study of the migration of PVC plasticizers. *Journal of Analytical and Applied Pyrolysis, 71*(2), 457-463. https://doi.org/10.1016/S0165-2370(03)00131-1

Marschner, S. (2019). *Blood Bag Systems*. TERUMOBCT. https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/ev_20190404_co05_en.pdf

Merced-Nieves, F. M., Dzwilewski, K. L. C., Aguiar, A., Musaad, S., Korrick, S. A., & Schantz, S. L. (2021, Feb 13). Associations of Prenatal Exposure to Phthalates with Measures of Cognition in 4.5-Month-Old Infants. *Int J Environ Res Public Health, 18*(4). https://doi.org/10.3390/ijerph18041838

Morton, W. J., Muller, C. T., Goodwin, N., Wilkes, A. R., & Hall, J. E. (2013, Apr). Investigation of phthalate release from tracheal tubes. *Anaesthesia, 68*(4), 377-381. https://doi.org/10.1111/anae.12083

Münch, F., Hollerer, C., Klapproth, A., Eckert, E., Ruffer, A., Cesnjevar, R., & Goen, T. (2018, Jul). Effect of phospholipid coating on the migration of plasticizers from PVC tubes. *Chemosphere, 202*, 742-749. https://doi.org/10.1016/j.chemosphere.2018.03.136

Paus, R., Langan, E. A., Vidali, S., Ramot, Y., & Andersen, B. (2014, Oct). Neuroendocrinology of the hair follicle: principles and clinical perspectives. *Trends Mol Med, 20*(10), 559-570. https://doi.org/10.1016/j.molmed.2014.06.002

Pearson, M. A., Lu, C., Schmotzer, B. J., Waller, L. A., & Riederer, A. M. (2009, Mar). Evaluation of physiological measures for correcting variation in urinary output: Implications for assessing environmental chemical exposure in children. *J Expo Sci Environ Epidemiol, 19*(3), 336-342. https://doi.org/10.1038/jes.2008.48

Pinguet, J., Kerckhove, N., Eljezi, T., Lambert, C., Moreau, E., Bernard, L., Boeuf, B., Decaudin, B., Genay, S., Masse, M., Storme, L., Sautou, V., Richard, D., & Group, A. S. (2019, Jun 1). New SPE-LC-MS/MS method for the simultaneous determination in urine of 22 metabolites of DEHP and alternative

plasticizers from PVC medical devices. *Talanta, 198*, 377-389. https://doi.org/10.1016/j.talanta.2019.01.115

Ponsonby, A. L., Symeonides, C., Saffery, R., Mueller, J. F., O'Hely, M., Sly, P. D., Wardrop, N., Pezic, A., Mansell, T., Collier, F., Burgner, D., Thompson, K., Vijayasarathy, S., Sugeng, E. J., Dwyer, T., Ranganathan, S., Anderson, P. J., Anderson, V., Vuillermin, P., & Group, B. I. S. I. (2020, Sep). Prenatal phthalate exposure, oxidative stress-related genetic vulnerability and early life neurodevelopment: A birth cohort study. *Neurotoxicology, 80*, 20-28. https://doi.org/10.1016/j.neuro.2020.05.006

Radke, E. G., Braun, J. M., Nachman, R. M., & Cooper, G. S. (2020, Apr). Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence. *Environ Int, 137*, 105408. https://doi.org/10.1016/j.envint.2019.105408

Radke, E. G., Galizia, A., Thayer, K. A., & Cooper, G. S. (2019, Nov). Phthalate exposure and metabolic effects: a systematic review of the human epidemiological evidence. *Environ Int, 132*, 104768. https://doi.org/10.1016/j.envint.2019.04.040

Rael, L. T., Bar-Or, R., Ambruso, D. R., Mains, C. W., Slone, D. S., Craun, M. L., & Bar-Or, D. (2009, Jul-Aug). Phthalate esters used as plasticizers in packed red blood cell storage bags may lead to progressive toxin exposure and the release of pro-inflammatory cytokines. *Oxid Med Cell Longev, 2*(3), 166-171. https://doi.org/10.4161/oxim.2.3.8608

Rafael-Vazquez, L., Garcia-Trejo, S., Aztatzi-Aguilar, O. G., Bazan-Perkins, B., & Quintanilla-Vega, B. (2018, Sep 15). Exposure to diethylhexyl phthalate (DEHP) and monoethylhexyl phthalate (MEHP) promotes the loss of alveolar epithelial phenotype of A549 cells. *Toxicol Lett, 294*, 135-144. https://doi.org/10.1016/j.toxlet.2018.05.012

Raybaud, C., Ahmad, T., Rastegar, N., Shroff, M., & Al Nassar, M. (2013, Sep). The premature brain: developmental and lesional anatomy. *Neuroradiology, 55 Suppl 2*, 23-40. https://doi.org/10.1007/s00234-013-1231-0

Rios, D. R., Rhee, C. J., Elizondo, L., Brady, K. M., Rusin, C. G., & Acosta, S. (2021, Mar). Creatinine filtration kinetics in critically Ill neonates. *Pediatr Res, 89*(4), 952-957. https://doi.org/10.1038/s41390-020-0977-4

Rose, R. J., Priston, M. J., Rigby-Jones, A. E., & Sneyd, J. R. (2012, May). The effect of temperature on di(2-ethylhexyl) phthalate leaching from PVC infusion sets exposed to lipid emulsions. *Anaesthesia, 67*(5), 514-520. https://doi.org/10.1111/j.1365-2044.2011.07006.x

Rosicarelli, B., & Stefanini, S. (2009, Apr). DEHP effects on histology and cell proliferation in lung of newborn rats. *Histochem Cell Biol, 131*(4), 491-500. https://doi.org/10.1007/s00418-008-0550-4

Roth, B., Herkenrath, P., Lehmann, H. J., Ohles, H. D., Homig, H. J., Benz-Bohm, G., Kreuder, J., & Younossi-Hartenstein, A. (1988, Jan). Di-(2-ethylhexyl)-phthalate as plasticizer in PVC respiratory tubing systems: indications of hazardous effects on pulmonary function in mechanically ventilated, preterm infants. *Eur J Pediatr, 147*(1), 41-46. https://doi.org/10.1007/bf00442609

Rowdhwal, S. S. S., & Chen, J. (2018). Toxic Effects of Di-2-ethylhexyl Phthalate: An Overview. *Biomed Res Int, 2018*, 1750368. https://doi.org/10.1155/2018/1750368

Sampson, J., & de Korte, D. (2011, Apr). DEHP-plasticised PVC: relevance to blood services. *Transfus Med, 21*(2), 73-83. https://doi.org/10.1111/j.1365-3148.2010.01056.x

Schug, T. T., Blawas, A. M., Gray, K., Heindel, J. J., & Lawler, C. P. (2015, Jun). Elucidating the links between endocrine disruptors and neurodevelopment. *Endocrinology, 156*(6), 1941-1951. https://doi.org/10.1210/en.2014-1734

Serrano, K., Levin, E., Chen, D., Hansen, A., Turner, T. R., Kurach, J., Reidel, A., Boecker, W. F., Acker, J. P., & Devine, D. V. (2016, Apr). An investigation of red blood cell concentrate quality during storage in

paediatric-sized polyvinylchloride bags plasticized with alternatives to di-2-ethylhexyl phthalate (DEHP). *Vox Sang, 110*(3), 227-235. https://doi.org/10.1111/vox.12355

Shneider, B., Schena, J., Truog, R., Jacobson, M., & Kevy, S. (1989, Jun 8). Exposure to di(2-ethylhexyl)phthalate in infants receiving extracorporeal membrane oxygenation. *N Engl J Med, 320*(23), 1563. https://doi.org/10.1056/NEJM198906083202323

Simon, D. M., Arikan, M. C., Srisuma, S., Bhattacharya, S., Tsai, L. W., Ingenito, E. P., Gonzalez, F., Shapiro, S. D., & Mariani, T. J. (2006, Jul). Epithelial cell PPAR[gamma] contributes to normal lung maturation. *FASEB J, 20*(9), 1507-1509. https://doi.org/10.1096/fj.05-5410fje

Smith, C. A., Macdonald, A., & Holahan, M. R. (2011, Oct 13). Acute postnatal exposure to di(2-ethylhexyl) phthalate adversely impacts hippocampal development in the male rat. *Neuroscience, 193*, 100-108. https://doi.org/10.1016/j.neuroscience.2011.06.082

Strommen, K., Lyche, J. L., Blakstad, E. W., Moltu, S. J., Veierod, M. B., Almaas, A. N., Sakhi, A. K., Thomsen, C., Nakstad, B., Braekke, K., Ronnestad, A. E., Drevon, C. A., & Iversen, P. O. (2016, Apr-May). Increased levels of phthalates in very low birth weight infants with septicemia and bronchopulmonary dysplasia. *Environ Int, 89-90*, 228-234. https://doi.org/10.1016/j.envint.2016.01.024

Stroustrup, A., Bragg, J. B., Andra, S. S., Curtin, P. C., Spear, E. A., Sison, D. B., Just, A. C., Arora, M., & Gennings, C. (2018). Neonatal intensive care unit phthalate exposure and preterm infant neurobehavioral performance. *PLoS One, 13*(3), e0193835. https://doi.org/10.1371/journal.pone.0193835

Stroustrup, A., Bragg, J. B., Busgang, S. A., Andra, S. S., Curtin, P., Spear, E. A., Just, A. C., Arora, M., & Gennings, C. (2018, Sep 21). Sources of clinically significant neonatal intensive care unit phthalate exposure. *J Expo Sci Environ Epidemiol*. https://doi.org/10.1038/s41370-018-0069-2

Stroustrup, A., Bragg, J. B., Spear, E. A., Aguiar, A., Zimmerman, E., Isler, J. R., Busgang, S. A., Curtin, P. C., Gennings, C., Andra, S. S., & Arora, M. (2019, Nov 25). Cohort profile: the Neonatal Intensive Care Unit Hospital Exposures and Long-Term Health (NICU-HEALTH) cohort, a prospective preterm birth cohort in New York City. *BMJ Open, 9*(11), e032758. https://doi.org/10.1136/bmjopen-2019-032758

Su, P. H., Chang, Y. Z., Chang, H. P., Wang, S. L., Haung, H. I., Huang, P. C., & Chen, J. Y. (2012, Nov). Exposure to di(2-ethylhexyl) phthalate in premature neonates in a neonatal intensive care unit in Taiwan. *Pediatr Crit Care Med, 13*(6), 671-677. https://doi.org/10.1097/PCC.0b013e3182455558

Subotic, U., Hannmann, T., Kiss, M., Brade, J., Breitkopf, K., & Loff, S. (2007, Jan). Extraction of the plasticizers diethylhexylphthalate and polyadipate from polyvinylchloride nasogastric tubes through gastric juice and feeding solution. *J Pediatr Gastroenterol Nutr, 44*(1), 71-76. https://doi.org/10.1097/01.mpg.0000237939.50791.4b

Takatori, S., Okamoto, Y., Kitagawa, Y., Hori, S., Izumi, S., Makino, T., & Nakazawa, H. (2008, Mar 20). Simulated neonatal exposure to DEHP and MEHP from PVC enteral nutrition products. *Int J Pharm, 352*(1-2), 139-145. https://doi.org/10.1016/j.ijpharm.2007.10.020

Testai, E., Hartemann, P., Rastogi, S. C., Bernauer, U., Piersma, A., De Jong, W., Gulliksson, H., Sharpe, R., Schubert, D., & Rodriguez-Farre, E. (2016, Apr). The safety of medical devices containing DEHP plasticized PVC or other plasticizers on neonates and other groups possibly at risk (2015 update, version Feb 2016). *Regul Toxicol Pharmacol, 76*, 209-210. https://doi.org/10.1016/j.yrtph.2016.01.013

Van Vliet, E. D., Reitano, E. M., Chhabra, J. S., Bergen, G. P., & Whyatt, R. M. (2011, Aug). A review of alternatives to di (2-ethylhexyl) phthalate-containing medical devices in the neonatal intensive care unit. *J Perinatol, 31*(8), 551-560. https://doi.org/10.1038/jp.2010.208

Verstraete, S., Vanhorebeek, I., Covaci, A., Guiza, F., Malarvannan, G., Jorens, P. G., & Van den Berghe, G. (2016, Mar). Circulating phthalates during critical illness in children are associated with long-term attention deficit: a study of a development and a validation cohort. *Intensive Care Med, 42*(3), 379-392. https://doi.org/10.1007/s00134-015-4159-5

Wallner, P., Kundi, M., Hohenblum, P., Scharf, S., & Hutter, H. P. (2016, Jul 15). Phthalate Metabolites, Consumer Habits and Health Effects. *Int J Environ Res Public Health, 13*(7). https://doi.org/10.3390/ijerph13070717

Wang, Y., Zhu, H., & Kannan, K. (2019, Apr 5). A Review of Biomonitoring of Phthalate Exposures. *Toxics, 7*(2). https://doi.org/10.3390/toxics7020021

Welle, F., Wolz, G., & Franz, R. (2005). Migration of plasticizers from PVC tubes into enteral feeding solutions. *Pharma International*, 17-21.

Weuve, J., Sanchez, B. N., Calafat, A. M., Schettler, T., Green, R. A., Hu, H., & Hauser, R. (2006, Sep). Exposure to phthalates in neonatal intensive care unit infants: urinary concentrations of monoesters and oxidative metabolites. *Environ Health Perspect, 114*(9), 1424-1431. https://doi.org/10.1289/ehp.8926

Wheeler, C. R., & Smallwood, C. D. (2020, May). 2019 Year in Review: Neonatal Respiratory Support. *Respir Care, 65*(5), 693-704. https://doi.org/10.4187/respcare.07720

Wirnitzer, U., Rickenbacher, U., Katerkamp, A., & Schachtrupp, A. (2011, Aug 10). Systemic toxicity of di-2-ethylhexyl terephthalate (DEHT) in rodents following four weeks of intravenous exposure. *Toxicol Lett, 205*(1), 8-14. https://doi.org/10.1016/j.toxlet.2011.04.020

Woods, J. C. S., J. C. (2016). Lung Structure at Preterm and Term Birth. In A. H. U. o. C. W. Jobe, J. A.; Abman, S. H. (Ed.), *Fetal and Neonatal Lung Development* (pp. 126-140). Cambridge University Press.

Wu, L., Wang, G., Qu, P., Yan, C., & Du, H. (2011, May). Overexpression of dominant negative peroxisome proliferator-activated receptor-gamma (PPARgamma) in alveolar type II epithelial cells causes inflammation and T-cell suppression in the lung. *Am J Pathol, 178*(5), 2191-2204. https://doi.org/10.1016/j.ajpath.2011.01.046

Wu, W., Wu, C., Ji, C., Diao, F., Peng, J., Luo, D., Mu, X., & Ruan, X. (2020, Jul). Association between phthalate exposure and asthma risk: A meta-analysis of observational studies. *Int J Hyg Environ Health, 228*, 113539. https://doi.org/10.1016/j.ijheh.2020.113539

Xu, H., Musi, B., Wang, Z., Zhou, T., Huang, Q., Liu, J., Li, T., Jiang, Z., Liao, S., Jill, G., & Koo, E. (2019, Jun). Systemic toxicity of di (2-ethylhexyl) adipate (DEHA) in rats following 28-day intravenous exposure. *Regul Toxicol Pharmacol, 104*, 50-55. https://doi.org/10.1016/j.yrtph.2019.02.016

Yadav, S., Lee, B., & Kamity, R. (2021). Neonatal Respiratory Distress Syndrome. In *StatPearls*. https://www.ncbi.nlm.nih.gov/pubmed/32809614

Yin, S., Been, F., Liu, W., & Covaci, A. (2019, Jan 1). Hair as an alternative matrix to monitor human exposure to plasticizers - Development of a liquid chromatography - tandem mass spectrometry method. *J Chromatogr B Analyt Technol Biomed Life Sci, 1104*, 94-101. https://doi.org/10.1016/j.jchromb.2018.09.031

Zarean, M., Keikha, M., Poursafa, P., Khalighinejad, P., Amin, M., & Kelishadi, R. (2016, Dec). A systematic review on the adverse health effects of di-2-ethylhexyl phthalate. *Environ Sci Pollut Res Int, 23*(24), 24642-24693. https://doi.org/10.1007/s11356-016-7648-3

Zhang, Q., Chen, X. Z., Huang, X., Wang, M., & Wu, J. (2019, Jul). The association between prenatal exposure to phthalates and cognition and neurobehavior of children-evidence from birth cohorts. *Neurotoxicology, 73*, 199-212. https://doi.org/10.1016/j.neuro.2019.04.007

Zhou, S., Han, M., Ren, Y., Yang, X., Duan, L., Zeng, Y., & Li, J. (2020, Aug). Dibutyl phthalate aggravated asthma-like symptoms through oxidative stress and increasing calcitonin gene-related peptide release. *Ecotoxicol Environ Saf, 199*, 110740. https://doi.org/10.1016/j.ecoenv.2020.110740