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Estimated daily intake of phthalates, parabens, and bisphenol A in hospitalised very low birth weight infants

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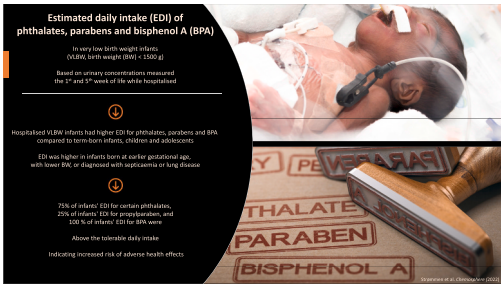
HIGHLIGHTS

- EDI was higher in infants born at earlier GA, with lower BW, LOS or BPD.
- HQ for BPA was >1 (EDI > TDI) in all infants indicating risk of adverse effects.
- More than 75% of infants' EDI for ΣBBzP+DnBP+DEHP+DiNP was higher than TDI.
- More than 75% of infants' EDI for DEHP was higher than TDI with HQ > 1.
- 25% had EDI for PrPa above TDI with HQ > 1 indicating risk of adverse effects.

GRAPHICAL ABSTRACT



Abbreviations: BBzP, Butyl benzyl phthalate; BPA, Bisphenol a; BPD, Bronchopulmonary dysplasia; BuPa, Butylparaben; BW, Birth weight; Cx-MiNP, Mono-4-methyl-7-carboxyoctyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEP, Diethyl phthalate; DiBP, di-iso-butyl phthalate; DiNP, di-iso-nonyl phthalate; DnBP, di-*n*-butyl phthalate; EDI, Estimated daily intake; ∑, Sum of; EtPa, Ethylparaben; F_{ue}, Urinary excretion fraction; GA, Gestational age; HQ, Hazard quotient; LOS, Late-onset septicaemia; LOQ, Limit of quantification; MBzP, Mono-benzyl phthalate; MECPP, Mono-2-ethyl 5-carboxypentyl phthalate; MEHP, Mono-2-ethylhexyl phthalate; MEHHP, Mono-2-ethyl-5-hydroxyhexyl phthalate; MEOHP, Mono-2-ethyl-5-oxohexyl phthalate; MePa, Methylparaben; MiBP, Mono-iso-butyl phthalate; MnBP, Mono-*n*-butyl phthalate; MMCHP, Mono-2-carboxymethyl hexyl phthalate; MEP, Monoethyl phthalate; MW_m, Molecular weight of metabolites; MW_p, Molecular weight of parent compounds; Oh-MiNP, Mono-4-methyl-7-hydroxyoctyl phthalate; Oxo-MiNP, Mono-4-methyl-7-oxooctyl phthalate; PrPa, Propylparaben; TDI, Tolerable daily intake; UCm, Measured unadjusted urinary concentrations; VLBW, Very low birth weight.

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ABSTRACT

Very low birth weight infants (VLBW, birth weight (BW) < 1500 g) are exposed to phthalates, parabens and bisphenol A (BPA) early in life. We estimated daily intake (EDI) of these excipients in 40 VLBW infants the first and fifth week of life while hospitalised. Based on urinary samples collected in 2010, EDI was calculated and compared to the tolerable daily intake (TDI) with hazard quotients (HQs) evaluated. A HQ > 1 indicates that EDI exceeded TDI with increased risk of adverse health effects. EDI was higher in VLBW infants compared to term-born infants and older children. VLBW infants born at earlier gestational age (GA), or with lower BW, had higher EDI than infants born at later GA or with higher BW. First week median EDI for BPA was higher than TDI in 100% of infants, in 75% for di(2-ethylhexyl) phthalate (DEHP), 90% for the sum of butyl benzyl phthalate (BBzP), di-*n*-butyl phthalate (DnBP), DEHP and di-iso-nonyl phthalate (DiNP) = ∑BBzP+DnBP+DEHP+DiNP, and in 50% of infants for propylparaben (PrPa), indicating increased risk of adverse effects. Fifth week EDI remained higher than TDI in all infants for BPA, in 75% for DEHP and ∑BBzP+DnBP+DEHP+DiNP, and 25% of infants for PrPa, indicating prolonged risk. Maximum EDI for di-iso-butyl phthalate was higher than TDI suggesting risk of adverse effects at maximum exposure. VLBW infants born earlier than 28 weeks GA had higher EDI, above TDI, for PrPa compared to infants born later than 28 weeks GA. Infants with late-onset septicaemia (LOS) had higher EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP and BPA, above TDI, compared to infants without LOS. More 75% of the infants' EDI for DEHP and ∑BBzP+DnBP+DEHP+DiNP, 25% for PrPa, and 100% of infants' EDI for BPA, were above TDI resulting in HQs > 1, indicating increased risk of adverse health effects.

1. Introduction

Very low birth weight (VLBW; birth weight (BW) < 1500 g) infants are exposed to phthalates, parabens and bisphenol A (BPA) during their stay in the neonatal intensive care unit (Strommen et al., 2016, 2021). These are excipients added to pharmaceuticals and medical equipment to improve product quality, stability and patient acceptability. They are known as endocrine disruptors (Witorsch and Thomas, 2010) that can cause adverse health effects on hormone-regulated biological functions in humans, with children being particularly vulnerable (WHO, 2013).

Phthalates, esters of phthalic acid, are used in pharmaceuticals for timed release and in medical equipment containing plastic to enhance the flexibility (Hauser and Calafat, 2005). Phthalates are not covalently bound to the device matrix and are easily released for human exposure before being hydrolysed, conjugated and excreted in the urine. Phthalate exposure has been associated with preterm birth and low BW (Ferguson et al., 2014, 2022; Welch et al., 2022; Street and Bernasconi, 2020), adverse immune responses (Bornehag and Nanberg, 2010), inflammatory cytokine release (Bolling et al., 2012) and reduced anti-inflammatory signalling, possibly increasing the risk of inflammatory disorders such as bronchopulmonary dysplasia (BPD) (Fischer et al., 2013) and septicaemia (Vetrano et al., 2010). Studies on phthalate exposure in premature infants are rare. Premature infants are exposed to di(2-ethylhexyl) phthalate (DEHP) from medical equipment making them a high-risk population to DEHP exposure (European Commission, 2015). A longitudinal study performed in Finland, between 2006 and 2008, showed that more than 80% of premature born infants were exposed to phthalate levels exceeding the established health based guidance values the first week of life (Frederiksen et al., 2014).

Parabens, esters of *p*-hydroxybenzoic acid, are used as preservatives in pharmaceuticals and parenteral products. Common parabens are methyl-, ethyl, propyl- and butylparaben (MePa, EtPa, PrPa and BuPa, respectively), which are hydrolysed and/or conjugated before being excreted in the urine. Paraben exposure has been associated with preterm birth and low BW (Aung et al., 2019; Uldbjerg et al., 2022) where daily exposure to pharmaceuticals containing parabens can result in prolonged systemic exposure in neonates (Mulla et al., 2015). In 2010, the Scientific Committee on Consumer Safety in the European Union concluded that use of MePa and EtPa below permitted levels is safe, whereas some uncertainty existed regarding use of PrPa and BuPa due to lack of data (SCCS, 2013). A combination of MePa and PrPa was found in most commercial pharmaceuticals administered to hospitalised neonates in France in 2017 (Binson et al., 2020). EtPa exposure might be associated with altered respiratory health (Vernet et al., 2017) and reduced forced expiratory volume in children (Agier et al., 2019). As with phthalates, studies on paraben levels in preterm infants are scarce. Calafat et al. measured higher urinary concentrations of MePa and PrPa in premature infants compared to adults, and expressed concern about this because these infants had been exposed during a critical period of development (Calafat et al., 2009).

BPA is a phenol used in the production of polycarbonate plastics that can be detected in medical equipment made of plastic, with risk of BPA exposure in patients who are dependent on the use this equipment. BPA is quickly metabolised and excreted in urine. BPA exposure has been associated with preterm birth and low BW (Aung et al., 2019; Uldbjerg et al., 2022), reduced lung function in childen (Spanier et al., 2014), altered immune response (Xu et al., 2016; The European Food Safety Authority, 2021), and increased risk of respiratory tract infections (Gascon et al., 2015). As with phthalates and parabens, studies on BPA exposure in premature infants are few. Urinary BPA concentrations in premature infants undergoing intensive therapeutic interventions were one order of magnitude higher than in the general population in the USA (Calafat et al., 2009), where the exposure to BPA correlated with the number of medical devices used (Duty et al., 2013). The calculated daily exposure of BPA was lower than the threshold value for toxicity, however 16- to 32-fold higher than in non-hospitalised infants and children (Duty et al., 2013). In 2011, the European Union banned the use of baby bottles containing BPA, and four years later, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks, concluded that the risk of adverse effects of BPA may exist especially for infants in the neonatal intensive care unit (SCENIHR, 2015). In December 2021, the European Food Safety Authority reduced the level of exposure to BPA that was considered safe based on new scientific data (The European Food Safety Authority, 2021).

To assess human health risk related to exposure to a specific compound, the ratio between the daily intake and its corresponding health-based guidance value is used. The estimated daily intake (EDI) of phthalates, parabens and BPA can be determined by back-calculating the exposure from urinary concentrations when toxicokinetic details are available. EDI can then be compared to the tolerable daily intake (TDI, the daily intake of a chemical that has been assessed to be safe for a person on a lifetime basis) and used to calculate hazard quotients (HQ). A HQ > 1 indicates that EDI exceeded TDI with increased likelihood of adverse effects. Cumulative risk assessment considers the concurrent human exposure to several chemicals with similar toxicological mechanisms, thus a group-TDI has been established for some phthalates (Efsa Panel on Food Contact Materials et al., 2019).

In 2010, we performed a randomised controlled trial to evaluate the impact of a nutritional intervention in hospitalised VLBW infants (Moltu et al., 2014). A pre-planned safety analysis revealed a higher occurrence

of late-onset septicaemia (LOS; age ≥ 4 days with growth of bacteria in blood culture and clinical signs of septicaemia) in the intervention group (Moltu et al., 2013). Infants with lower BW, BPD or LOS, experienced prolonged use of medical equipment containing phthalates, with higher urinary phthalate levels measured, compared to infants with higher BWs and without BPD or LOS (Strommen et al., 2016). The total study cohort also had very high urinary concentrations of parabens and BPA, where infants with BPD and LOS had higher BPA levels than infants without these diagnoses (Strommen et al., 2021). EDI of phthalates, parabens and BPA in hospitalised VLBW infants are virtually non-existent. Thus, the aim of this study was to calculate EDI and HQ, based on urinary concentrations of phthalates, parabens, and BPA, for assessment of risk in hospitalised VLBW infants.

2. Materials and methods

2.1. Design

VLBW infants, admitted to three neonatal intensive care units in Oslo, Norway in 2010, participated in a randomised controlled nutritional trial after informed parental consent was obtained. The study was performed in accordance with the Helsinki Declaration and approved by the Regional Committee for Medical and Health Research Ethics in Norway. VLBW infants were eligible for inclusion and randomised as previously described (Moltu et al., 2014). Exclusion criteria were congenital malformations, chromosomal abnormalities, syndromes known to affect growth and development, and critical illness with short life expectancy. Infants in the intervention group received an enhanced nutrient supply, whereas infants in the control group received a nutrient supply according to recommendations at that time. Urinary samples from the included infants were analysed for phthalates, parabens and BPA.

2.2. Urine processing

Urinary samples were collected, during the first and fifth week of life, from cotton pads soaked in urine after being placed in the diaper to register 24-h diuresis. 0.5–2.0 mL of urine was transferred to Nunc Cryo Tubes (Thermo Fischer Scientific, Inc., MA, USA) and stored at −80 °C until analyses of phthalates, parabens, and total BPA were performed.

Twelve phthalate metabolites from six parent compounds (Table 1) were analysed by on-line column switching liquid chromatography coupled to tandem mass spectrometry (Sabaredzovic et al., 2015). Briefly, isotope-labelled internal standards (Cambridge Isotope Laboratories Inc. Andover, MA, USA), and enzyme beta-glucuronidase (Roche Diagnostics GmbH, Mannheim, Germany), were added to 300 μL of urine. The samples were incubated for 90 min at 37 °C and 100 μL of 20% formic acid was added to stop the reaction before the samples were vortexed and centrifuged. Urinary samples were transferred to 2 mL injection vials (Agilent Technologies, Santa Clara, USA) and 250 μL was injected into the system (Agilent 1200 Series LC-instrument and a Triple Quad LC-MS/MS 6460 Series from Agilent Technologies, Santa Clara, CA, USA). Both procedural blanks, in-house and external quality control samples were included. External urine samples were provided by External Quality Assessment Scheme, organized by Consortium, to perform human biomonitoring on a European scale. These samples were a gift from Dr. Holger Koch, Bochum University. The limit of quantification (LOQ) ranged from 0.1 to 0.5 ng/mL and the accuracy of the method was between 80 and 120%. For confirmation of phthalate metabolites, both retention time and qualifier ratio were used. Phthalate metabolites that did not fulfil the above two criteria were reported as missing and omitted from the calculations. Sixteen (1.2%) phthalates concentrations were detected as below LOQ and replaced with LOQ/2 (Cohen and Ryan, 1989).

Four parabens and total BPA (Table 1) were analysed by on-line solid phase extraction prior to ultra-high performance liquid chromatography coupled to tandem mass spectrometry. Internal standards (Cambridge Isotope Laboratories Inc., Andover, MA, USA and Chiron AS, Norway) and enzyme solution (beta-glucuronidase/sulfatase in ammonium acetate buffer, pH 5.0) were added to 200 μL of the sample before incubating at 37 °C. Formic acid (40%) was added after 4 h to stop the enzymatic reaction, the samples were centrifuged and the supernatant was transferred to 2 mL amber injection vials (Agilent Technologies, Santa Clara, USA) before 80 μL was injected into the system (Agilent 1200 Series LC-instrument and Triple Quad MS/MS 6490, Agilent Technologies, Santa Clara, CA, USA). The accuracy of the method ranged from 75 to 120% with precision below 26%. Both procedural blanks and in-house pooled urine samples controls were analysed along with the samples. Twenty-four (8.1%) paraben concentrations were below the LOQ, one (0.3%) was without signal and one (0.3%) was outside the calibration curve. One (1.4%) BPA concentration was without signal, and none were below the LOQ or outside the calibration curve. Results below the LOQ and without signal were replaced with $LOQ/\sqrt{2}$,[34] whereas the one result outside the calibration curve was omitted from the calculations. The results were reported in μg/L with no adjustments for creatinine or specific gravity.

Table 1
Molecular weights and excretion fractions for phthalates, parabens, and BPA analysed.

Parent compounds		MW_p	Metabolites		MW_m	F_{ue}
DEP	Diethyl phthalate	222.2	MEP	Monoethyl phthalate	194.2	0.69 (Angerer and H. M. K. a. J., 2011)
BBzP	Butyl benzyl phthalate	312.4	MBzP	Mono-benzyl phthalate	256.3	0.73 (Anderson et al., 2001)
DiBP	Di-iso-butyl phthalate	278.3	MiBP	Mono-iso-butyl phthalate	222.2	0.70 (Koch et al., 2012)
DnBP	Di-*n*-butyl phthalate	278.3	MnBP	Mono-*n*-butyl phthalate	222.2	0.84 (Koch et al., 2012)
DEHP	Di(2-ethylhexyl) phthalate	390.6	MEHP	Mono-2-ethylhexyl phthalate	278.3	0.06 (Koch et al., 2005)
			MEHHP	Mono-2-ethyl-5-hydroxyhexyl phthalate	294.3	0.23 (Koch et al., 2005)
			MEOHP	Mono-2-ethyl-5-oxohexyl phthalate	292.3	0.15 (Koch et al., 2005)
			MECPP	Mono-2-ethyl 5-carboxypentyl phthalate	308.3	0.19 (Koch et al., 2005)
			MMCHP	Mono-2-carboxymethyl hexyl phthalate	308.3	0.04 (Koch et al., 2005)
Sum of DEHP metabolites (calculated)						0.67 (Koch et al., 2005)
DiNP	Di-iso-nonyl phthalate	418.6	oh-MiNP	Mono-4-methyl-7-hydroxyoctyl phthalate	308.4	0.18 (Koch and Angerer, 2007)
			oxo-MiNP	Mono-4-methyl-7-oxooctyl phthalate	306.4	0.10 (Koch and Angerer, 2007)
			cx-MiNP	Mono-4-methyl-7-carboxyoctyl phthalate	322.4	0.09 (Koch and Angerer, 2007)
Sum of DiNP metabolites (calculated)						0.37[a] (Koch and Angerer, 2007)
MePa	Methylparaben					0.17 (Moos et al., 2016)
EtPa	Ethylparaben					0.14 (Moos et al., 2017)
PrPa	Propylparaben[b]					0.10[c] (Moos et al., 2017)
BuPa	Butylparaben					0.06[c] (Moos et al., 2016)
BPA	Bisphenol A					1.00[c] (Thayer et al., 2015)

MW_p and MW_m = molecular weight of parent compounds and metabolites (g/mol), respectively; F_{ue} = urinary excretion fraction.
[a] Based on three DiNP metabolites. [b] n-propylparaben. [c] Calculated as the mean of F_{ue} values for the iso- and n-isomers.

2.3. Estimated daily intake and hazard quotient calculation

EDI of phthalate metabolites was calculated using formula 1 (Koch et al., 2007; Koch and Calafat, 2009; Wittassek et al., 2007), whereas formula 2 was used to calculate EDI for parabens and BPA (Sakhi et al., 2018):

$$\text{Formula 1}: \quad \text{EDI}\ (\mu g/kg/day) = \frac{\text{UCm}\ (\mu g/L) \times (\text{MWp}\ (g/mol)\ /\ \text{MWm}\ (g/mol)\ ) \times 24\ \text{hour urine volume}\ (L/day)}{\text{Fue} \times \text{Body weight}\ (kg)}$$

$$\text{Formula 2}: \quad \text{EDI}\ (\mu g/kg/day) = \frac{\text{UCm}\ (\mu g/L) \times 24\ \text{hour urine volume}\ (L/day)}{\text{Fue} \times \text{Body weight}\ (kg)}$$

UCm are measured, unadjusted and non-transformed urinary concentrations of phthalate metabolites, parabens or BPA; MW_p and MW_m the molecular weights of parent phthalates and phthalate metabolites, respectively; 24-h urine volume was measured or estimated the day the urinary samples were collected; Fue is the fraction of phthalates, parabens or BPA excreted in the urine, and body weight the actual or estimated weight when urinary samples were collected. EDI for the sum of DEHP metabolites, and for the sum of di-iso-nonyl phthalate metabolites (DiNP), was calculated by dividing each metabolite concentration by its molecular weight, then summed and used in formula 1. Molecular weights of parent phthalates with metabolites, and Fue of phthalates, parabens and BPA are shown in Table 1. The 24-h urine volume was measured in most infants the first week of life as the cumulative sum of differences in weight of cotton pads before and after urination registered throughout the day. The 24-h urine output was divided by the weight at urinary sampling resulting in a 24-h urine output (mL/kg/day). Fifth week of age 24-h urine output was estimated to 4.20 mL/kg/day as an average of results from two studies reporting 24-h urine volumes at three to four weeks of age in infants with similar characteristics (Vuohelainen et al., 2011; Aly et al., 2013). EDI for butyl benzyl phthalate (BBzP), di-*n*-butyl phthalate (DnBP), DEHP and DiNP were merged to ∑BBzP+DnBP+DEHP+DiNP and evaluated against a group-TDI due to common toxicological mechanisms (Efsa Panel on Food Contact Materials et al., 2019). Formula 3 was used to calculate HQ where EDI was divided by the current TDI.

$$\text{Formula 3}: \quad \text{HQ} = \frac{\text{EDI}\ (\mu g/kg/day)}{\text{TDI}\ (\mu g/kg/day)}$$

2.4. Statistics

Statistical analyses were performed with Statistical Package for Social Sciences (SPSS version 27 & 28; IBM Inc., Chicago, IL, USA) with p-values < 0.05 considered significant. Results are presented as means with 95% confidence intervals, or as medians with minimum, maximum and percentiles for continuous data, number and percentage for categorical variables, percentiles for EDI, calculated HQ, and numerical differences between fifth and first week EDIs. Wilcoxon signed rank test was used to compare change in EDI from the first to the fifth week of age. To evaluate differences between groups we used the Mann-Whitney *U* test for continuous variables and multiple linear regression were applied to adjust for BW. Spearman's correlation coefficients (r) were calculated for urinary concentrations of analytes and gestational age (GA) at birth and BW. Curve estimation regression statistics were used to find the best fitting linear or non-linear regression model between EDI of selected excipients and BW.

Table 2
Characteristics of the included infants (n = 40).

Mean GA at birth (95% CI), weeks^{days}	28^{3} (27^{5}-29^{1})
Min-max, weeks^{days}	25^{0}-33^{4}
Mean BW (95% CI), g	1026 (950–1102)
Min-max, g	460–1414
Small for gestational age, n (%)	14 (35)
Born by caesarean section, n (%)	28 (70)
Sex (girls), n (%)	17 (42.5)
Mean 24-h urine output the first week of life, mL/kg/day (95% CI), mL/kg/day	3.88 (3.42–4.33) [a]
Min-max, mL/kg/day	2.40–7.46
Mean 24-h urine output the fifth week of age, mL/kg/day	4.20 (Vuohelainen et al., 2011, Aly et al., 2013)
Median (min-max) number of days on parenteral nutrition	9 (4–29) [b]
10^{th} - 90^{th} percentile, days	5–19
Median (min-max) number of days on intravenous antibiotics	12.5 (0–42)
10^{th} - 90^{th} percentile, days	2–34
Median (min-max) number of days on breathing support	27.5 (0–88)
10^{th} - 90^{th} percentile, days	2–66
LOS, n (%)	19 (47.5)
BPD, n (%)	8 (20)
Necrotizing enterocolitis, n (%)	2 (5)
Severe intraventricular haemorrhage, n (%)	3 (7.5)
Death, n (%)	2 (5)

GA = gestational age; CI = confidence interval; Min = minimum; Max = maximum; BW = birth weight; Small for gestational age = BW below the 10^{th} percentile for GA; Breathing support include non-invasive and invasive methods; LOS = late-onset septicaemia; BPD = bronchopulmonary dysplasia. [a] = n = 33. [b] n = 37.

3. Results

All but one VLBW infant was exposed to phthalates by use of phthalate-containing invasive and/or non-invasive breathing support (tracheal tubes and breathing circuit sets) (Strommen et al., 2016). All included infants were exposed to parabens or BPA from use of pharmaceuticals such as respiratory stimulants (caffeine), antibiotics (gentamycin), vitamins for parenteral administration, and use of plastic medical and non-medical equipment like intravenous cannulas, breathing support equipment, bags for storing parenteral nutrient solutions and baby bottles (Strommen et al., 2021). The urinary samples were collected during the first (n = 38–40) and fifth (n = 34–36) week of life, while hospitalised, and analysed for the presence of phthalates, parabens, and BPA. The number of infants varied because some results were below the qualifier ratio, out of range or missing. Characteristics of the included infants (n = 40) are presented in Table 2.

3.1. Estimated daily intake and hazard quotients

Table 3 shows current TDIs with calculated EDIs and HQs for phthalates, parabens and BPA the first and fifth week of life. The majority of median EDIs were below TDI with HQs < 1, with some exceptions. First week EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP, PrPa, and BPA, were higher than their corresponding TDIs with HQ > 1. At five weeks of age, EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP and BPA remained higher than TDI with HQ > 1. EDIs decreased from first to fifth week of age for diethyl phthalate (DEP), BBzP, di-iso-butyl phthalate (DiBP) and DnBP, whereas DiNP, EtPa and BuPa had increasing EDIs during this time-period. EDI for ∑BBzP+DnBP+DEHP+DiNP, with common toxicological mechanisms, exceeded their group-TDI in more than 90% of the included infants the first week of life, and in 75% of them the fifth week. The maximum EDI for several metabolites were close to, or above, their corresponding TDI (first week of life: DiBP, DnBP and DiNP; fifth week of age: DiBP, DiNP, PrPa and BuPa), with HQ > 1.

Tables 4–6 compare the present study's EDI for phthalates, parabens and BPA with EDIs published in other studies on infants, children, and adolescents. EDIs were higher in premature infants compared to term infants, children, and adolescents. The HQ for DEHP and PrPa for premature infants, in addition to all infants, children, and adolescents' EDI for BPA, was higher than 1.

3.2. Group affiliation

No differences in median EDI for parabens were seen among infants in the intervention and control group. However, first week of life EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP, and BPA, were higher among infants in the intervention group compared to the control group (Table 7). Infants in the intervention group were born with lower BW compared to infants in the control group (932 g vs 1141 g, p = 0.002). The above-mentioned differences in EDI disappeared when we adjusted for BW, and because the present study did not evaluate the effects of a nutrient intervention, infants in the intervention and control group were merged for analyses of pooled data.

3.3. Gestational age at birth, birth weight and sex

The majority of EDIs of phthalates, parabens and BPA were negatively correlated with GA at birth (first week of life: DEP: r = −0.49, p = 0.001; PrPa: r = −0.57, p < 0.001; fifth week of age: ∑BBzP+DnBP+DEHP+DiNP: r = −0.63, p < 0.001). First week of life EDI of DEP and DnBP was higher in infants born before 28 weeks GA, but lower than TDI. No differences were seen for first week of life EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP, and BPA, in infants born before or after 28 weeks GA, although their EDIs were above TDI. Infants born before 28 weeks GA had a higher first week of life EDI for PrPa which was above TDI (Table 7). Similarly, most EDIs were negatively correlated with BW (first week of life: DEP: r = −0.63, p < 0.001; DEHP: 0.63, p < 0.001; ∑BBzP+DnBP+DEHP+DiNP: r = −0.53, p < 0.001; BuPa: 0.43, p = 0.008 and BPA: r = −0.46, p = 0.004) suggesting that EDI increases with lower GA and weight at birth. Looking at this in reverse, i.e., evaluating possible associations between prenatal exposure and BW, non-linear associations between first week EDI of DEP, DEHP, ∑BBzP+DnBP+DEHP+DiNP, BuPa and BPA, and BW were observed. Approximately 46% of the variation in BW could be explained by first week for life EDI for DEP, 28% by DEHP, 28% by ∑BBzP+DnBP+DEHP+DiNP, 23% by BuPa, and 21% by first week EDI for BPA. No significant differences in use of exposure sources (medical equipment or pharmaceuticals), or EDI, were detected between girls and boys (data not shown).

3.4. Late-onset septicaemia and bronchopulmonary dysplasia

Infants with LOS (48%) had higher first week of life EDI for DEP, DEHP, ∑BBzP+DnBP+DEHP+DiNP, and BPA, compared to infants without LOS. HQ was higher than 1 for DEHP, ∑BBzP+DnBP+DEHP+DiNP, PrPa, and BPA. Infants with BPD (20%) had higher first week of life EDI for DEP, BBzP and EtPa, as compared to infants without these diagnoses. HQ was higher than 1 for DEHP, ∑BBzP+DnBP+DEHP+DiNP, PrPa, and BPA (Table 7).

4. Discussion

All included infants were exposed to either phthalates, parabens or BPA through necessary use of pharmaceuticals and medical equipment. Other likely sources of exposure were from parents, healthcare personnel, the environment and human milk, were not evaluated in this study. We calculated EDI and HQ from urinary concentrations of phthalates, parabens, and BPA in hospitalised VLBW infants born in 2010. VLBW infants had higher EDIs for phthalates, parabens and BPA if born at earlier GA or with lower BW, and higher EDIs than term-born infants, children, and adolescents. More than 75% of the infants' EDI for DEHP and ∑BBzP+DnBP+DEHP+DiNP, 25% for PrPa, and all infants' EDI for BPA, were above their corresponding TDI with HQ > 1, indicating increased risk of adverse health effects. Maximum EDI for DiBP exceeded TDI with possible risks of adverse effects at maximum daily intake. VLBW infants born earlier than 28 weeks GA, and those diagnosed with LOS and BPD, all had first week of life EDI for DEHP, ∑BBzP+DnBP+DEHP+DiNP, PrPa and BPA above TDI with HQs > 1, indicating increased risk of adverse effects.

We measured significantly higher concentrations of phthalates in infants with lower BW and those diagnosed with LOS and BPD (Strommen et al., 2016). EDI for DEP was higher in infants with BPD compared to infants without BPD, although below TDI. An association between DEP exposure and airway inflammation has been observed in children (Just et al., 2012). Infants born earlier than 28 weeks GA also had significantly higher concentrations of parabens and BPA compared to infants born at later GAs, and those diagnosed with LOS or BPD had higher levels of BPA compared to infants without these diagnoses (Strommen et al., 2021). Increased EDI in VLBW infants born at earlier GA may be explained by lower BWs and increased likelihood of developing LOS and BPD, which require higher exposure to phthalates, parabens and BPA by necessary use of pharmaceuticals and medical equipment. Higher exposure in infants with lower BW may be due to immature organ systems and metabolic pathways causing reduced elimination (Fabiano et al., 2011). Lower EDI and HQ for some analytes at five weeks of age might be due to reduced exposure and improved maturation of metabolic pathways. Analytes with increasing EDIs might be explained use of different pharmaceuticals and medical equipment at this time during the hospital stay.

Experimental- and epidemiological data show that phthalates, parabens and BPA have the potential to cause adverse health effects.

Table 3
Current TDIs with calculated EDIs and HQs for phthalates, parabens, and BPA.

Compound	TDI	First week n = 38–40[a]								Fifth week n = 34–36[a]									
		EDI							HQ	EDI							HQ	Δ EDI	P-value
		Min	10th	25th	50th	75th	90th	Max		Min	10th	25th	50th	75th	90th	Max			
DEP	500[1]	0.40	1.08	2.09	4.41	7.97	14.9	45.4	<1	0.20	0.50	1.24	2.50	4.49	6.64	21.4	<1	−1.91	<0.01*
BBzP	500[b,2]	0.09	0.40	0.70	1.53	2.86	11.0	15.9	<1	0.06	0.08	0.13	0.38	0.98	4.70	13.3	<1	−1.15	<0.01*
DiBP	10[b,c,2]	0.87	1.69	2.13	3.36	5.03	8.72	23.5	<1	0.39	0.51	1.24	2.24	4.26	6.17	11.0	<1	−1.12	<0.01*
DnBP	10[b,2]	0.31	0.69	1.14	1.95	5.47	8.46	15.9	<1	0.10	0.19	0.55	0.90	1.77	2.82	4.38	<1	−1.05	<0.001*
DEHP	50[b,2]	14.1	46.6	83.9	256	695	974	2521	**5.12**	7.59	12.8	63.3	212	589	1078	1914	**4.24**	−44.0	0.61
DiNP	15[b,2]	1.13	1.32	1.78	4.50	8.23	16.9	147	<1	1.79	2.11	3.56	9.78	16.6	72.8	141	<1	5.28	0.01*
∑BBzP+DnBP+DEHP+DiNP	50[b,d,2]	23.2	53.8	90.2	260	704	981	2545	**5.20**	9.97	16.1	73.2	227	691	1129	1959	**4.54**	−33.0	0.83
MePa	n/a	7.39	25.3	104	260	480	1159	2593	n/a	1.02	4.72	28.3	155	418	829	2531	n/a	−105	0.35
EtPa	n/a	0.02	0.09	0.27	0.58	1.05	1.85	3.49	n/a	0.03	0.11	0.27	0.86	7.28	58.1	442	n/a	0.28	0.02*
∑MePa + EtPa	0 - 10,000[3]	7.56	25.4	106	261	481	1161	2596	–	1.05	5.19	33.7	155	431	833	2973	–	−106	0.55
PrPa	n/a[3], 20[e]	0.48	3.07	7.18	22.6	49.2	126	415	**1.13**	0.15	0.72	2.46	12.0	72.7	296	361	<1	−10.6	0.71
BuPa	n/a[3], 20[e]	0.04	0.04	0.05	0.27	0.89	1.32	3.36	<1	0.06	0.06	0.20	0.58	2.78	30.1	205	<1	0.31	0.01*
BPA	0.00004[4]	0.002	0.21	0.53	1.07	2.15	3.54	12.0	**26,750**	0.11	0.16	0.42	0.73	2.08	4.03	9.87	**18,250**	−0.34	0.40

TDI = tolerable daily intake (μg/kg/day); EDI = estimated daily intake (μg/kg/day); HQ = hazard quotient; Min = minimum; 10th percentile; 25th percentile; 50th percentile; 75th percentile; 90th percentile and max = maximum values; Δ EDI = fifth week median EDI value - first week median EDI value; n/a = not available. [a] Varying n due to some results below qualifier ratio, out of range or missing. [b] Temporary TDI; [c] TDI assumed to be the same as for DnBP. [d] Group-TDI for ∑BBzP+DnBP+DEHP+DiNP. [e] Based upon a no observed effect level of 2 mg/kg/day with an uncertainty factor of 100. HQ in bold is where EDI exceeded current TDI with increased risk of adverse effects. P-values with an asterisk are significant.

References: 1 Committee on toxicity of chemicals, 2011; 2 Efsa Panel on Food Contact Materials et al., 2019; 3 Opinion of the Scientific Panel, 2004; 4 The European Food Safety Authority, 2021.

Table 4
Median EDI of phthalates in infants, children, and adolescents.

Period	Location	Study population	n	DEP	BBzP	DiBP	DnBP	DEHP	DiNP	Reference
2006–2008	Finland	Premature infants at 7 days of age	67	1.81	30.4	4.35	2.66	**243**	22.9	Frederiksen et al., (2014)
2006–2008	Finland	Premature infants at 2 months of age	67	1.86	5.18	4.29	2.09	7.27	0.88	Frederiksen et al., (2014)
2010	Norway	Premature infants the first week of life	39–40	4.41	1.53	3.63	1.95	**256**	4.50	Present study
2010	Norway	Premature infants the fifth week of age	34–35	2.50	0.38	2.24	0.90	**212**	9.78	Present study
2012	China	0–2 days of age	748	0.04	0.00		0.22	0.03		Li et al., (2019)
2006–2008	Finland	7 days of age	58	1.43	5.99	4.85	2.45	4.34	0.70	Frederiksen et al., (2014)
2008	Germany	1–5 months of age	47	0.86[a]	0.18[a]	1.92[a]	0.80[a]	1.28[a]		Volkel et al., (2014)
2014	China	0–1 year of age	152		0.08	5.45	2.04	2.96[b]		Dong et al., (2018)
2016–2018	Denmark	0–1 year of age	104	0.37	0.04	0.52	0.42	0.57	0.12	Frederiksen et al., (2022)
2012–2013	Korea	3–15 months of age	171	0.12		0.56	0.24	1.20		Kim et al., (2017)
2009–2010	Germany	15–21 months of age	25	1.50	0.30	2.20	1.60	2.60	0.90	Fromme et al. (2013a)
2009–2011	Greece	2 years of age	239	1.40	0.20	1.40	1.00	4.00		Myridakis et al., (2015)
2011–2012	Greece	4 years of age	500	1.30	0.17	1.20	0.70	4.02		Myridakis et al., (2016)
2008–2009	Denmark	3–6 years of age	431	0.62	0.49	2.93	3.26	4.42		Beko et al., (2013)
2007	Germany	5–6 years of age	108		0.30	2.10	1.90	4.50	2.40	Koch et al., (2011)
2011–2012	Germany	1–6 years of age	663	0.88	0.43	1.80	1.31	3.26	2.21	Fromme et al. (2013b)
2005–2008	USA	6–11 years of age	742		0.70	0.40	0.90	6.00	2.50	Christensen et al., (2014)
2011	Denmark	6–11 years of age	141	0.53	0.20	2.55	0.78	2.56	1.15	Frederiksen et al., (2013)
2013	Belgium	1–12 years of age	52	1.47	0.42	2.29	2.38	3.37		Dewalque et al., (2014)
2001–2002	Germany	2–14 years of age	239		0.77		7.61	7.80		Wittassek et al., 2007; Koch et al., (2007)
2012–2013	Brazil	6–14 years of age	300	2.14		1.75	1.70	7.16		Rocha et al., (2017)
2014–2015	Portugal	4–18 year of age	112	1.46	0.07	0.51	0.27	1.89	1.04	Correia-Sa et al., (2018)
2017–2018	Belgium	14–15 year of age	407	0.94	0.09	0.85	0.58	1.20	0.65	Bastiaensen et al., (2021)

EDI = estimated daily intake (μg/kg/day).). [a] Values estimated from bar chart. [b] Based on the urinary concentration of MEHHP. EDI in bold is where EDI exceeded current TDI with increased risk of adverse effects.

Table 5
Median EDI of parabens in in infants, children, and adolescents.

Period	Location	Study population	n	MePa	EtPa	PrPa	BuPa	Reference
2010	Norway	Premature infants the first week of life	38	260	0.58	**22.6**	0.27	Present study
2010	Norway	Premature infants the fifth week of age	35–36	155	0.86	12.0	0.58	Present study
2009–2011	Greece	2 years of age	239	66.6	5.80	3.40		Myridakis et al., (2015)
2012–2013	China	3 years of age	436	12.1	5.68	4.50	0.06	Guo et al., (2017)
2011–2012	Greece	4 years of age	500	25.8	2.01	1.93		Myridakis et al., (2016)
2015	China	3–6 years of age	96	10.5	0.68	1.24	0.37	Lu et al., (2019)
2016–2019	China	0–7 years of age	47	2.42	0.16	0.09		Shi et al., (2021)
2012	USA	3–10 years of age	40	0.61[a]		0.01[a]		Wang et al., (2013)
2012	China	9–10 years of age	70	0.58[a]		0.22[a]		Wang et al., (2013)
2015	China	7–11 years of age	159	3.57	0.91	1.28	0.002	Lu et al., (2019)
2012	Norway	6–12 years of age	56	1.00	0.14	0.22		Sakhi et al., (2018)
2014–2017	Germany	3–17 year of age	516	0.44	0.09	0.05	0.06	Murawski et al., (2021)
2018	Iran	12–20 years of age	100	14.1	1.64	3.19	0.32	Kiani Feizabadi et al., (2020)

EDI = estimated daily intake (μg/kg/day). [a] Geometric mean. EDI in bold is where EDI exceeded current TDI with increased risk of adverse effects.

Table 6
Median EDI of BPA in infants, children, and adolescents.

Period	Location	Study population	n	BPA	Reference
2003	USA	Premature infants during hospitalization	41	**1.09**	Calafat et al., 2009 [a]
2009–2010	USA	Premature infants at 4 of weeks of age	55	**0.65**	Duty et al., (2013)
2010	Norway	Premature infants the first week of life	38	**1.07**	Present study
2010	Norway	Premature infants the fifth week of age	35–36	**0.73**	Present study
2008	Germany	1–5 months of age	47	**< 0.02**	Volkel et al., 2011[a]
2000–2016	4 countries	0–1 year of age	350	**0.09**	Huang et al., (2017)
2009–2011	Greece	2 years of age	239	**0.05**	Myridakis et al., (2015)
2011–2012	Greece	4 years of age	500	**0.03**	Myridakis et al., (2016)
2015–2016	Turkey	3–6 years of age	125	**0.04**[b]	Cok et al., (2020)
2016–2019	China	0–7 years of age	47	**0.08**	Shi et al., (2021)
2003–2014	USA	1–8 years of age	1274	**0.08**	Stacy et al., (2016)
2005–2006	USA	6–11 years of age	355	**0.05**	Lakind and Naiman, (2011)
2011	Denmark	6–11 years of age	141	**0.04**	Frederiksen et al., (2013)
2012	Norway	6–12 years of age	56	**0.09**	Sakhi et al., (2018)
2014–2015	Poland	7 years of age	250	**0.05**	Gari et al. (2021)
2011–2012	Six European countries	5–12 years of age	633	**0.04**	Covaci et al., (2015)
2015–2017	Italy	4–14 years of age	900	**0.17**[b]	Tait et al., (2021)
2003–2006	Germany	3–14 years of age	599	**0.06**[b]	Becker et al., (2009)
2000–2016[b]	18 countries	2–17 years of age	22,406	**0.06**	Huang et al., (2017)

EDI = estimated daily intake (μg/kg/day). [a] The estimated daily intake was published by (Duty et al., 2013). [b] Geometric mean. EDI in bold is where EDI exceeded current TDI with increased risk of adverse effects.

Table 7
First week of life median EDI (with HQ for selected analytes) by group affiliation, GA at birth, LOS and BPD.

Compound	Group affiliation			GA at birth			LOS			BPD		
	Intervention	Control	P-value	<28 weeks	>28 weeks	P-value	Yes	No	P-value	Yes	No	P-value
	n = 21–22[a]	n = 17–18[a]		n = 18–20[a]	n = 19–20[a]		n = 18–19[a]	n = 20–21[a]		n = 8[a]	n = 30–32[a]	
DEP	4.68	4.41	0.30	6.03	3.34	<0.01*	5.74	3.98	0.05*	10.9	4.07	0.03*
BBzP	1.58	1.21	0.56	1.93	1.27	0.09	1.38	1.54	0.59	3.48	1.27	0.04*
DiBP	3.97	2.90	0.14	3.31	3.48	0.99	2.54	3.84	0.41	3.49	3.36	0.70
DnBP	2.17	1.58	0.35	3.36	1.58	0.05*	3.10	1.50	0.16	5.80	1.79	0.15
DEHP	313	94.2	0.004*	304 (**6.08**)	158	0.14	325 (**6.50**)	156	0.03*	570 (**11.4**)	164	0.11
DiNP	4.59	3.27	0.29	3.89	5.45	0.48	4.47	5.22	0.63	4.80	3.95	0.65
∑BBzP+DnBP+DEHP+DiNP	323	107	0.005*	317 (**6.34**)	166	0.13	332 (**6.64**)	162	0.03*	582 (**11.6**)	169	0.11
MePa	257	279	0.71	271	199	0.35	227	268	0.99	287	260	0.33
EtPa	0.46	0.73	0.27	0.54	0.64	0.50	0.76	0.42	0.16	1.07	0.53	0.05*
∑MePa + EtPa	258	279	0.71	272	200	0.35	228	269	0.99	288	261	0.33
PrPa	16.8	38.6	0.20	38.1 (**1.91**)	16.5	0.003*	31.2 (**1.56**)	16.5	0.22	27.1 (**1.36**)	21.0	0.54
BuPa	0.53	0.20	0.11	0.56	0.10	0.06	0.34	0.16	0.17	0.58	0.19	0.15
BPA	1.72	0.64	0.03*	1.04 (**26,000**)	1.19	0.36	1.99 (**49,750**)	0.65	0.005*	2.00 (**50,000**)	0.98	0.13

EDI = estimated daily intake (μg/kg/day); HQ = hazard quotient; GA = gestational age; LOS = late-onset septicaemia; BPD = bronchopulmonary dysplasia.[a] Varying n due to some results below qualifier ratio, out of range or missing. Selected HQs > 1 marked in bold where EDI exceeded TDI indicating increased risk of adverse effects. P-values with an asterisk are significant.

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natal exposure to these excipients may be associated with increased risk of preterm birth and low BW (Ferguson et al., 2014, 2022; Welch et al., 2022; Aung et al., 2019; Uldbjerg et al., 2022). Results from studies reporting such risks or relationships should be interpreted with some caution due multiple and variable exposures during gestation, often not optimally designed studies with low statistical power, and not fully understood mechanisms that could explain a possible causal relationship. However, mechanistic explanations could be epigenetic (Street and Bernasconi, 2020) and/or hormonal, as both may influence placental function, foetal growth and the developing foetus directly (Uldbjerg et al., 2022). Prenatal exposure may promote epigenetic alterations that modify foetal programming, in addition to influence insulin, thyroid- and growth hormones involved in placental function and foetal growth (Street and Bernasconi, 2020), which enables a potential causal relationship between exposure to phthalates, parabens and BPA, and low BW. Our study was not designed to evaluate this. Other possible adverse effects from exposure to phthalates are immunological (Bornehag and Nanberg, 2010) and inflammatory (Bolling et al., 2012) suggesting that these contaminants may reduce anti-inflammatory responses and thereby increase the risk of inflammatory disorders like BPD (Fischer et al., 2013) and LOS (Vetrano et al., 2010). Other possible adverse effects from paraben exposure are endocrine effects (Baker et al., 2020; SCSS, 2011; Iribarne-Duran et al., 2019; Wong and Durrani, 2017) and reduced respiratory health (Vernet et al., 2017; Agier et al., 2019). Additional adverse effects from BPA exposure are cryptorchidism (Fisher et al., 2020), short anogenital distance (Sun et al., 2018), altered body weight (Mikolajewska et al., 2015), reduced lung function (Spanier et al., 2014), altered immune function (Xu et al., 2016; The European Food Safety Authority, 2021), and increased risk of respiratory tract infections (Gascon et al., 2015). Among the included VLBW infants, all were born prematurely and 35% had lower BW than expected. Non-linear associations were found between first week of life EDI of selected excipients and BW. Twenty to 46% of the variation in BW could be explained by the exposure, although this association should be interpreted with caution. Our study was not designed to evaluate the risk of being born with low BW due to prenatal exposure to phthalates, parabens or BPA. Most urine samples were collected after maternal exposure with subsequent transfer of excipients to the foetus, and after postnatal exposure due to immediate use of medical equipment and pharmaceuticals at birth, which makes it difficult to assess whether prenatal exposure could have affected BW in our study. Forty eight percent were diagnosed with infection and 20% with and an inflammatory lung disorder. We did not register information on endocrine, reproductive or other immune disorders in the study group.

Frederiksen et al. calculated EDI for phthalates in 67 Finnish premature infants born between 2006 and 2008. Eighty percent of these infants were exposed to phthalates during the first 2–3 months of age with urinary levels exceeding TDI indicating risk of adverse effects (Frederiksen et al., 2014). This Finnish data is comparable with ours, although we found higher EDI for DEHP and DiNP the fifth week of age compared to Finnish infants at 2 months of age (Table 4). This may be explained by lower GA at birth and BW in our infants (GA at birth: 32–33 weeks vs 28 weeks; BW: 1729 g vs 1026 g). To our knowledge, we are the first to report EDI for parabens in VLBW infants based on estimation from urinary concentrations. However, a French study quantified paraben exposure from drug administration during hospitalization in term and preterm newborns. All hospitalised newborns were exposed to at least one paraben, where premature infants were exposed to higher cumulative doses that were below TDI (Binson et al., 2020). Our premature VLBW infants had higher EDI for parabens compared to studies on term infants, children, and adolescents (Table 5), where paraben sources were certain pharmaceuticals as shown in the French study (Binson et al., 2020). Other possible explanations for reduced exposure at older ages may be higher body weight and a more mature metabolism, suggesting that the risk of being exposed to potential harmful levels are higher for preterm infants than other age groups.

Calafat et al. (2009) and Duty et al. (2013) examined potential sources of BPA in neonatal intensive care units in the USA. The number of medical devices used, not nutritional intake, was positively associated with exposure to BPA. The EDI was based on urinary BPA concentrations and similar to EDI in our study (Table 6), all with HQ $>$ 1. The TDI for BPA was recently considerably lowered from 4 μg/kg/day to 0.04 ng/kg/day, based on new data documenting possible adverse effects of BPA on white blood cells and inflammation (Xu et al., 2016; The European Food Safety Authority, 2021). The consequences of this reduction in TDI on risk assessment of LOS (infection) and BPD (inflammation) are unclear. Indeed, we speculate whether BPA exposure may have contributed to the development of LOS or BPD in our VLBW infants, but this requires further investigation.

Calculating EDI in infants can be challenging. Different routes of exposure, often unknown time interval between exposure and urine sampling, individual variability in spot urine samples, comparison of EDI with TDI values based on studies in rodents and adults, different metabolism and Fue in adults and neonates, temporarily set and occasional change of TDIs, cause uncertainty when calculating EDI from urinary concentrations in infants. The Fue is usually calculated using urinary concentrations, urinary flow or volume, plasma concentrations, or glomerular filtration rates. Premature infants have reduced glomerular filtration rate, tubular secretion and reabsorption compared to adults. As a result, pharmaceuticals with excipients are excreted more slowly and drug accumulation occur, often promoting higher urinary levels, EDI and risk of adverse effects, as seen in our study.

Our study has strengths and limitations. It was performed in 2010 and was not designed to evaluate if prenatal or postnatal exposure to phthalates, parabens, and BPA could have potential adverse effects. We did not collect information on maternal exposure or pre-screen pharmaceuticals, medical equipment, or sampling devices for presence of these chemicals. Furthermore, we did not collect field blanks of the sampling devices or correct for infant hydration status. We did not adjust for urine dilution because the urine volumes were insufficient and creatinine excretion varies with muscle mass and age. VLBW infants have very low muscle mass resulting in extremely high creatinine-adjusted levels, as seen for phthalate metabolites in preterm and term-born infants (Frederiksen et al., 2014; Dassios et al., 2018). Barr et al. recommended caution interpreting creatinine-adjusted levels in children of different ages (Barr et al., 2005), and others even recommends cautiously use of creatinine correction in general (Lorber et al., 2011). One could also argue that exposure to phthalates, parabens, and BPA in 2010 may not reflect exposure today. We have no indications that the including neonatal intensive care units have significantly changed pharmaceuticals or medical equipment containing alternative phthalates, parabens, or BPA. Our results should be interpreted with caution due to study design, low n and statistical power. We chose not to adjust for possible confounding factors such as the nutritional intervention itself, maternal or paternal age and education, nor did we collect details on potential adverse effects of excipient exposure, and our study had a small number of included infants. The study was terminated earlier than planned due to a higher occurrence of LOS in the intervention group (Moltu et al., 2013). However, studies on phthalate-, paraben- and BPA exposure in VLBW infants are few. Our study contributes with urinary levels (Strommen et al., 2016, 2021) and EDIs of these excipients in a vulnerable population where increased knowledge is warranted. Our EDIs were compared to current TDIs published from reputable sources, and a new group-TDI was used for chemicals with similar toxicological mechanisms (Efsa Panel on Food Contact Materials et al., 2019; Committee on toxicity of chemicals, 2011; Opinion of the Scientific Panel, 2004; EFSA Panel on Food Contact Materials Enzymes and Aids, 2015). To increase the accuracy, we used actual 24-h urine volumes to calculate EDI the first week of life, where others have estimated this with uncertainty. We estimated the 24-h urine volume at five weeks of age based on studies among infants with similar characteristics as our included infants. Our results were compared to other known published studies in

premature infants, and thus may be an important contributor to increased knowledge.

Hospitalised VLBW infants are exposed to potentially harmful excipients which should be reduced by using pharmaceuticals and medical equipment with low release potential, alternatives that do not contain these excipients, or with new substances. Some manufacturers have successfully removed phthalates, parabens and BPA from pharmaceuticals and medical equipment with altered exposure patterns and lower levels measured (Strommen et al., 2016, 2021; Frederiksen et al., 2014; Su et al., 2012; Testai et al., 2016). In a recent paper on global monitoring of DEHP exposure, in 45 nations from 1982 to 2017, children had higher DEHP exposure than other groups with a sharply downtrend in EDI that followed the production and consumption volume (Qu et al., 2022). European plastic manufacturers no longer use BPA in the production of medical devises (Testai et al., 2016), but BPA-containing medical devices produced outside Europe may still be available. In 2015, the European Commission's Scientific Committee on Emerging and Newly Identified Health Risks concluded that the risk of adverse effects following BPA exposure is of particular concern to hospitalised neonates undergoing prolonged medical procedures. In 2021, the TDI for BPA was significantly lowered based on new data (The European Food Safety Authority, 2021), and although the benefits of the medical devices should be considered, international expertise recommend use of medical devises that don't leach BPA when possible (SCENIHR, 2015).

Many neonatal intensive care units are using pharmaceuticals and medical equipment containing old and new phthalates, parabens and BPA. Studies on neonatal exposure to alternative or new excipients are few. A recent study confirmed exposure to alternative phthalates in Danish infants where the authors were surprised that regulated and banned phthalates were detected (Frederiksen et al., 2022). Another recent study concluded that exposure levels of the same phthalates as evaluated in our study had decreased in adolescents, while the exposure to new and alternative phthalates was considerable (Bastiaensen et al., 2021). Manufacturers of pharmaceuticals and medical equipment, and healthcare professionals, should focus on measures that reduce exposure of phthalates, parabens, and BPA in hospitalised VLBW infants, while taking into account their beneficial effects.

5. Conclusions

The present study highlights that hospitalised VLBW infants have higher EDI for phthalates, parabens and BPA compared to term-born infants, children, and adolescents. Infants born earlier than 28 weeks GA, and infants with LOS or BPD, all had first week of life EDI for DEHP, $\sum$BBzP+DnBP+DEHP+DiNP, and PrPa, above TDI with HQs >1. More than 75% of our VLBW infants' EDI for DEHP and $\sum$BBzP+DnBP+DEHP+DiNP, 25% of infants' EDI for PrPa, and all infants' EDI for BPA, were above TDI with HQs > 1, indicating increased risk of adverse effects.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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