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High urinary concentrations of parabens and bisphenol A in very low birth weight infants

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HIGHLIGHTS

- VLBW infants were exposed to parabens and BPA during their hospital stay.
- Confirmed sources of parabens were certain pharmaceuticals.
- Confirmed sources of BPA were medical equipment containing plastic.
- VLBW infants had very high urinary levels of parabens and BPA.
- Lower GA at birth was associated with higher urinary levels of parabens and BPA.

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ABSTRACT

Very low birth weight infants (VLBW; birth weight < 1500 g) are treated with pharmaceuticals and medical equipment containing parabens and bisphenol A (BPA). Parabens are used in pharmaceuticals, whereas BPA in medical equipment where concentrations are rarely reported in hospitalised VLBW infants. We measured urinary concentrations of parabens and BPA and hypothesised high and increasing concentrations in infants born at lower gestational ages (GAs), and among infants with bronchopulmonary dysplasia (BPD) and late-onset septicaemia (LOS) due to higher exposure from pharmaceuticals and medical equipment. Urinary samples were collected during the first (n = 38) and fifth (n = 36) week of life. Methylparaben, ethylparaben, propylparaben, butylparaben, and BPA concentrations were measured using ultra high-performance liquid chromatography coupled to tandem mass spectrometry. VLBW infants had very high urinary concentrations of parabens and BPA compared to term infants and older children. The Σ paraben concentration was higher than detected in previous studies on premature infants. Lower GA at birth was associated with higher concentrations of parabens and BPA. Infants born before 28 weeks GA had higher first week concentrations of propylparaben (38.6 vs. 9.05 ng/mL, p = 0.007), butylparaben (0.28 vs. 0.09 ng/mL, p = *0.05*) and fifth week concentrations of BPA (15.1 vs. 6.02 ng/mL, p = 0.02) than infants born after 28 weeks GA. Infants with LOS and BPD had higher fifth

Abbreviations: BPA, bisphenol A; BPD, bronchopulmonary dysplasia; BuP, butylparaben; BW, birth weight; CI, confidence interval; EtP, ethylparaben; GA, gestational age; iv, intravenous; LOQ, limit of quantification; LOS, late-onset septicaemia; MeP, methylparaben; NICU, neonatal intensive care unit; No, number of; PrP, propylparaben; VLBW, very low birth weight (BW < 1500 g); Σ parabens, sum of parabens.

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week concentrations of BPA than infants without LOS and BPD (LOS: 14.2 vs. 6.77 ng/mL, p = 0.07; BPD: 18.6 vs. 7.62 ng/mL, p = 0.05).

1. Introduction

Hospitalised neonates are often exposed to multiple pharmaceutical products and medical equipment containing excipients to improve product quality, stability, bioavailability, and patient acceptability. Excipients are used as diluents, solvents, emulsifiers, binders, lubricants, sweeteners, preservatives, stabilizers, and as flavouring and colouring agents. Common excipients like ethanol and propylene glycol are used as solvents, benzyl alcohol and parabens as preservatives, bisphenol A (BPA) as a precursor to plastics, and phthalates to soften plastics (Mikolajewska et al., 2015; Cuzzolin, 2018). Excipients are particularly important in pharmaceutical products intended for children as they play a critical role in preparation of suitable paediatric formulations (Fabiano et al., 2011). Recently, there has been increasing focus on neonatal exposure to excipients for safety reasons (Fabiano et al., 2011; Cuzzolin, 2018; Iribarne-Duran et al., 2019). In a web-based point prevalence study, from 89 neonatal intensive care units (NICUs) in 21 European countries, potentially harmful excipients were found in 31% of prescriptions and administered to 63% of the infants (Nellis et al., 2015). In a retrospective record review of very low birth weight infants (VLBW; birth weight (BW) < 1500 g) in the USA, 98% of infants were exposed to at least one excipient, of which 5–9% received doses higher than recommended for adults (Akinmboni et al., 2018). A recent exploratory study reported that neonates in the NICU were exposed to BPA via three-way stopcocks, transparent film dressings, feeding tubes, umbilical catheters and infusion extension sets, whereas light therapy protection glasses, transparent film dressings, winged infusion catheters and extension sets were main sources of paraben exposure (Iribarne-Duran et al., 2019). This is equipment commonly used in NICUs worldwide.

Parabens are man-made esters of 4-hydroxybenzoic acid. Common parabens include methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP) and butylparaben (BuP). Parabens are used as preservatives in pharmaceuticals due to their bactericidal and fungicidal properties, although their mode of action is not well understood. Human studies have shown associations between several parabens and preterm birth, in addition to possible endocrine effects and reduced lung function in children. Maternal EtP exposure has been associated with increased risk of preterm birth (Aung et al., 2019) and MeP exposure with preterm birth, decreased BW and maternal hormone dysfunction (Baker et al., 2020). Endocrine effects might be due to estrogenic and anti-androgenic activity of parabens (Scientific Committee, 2011; Wong and Durrani, 2017; Iribarne-Duran et al., 2019). Postnatal exposure to EtP has also been associated with lower forced expiratory volume in children (Agier et al., 2019).

BPA is a phenol used in the production of plastics, medical equipment and epoxy resins and is used in food contact materials such as baby bottles and food containers (Mikolajewska et al., 2015). Exposure to BPA during pregnancy may be a potential risk factor for preterm birth (Huang et al., 2019). High urinary BPA concentrations has been described in women delivering prematurely (Cantonwine et al., 2010), but data on the relationship between BPA exposure and preterm birth is limited (Mikolajewska et al., 2015). BPA binds to estrogen-, androgen- and thyroid receptors and may disrupt hormonal signalling. Similar to several parabens, BPA exposure has been associated with cryptorchidism (Fisher et al., 2020), short anogenital distance (Sun et al., 2018), and altered body and organ weight (Mikolajewska et al., 2015). Reduced lung function (Spanier et al., 2014) and increased risk of respiratory tract infections (Gascon et al., 2015) have also been described after BPA exposure in children.

Neonates are exposed to excipients in utero (Kolatorova et al., 2018) and after birth (Nellis et al., 2015; Akinmboni et al., 2018; Iribarne-Duran et al., 2019). Hospitalised neonates are exposed to parabens and BPA via inhalation, dermal, oral, and parenteral routes (Calafat et al., 2009; Iribarne-Duran et al., 2019). Calafat et al. detected higher urinary concentrations of parabens in hospitalised premature infants than in adults in the United States, whereas urinary BPA concentrations were one order of magnitude higher in premature infants undergoing intensive therapeutic interventions than the general population (Calafat et al., 2009). Duty et al. observed 16–32 fold higher BPA concentrations in hospitalised infants than in healthy infants and children in the general population, where premature infants had considerable higher concentrations than term infants (Duty et al., 2013).

VLBW infants are in a critical period of early development where exposure to even small doses of potentially toxic substances may have adverse health effects. They are disproportionately exposed to excipients due to low body weight and immature organ systems and metabolic pathways (Fabiano et al., 2011). Data on concentrations of parabens and BPA among VLBW infants are scarce. Thus, the aim of this study was to evaluate urinary concentrations of parabens and BPA in hospitalised VLBW infants. We hypothesised high and increasing urinary concentrations of parabens and BPA in infants born at lower gestational ages (GAs), and among infants with bronchopulmonary dysplasia (BPD) and late-onset septicaemia (LOS) due to high exposure from use of pharmaceuticals and medical equipment.

2. Materials and methods

2.1. Design

This is a secondary analysis of data from a randomised controlled trial evaluating the effects of a nutritional intervention on growth in VLBW infants admitted to three NICUs in Oslo, Norway in 2010 (Moltu et al., 2014). Infants in the intervention group received enhanced parenteral and enteral supply of energy, amino acids, fatty acids, and vitamin A, whereas infants in the control group received nutrient supply according to standard recommendations at that time. The study was approved by the Regional Committee for Medical and Health Research Ethics in Norway and performed in accordance with the Helsinki Declaration. All VLBW infants born in the participating units were eligible for inclusion and randomised as previously described (Moltu et al., 2014). Exclusion criteria were congenital malformations, chromosomal abnormalities, critical illness with short life expectancy, and clinical syndromes known to affect growth and development. Patient recruitment to the original nutritional study was terminated earlier than planned due to a higher incidence of late-onset septicaemia (LOS; defined as age ≥ 4 days with growth of bacteria in blood

culture and clinical signs of septicaemia) in the intervention group as compared to the control group (Moltu et al., 2013). Infants in the intervention group achieved improved postnatal growth with fewer discharged as growth restricted (Moltu et al., 2014), and had better head growth and indications of improved brain maturation (Blakstad et al., 2015; Strommen et al., 2015), as compared to the control group. Infants with LOS and BPD had higher urinary concentrations of phthalates compared to infants without LOS and BPD (Strommen et al., 2016). The objectives of the present study were to study concentrations of parabens and BPA in urinary samples from the first and fifth week of life and explore possible explanatory variables.

2.2. Parabens and bisphenol a exposure

Specific information on maternal use of pharmaceuticals, medical equipment, or other sources regarding potential exposure to parabens and BPA was not collected. Postnatal exposure was considered likely if the included infants were treated with pharmaceuticals or medical devices containing parabens or BPA. The tables of contents were carefully read to identify whether parabens and/or BPA were found in pharmaceuticals and medical equipment used. If not mentioned, manufactures were contacted and the information obtained. Other possible sources of exposure were not investigated.

2.3. Urine analysis of parabens and bisphenol A

We collected 0.5–2.0 mL of infant urine during the first and the fifth week of life from cotton swabs placed in diapers before transferral to Nunc Cryo Tubes (Thermo Fischer Scientific, Inc., MA, USA) and stored at −80 °C until analysis. MeP, EtP, PrP, BuP and total BPA were measured using on-line solid phase extraction prior to ultra-high performance liquid chromatography coupled to tandem mass spectrometry (Sakhi et al., 2018). Labelled internal standards and enzyme solution (beta-glucuronidase/sulfatase in ammonium acetate buffer, pH 5.0) were added to 200 μL of the sample before incubated at 37 °C. After 4 h, 40% formic acid was added to stop the enzymatic reaction, the samples were centrifuged and 80 μL of the supernatant were analysed for parabens and BPA concentrations. The accuracy of the method ranged from 75 to 120%. In-house pooled urine samples and standard reference material from National Institute of Standards and Technology were analysed concomitantly. The results are reported in ng/mL with no adjustments for urine creatinine or specific gravity. In total 296 and 74 urinary samples were evaluated for parabens and BPA, respectively. Twenty-four (8.1%) paraben concentrations were below the limit of quantification (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/$\sqrt{2}$, whereas the one result outside the calibration curve was omitted from the calculations. VLBW infants with insufficient urinary volumes collected, or those transferred to local hospitals were not included. Maternal urine, sampling devices, pharmaceuticals and medical equipment were not pre-screened for presence of parabens or BPA.

2.4. Statistical analyses

All statistical analyses were performed with the Statistical Package for Social Sciences (SPSS version 26; IBM Inc., Chicago, IL, USA) with p-values < 0.05 considered statistically significant and using parametric or non-parametric tests as appropriate. Urinary concentrations of parabens and BPA were $\log_{10}$-transformed to remove skewness and normalize the data. Statistical calculations were performed on $\log_{10}$-transformed data, whereas medians and geometric means are presented unless otherwise stated. To evaluate differences between groups we used the Student t-test or Mann-Whitney *U* test for continuous variables, and the Chi-square test or Fisher's exact test for categorical variables. The paired samples *t*-test or Wilcoxon signed rank test were used to compare paraben and BPA concentrations within separate groups at two different time points. To evaluate differences in concentrations of parabens and BPA, between premature infants and older children, average geometric mean values were compared with previously published studies. Pearson's or Spearman's correlation coefficients were calculated for urinary concentrations of selected excipients and GA at birth and duration of breathing support. To evaluate the numerical change in concentrations between the two time points, the change between the fifth week and first week geometric means were calculated and tested with the Student t-test or Mann-Whitney *U* test. P-values calculated using non-parametric tests are written in italics.

3. Results

Thirty-eight of 50 VLBW infants provided urinary samples during the first week of life, 36 infants the fifth week of life with a total of 28 infants providing samples at both time points. Characteristics of the study population are presented in Table 1. Similar urinary paraben and BPA concentrations were found in the intervention and control group of the original trial (first week: Σ parabens: 386 vs. 399 ng/mL, p = 0.95; BPA: 11.9 vs. 7.36 ng/mL, p = 0.13; fifth week: Σ parabens: 201 vs. 295 ng/mL, p = 0.58; BPA: 12.3 vs. 5.85 ng/mL, *p = 0.44*) respectively, thus the two study groups were merged and the following results are presented without emphasizing the effect of the nutritional intervention.

3.1. Urinary parabens and bisphenol a concentrations

Table 2 shows urinary concentrations of parabens and BPA during the first and fifth week of life, for all infants and those with samples from both time points. The highest concentrations of parabens were measured in the first week of life (MeP = 4795 ng/mL), whereas BPA the fifth week of life (98 ng/mL). Paraben concentrations were higher, whereas BPA concentrations were lower as compared to levels in infants born prematurely almost a decade earlier (Table 3). Concentrations of most parabens and BPA were very high and remained high compared to concentrations reported in term infants and older children (Table 3).

3.2. Gestational age at birth

Infants born before 28 weeks GA were more frequently diagnosed with LOS and BPD necessitating increased use of intravenous antibiotics, parenteral nutrition and breathing support (Table 4), which contained parabens and BPA. These infants had higher first week urinary concentrations of PrP, BuP and fifth week concentrations of BPA, compared to infants born after 28 weeks GA (Table 4). Negative correlation coefficients were found between GA at birth and urinary concentrations of parabens and BPA (GA at birth and first week Σ parabens: correlation coefficient = −0.39, p = 0.02; GA at birth and fifth week urinary BPA concentration: correlation coefficient = −0.33, p = 0.05), suggesting that infants born with lower GA had higher urinary concentrations of parabens and BPA. The change in Σ parabens from first to fifth week of life was negative (fifth week value - first week value = 219 ng/mL - 587 ng/mL = −368 ng/mL, p = 0.19) in VLBW infants born before 28 weeks GA, whereas the opposite was observed for BPA. Infants

Table 1
Characteristics of the study population.

	Infants in the original trial	Infants with data from both 1st and 5th week of life	P-value[c]
	n = 50	n = 28	n = 22
Mean GA at birth in weeks^{days} (SD in days)	28^{1} (18)	28^{2} (16)	0.44
Range, weeks^{days}	23^{0}–33^{4}	25^{0}–32^{6}	
Mean BW (SD), g	989 (255)	1009 (249)	0.54
Range, g	426–1414	460–1404	
Sex (girls), n (%)	20 (40)	13 (46)	0.39
LOS, n (%)	22 (44)	13 (46)	0.78
BPD, n (%)	11 (23)[a]	7 (25)	0.74
Median (range) number of days on parenteral nutrition	9 (4–29)[b]	9 (4–29)	*0.48*
Median (range) number of days with central lines	8 (0–36)	7 (0–26)	*0.08*
Median (range) number of days with iv antibiotics	12 (0–52)	12 (0–42)	*0.78*
Median (range) number of days on breathing support	29 (0–125)	29 (1–88)	*0.88*

GA = gestational age; weeks^{days} = duration of pregnancy in weeks and days; SD = standard deviation; BW = birth weight; LOS = late-onset septicaemia; BPD = bronchopulmonary dysplasia; central lines include umbilical and central venous/arterial catheters; iv = intravenous; breathing support defined as use of invasive (i.e., tracheal tubes) and non-invasive (i.e., nasal prongs for continuous positive pressure support) treatment methods. P-values in italics are calculated using non-parametric tests.
[a] n = 48.
[b] n = 44.
[c] Comparing results from infants with (n = 28) and without (n = 22) pairwise urinary samples.

Table 2
Urinary concentrations of paraben and bisphenol A (ng/mL) at two time points.

Analyte	Samples > LOQ (%)	1st week of life (n = 38)		5th week of life (n = 35–36)		1st week of life in infants with paired samples (n = 28)		5th week of life in infants with paired samples (n = 28)		
		Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	P-value[b]
MeP	100	13.5–541 - 4795	396 (4.01)	1.72–261 - 4369	187 (6.17)	13.5–437 - 4795	357 (4.15)	6.00–290 - 4269	217 (5.89)	*0.12*
EtP	97	0.04 - 0.87 - 5.32	0.78 (2.86)	0.04 - 1.19 - 614	2.05 (10.0)	0.04 - 0.67 - 5.32	0.69 (2.89)	0.04 - 1.65 - 614	2.43 (10.7)	**0.01**
PrP	100	0.51 - 23.8 - 640	23.7 (4.20)	0.14 - 11.9 - 358[a]	11.9 (8.08)	0.51 - 21.1 - 640	18.7 (4.36)	0.41 - 12.8 - 358	15.0 (7.00)	0.52
BuP	70	0.04 - 0.21 - 2.80	0.17 (3.93)	0.04 - 0.35 - 122[a]	0.52 (9.36)	0.04 - 0.16 - 2.80	0.16 (4.21)	0.04 - 0.35 - 122	0.68 (9.70)	***0.01***
Σ parabens	–	16.5–556 - 4908	438 (3.92)	1.94–284 –5242[a]	210 (6.09)	16.5–475 - 4908	392 (4.06)	7.15–294 - 5242	242 (5.81)	*0.19*
BPA	100	0.04–11.3 - 92.9	10.7 (3.88)	1.09 - 7.27 - 98.0	8.46 (3.03)	0.04–13.1 - 92.9	10.4 (4.26)	1.28 - 7.80 - 98.0	9.53 (2.91)	*0.40*

MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben; Σ parabens = sum of parabens (calculated); BPA = bisphenol A; LOQ = limit of quantification = 0.05 ng/mL; min = minimum; max = maximum; SD = standard deviation. P-values in italics are calculated using non-parametric tests.
[a] n = 35.
[b] Comparing geometric means from 1st and 5th week of life in infants with samples at both time points.

Table 3a
Summary of published data on urinary paraben concentrations in infants and children.

Sampling period	Location	Study population	n	MeP	EtP	PrP	BuP	Reference
2003	USA	Premature infants	41	203 (4.70)	–	16.8 (4.90) [a]	–	Calafat et al. (2009)
2010	**Norway**	**Premature infants**	**38**	**396 (4.01)**	**0.78 (2.86)**	**23.7 (4.20)**	**0.17 (3.93)**	**Present study**
2011	Korea	Term infants	46	79.6 (–) [b]	2.40 (–) [b]	3.40 (–) [b]	< LOQ	Kang et al. (2013)
2014–2017	France	2 months old infants	152	5.40 (–) [b]	0.52 (–) [b]	0.39 (–) [b]	< LOQ	Rolland et al. (2020)
2014–2017	France	1 year old children	100	29.5 (–) [b]	1.14 (–) [b]	0.87 (–) [b]	< LOQ	Rolland et al. (2020)
2009–2011	Greece	2 year old children	239	25.0 (–)	1.80 (–)	1.30 (–)	< LOQ	Myridakis et al. (2015)
2000–2005	Sweden	6–11 year old children	80	6.80 (–)	0.77 (–)	2.10 (–)	< LOQ	Larsson et al. (2014)
2006–2007	Denmark	4–9 year old children	848	10.4 (–)	0.95 (–)	1.02 (–)	0.16 (–)	Frederiksen et al. (2014)
2009–2010	Korea	3–12 year old children	659	56.2 (–)	7.43 (–)	5.00 (–)	0.44 (–)	Kang et al. (2016)
2012	Norway	6–12 year old children	56	14.9 (–)	0.91 (–)	1.50 (–)	< LOQ	Sakhi et al. (2018)
2013–2014	USA	6–11 year old children	409	28.6 (–)	< LOQ	2.96 (–)	< LOQ	CDC, (2019)
2013–2016	Europe	6–12 years old children	1284–1299	6.50 (–) [b]	0.67(–) [b]	0.22 (–) [b]	0.08 (–) [b]	Haug et al. (2018)

Values are geometric means (SD) in ng/mL. SD = standard deviation; MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben. LOQ = Limit of quantification.
[a] n = 42.
[b] Median value.

born before 28 weeks GA had increasing BPA concentrations (fifth week value - first week value = 15.1 ng/mL - 11.0 ng/mL = 4.10 ng/mL, p = 0.18) from the first to fifth week of life. No significant results were found for the change in concentrations from the first to fifth week of life for any parabens or BPAs when comparing infants born before or after 28 weeks GA.

Table 3b
Summary of published data on urinary bisphenol A concentrations in infants and children.

Sampling period	Location	Study population	n	BPA	Reference
2003	USA	Premature infants	41	30.3 (5.20)	Calafat et al. (2009)
2010	**Norway**	**Premature infants**	**38**	**10.7 (3.88)**	**Present study**
2009–2010	USA	Premature infants	50	17.2 (–) [a]	Duty et al. (2013)
2011–2012	Korea	Term infants	152	5.27 (4.18)	Lee et al. (2018)
2012–2014	China	Term infants	23	3.65 (–)	Wang et al. (2017)
2014–2017	France	2 months old infants	152	1.74 (–) [a]	Rolland et al. (2020)
2014–2017	France	1 year old children	100	3.31 (–) [a]	Rolland et al. (2020)
2009–2011	Greece	2 year old children	239	2.00 (–)	Myridakis et al. (2015)
2000–2005	Sweden	6–11 year old children	97	1.48 (–)	Larsson et al. (2014)
2006–2007	Denmark	5–9 year old children	25	1.40 (–)	Frederiksen et al. (2014)
2011–2012	Europe	5–12 year old children	653	1.97 (–)	Covaci et al. (2015)
2012	Norway	6–12 year old children	56	3.70 (–)	Sakhi et al. (2018)
2013–2014	USA	6–11 year old children	409	1.43 (–)	CDC, (2019)
2013–2016	Europe	6–12 year old children	1289	4.06 (–) [a]	Agier et al. (2019)

Values are geometric means (SD) in ng/mL. SD = standard deviation; BPA = bisphenol A.
[a] Median value.

Table 4
Urinary paraben and bisphenol A concentrations and possible influencing factors.

	Group affiliation			GA at birth			LOS			BPD		
	Intervention group	Control group	P-value	<28 weeks	>28 weeks	P-value	Yes	No	P-value	Yes	No	P-value
	n = 15	n = 13		n = 14	n = 14		n = 13	n = 15		n = 7	n = 21	
GA at birth, weeks^{days} [a]	27^{6}	28^{6}	0.27	–	–	–	27^{1}	29^{3}	***0.004***	26^{0}	29^{1}	**0.001**
BW, g [a]	908	1126	**0.02**	843	1176	**< 0.001**	926	1081	0.10	725	1104	**< 0.001**
Girls, n	7	6	0.99	8	5	0.45	6	7	0.99	3	10	0.83
LOS, n	8	5	0.48	10	3	**0.02**	–	–	–	5	2	0.20
BPD, n	5	2	0.40	7	0	**0.006**	5	2	0.20	–	–	–
Parenteral nutrition, days [b]	9	8	*0.06*	11	9	***0.01***	10	8	***0.007***	12	9	***0.02***
Central lines, days [b]	8	7	*0.37*	9	6	***< 0.001***	9	6	***0.04***	9	6	***< 0.001***
Iv antibiotics, days [b]	13	7	**0.04**	17	5	***< 0.001***	19	6	***0.001***	20	7	***0.02***
Breathing support, days [b]	38	14	*0.28*	45	9	***< 0.001***	43	14	**0.005**	43	24	***0.05***
1st week of life (ng/mL)[c]:												
MeP	354	360	0.98	518	245	0.17	296	419	*0.44*	633	294	0.22
EtP	0.54	0.90	0.21	0.74	0.63	0.70	0.68	0.70	0.94	1.31	0.55	0.06
PrP	15.6	23.0	0.50	38.6	9.05	**0.007**	23.7	15.2	0.44	25.8	16.8	0.52
BuP	0.25	0.10	*0.10*	0.28	0.09	***0.05***	0.19	0.14	*0.64*	0.27	0.14	*0.31*
Σ parabens	386	399	0.95	587	261	0.13	339	445	*0.50*	676	327	0.24
BPA	11.9	8.79	*0.13*	11.0	9.74	*0.25*	11.6	9.37	*0.24*	21.5	8.11	*0.10*
5th week of life (ng/mL)[c]:												
MeP	200	238	0.80	211	224	0.93	208	225	0.91	280	200	0.67
EtP	2.33	2.55	*0.82*	1.30	4.45	0.17	1.63	3.43	0.42	1.44	2.89	0.51
PrP	10.3	22.4	0.31	21.7	10.6	0.35	21.0	11.4	0.43	27.9	12.5	0.38
BuP	0.76	0.59	0.77	0.41	1.15	0.25	0.39	1.14	0.23	0.36	0.85	0.40
Σ parabens	201	295	0.58	219	266	0.78	214	267	0.76	261	237	0.91
BPA	11.9	7.36	*0.44*	15.1	6.02	**0.02**	14.2	6.77	0.07	18.6	7.62	0.05

GA = gestational age; weeks^{days} = duration of pregnancy in weeks and days; BW = birth weight; LOS = late-onset septicaemia; BPD = bronchopulmonary dysplasia; central lines include umbilical and central venous/arterial catheters; iv = intravenous; breathing support defined as use of invasive (i.e., tracheal tubes) and non-invasive (i.e., nasal prongs for continuous of positive pressure support) treatment methods. MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben; Σ parabens = sum of parabens (calculated); BPA = bisphenol A. P-values in italics are calculated using non-parametric tests.
[a] Means.
[b] Medians.
[c] Geometric means.

3.3. Late-onset septicaemia

The incidence of LOS was 44% among the included VLBW infants (Table 1). Infants with LOS were born at a lower GA with increased need of parenteral nutrition, intravenous antibiotics, and breathing supportas compared to infants without LOS (Table 4). Despite this, we did not find any differences in urinary paraben concentrations between infants with or without LOS. We measured numerically higher BPA concentrations among infants with LOS compared to infants without LOS, although this did not reach statistically significance. No significant differences were found for the change in concentrations of parabens or BPA measured between the first and fifth week of life among infants with or without LOS.

3.4. Bronchopulmonary dysplasia

Approximately one-fourth of the included infants was diagnosed with BPD (Table 1), a chronic lung disease defined as need of oxygen supplementation at 36 weeks gestation. Infants with BPD were born at a lower GA with increased use of parenteral nutrition, intravenous antibiotics and breathing support compared to infants without BPD (Table 4). We did not observe any significant

Table 5a
Correlation analyses between urinary concentrations of parabens and bisphenol A the first week of life.

Analyte	n	EtP		PrP		BuP		Σ parabens		BPA	
		Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
MeP	38	0.62	< **0.001**	0.68	< **0.001**	- 0.01	*0.97*	0.99	< **0.001**	0.09	*0.60*
EtP	38	1	–	0.47	**0.003**	0.02	*0.90*	0.62	< **0.001**	0.16	*0.35*
PrP	38			1	–	0.08	*0.63*	0.72	< **0.001**	0.02	*0.91*
BuP	38					1	-	- 0.03	*0.87*	- 0.01	*0.96*
Σ parabens	38							1	–	0.11	*0.51*
BPA	38									1	-

MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben; Σ Parabens = sum of parabens; BPA = bisphenol A. P-values in italics are calculated using non-parametric tests.

Table 5b
Correlation analyses between urinary concentrations of parabens and bisphenol A at five weeks of life.

Analyte	n	EtP		PrP		BuP		Σ parabens		BPA	
		Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value	Correlation coefficient	P-value
MeP	35–36	0.52	**0.001**	0.75	< **0.001**	0.27	*0.12*	0.99	< **0.001**	0.28	0.10
EtP	35–36	1	–	0.48	**0.003**	0.59	< ***0.001***	0.54	**0.001**	- 0.04	0.80
PrP	34–35			1	–	0.23	*0.20*	0.79	< **0.001**	0.32	0.06
BuP	34–35					1	-	0.29	*0.10*	- 0.21	*0.23*
Σ parabens	34–35							1	–	0.25	0.15
BPA	35–36									1	–

MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben; Σ Parabens = sum of parabens; BPA = bisphenol A. P-values in italics are calculated using non-parametric tests.

differences in urinary concentrations of parabens or BPA between infants with or without BPD. No significant differences were found for the change in concentrations measured between the first and fifth week of life among infants with or without BPD.

3.5. Correlation analyses of parabens and bisphenol A

With the exception of BuP, significant positive correlations were observed between concentrations of all parabens at both sampling times (Table 5). No significant correlations were found between parabens and BPA.

4. Discussion

In 2010 we measured urinary concentrations of parabens and BPA in hospitalised VLBW infants the first and fifth week of life. The concentration of parabens and BPA was very high in this group of VLBW infants born prematurely. The paraben levels were higher, whereas BPA levels were lower compared to levels in preterm infants born in 2003 (Calafat et al., 2009). The concentrations of parabens and BPA were substantially higher than reported in term infants and older children. VLBW infants born before 28 weeks GA were more often diagnosed with LOS and BPD, promoting increased exposure to both parabens and BPA, which in turn led to higher urinary concentrations of some parabens and BPA compared to infants born after 28 weeks GA. However, subgroup analyses of infants with LOS and BPD did not reveal any significant differences in parabens concentrations, although numerically higher BPA concentrations were measured in infants with BPD.

The high urinary concentrations of parabens and BPA in VLBW infants are probably caused by maternal exposure, use of pharmaceuticals and medical equipment, as well as reduced elimination due to immature organ systems with low GA at birth. Maternal exposure can be prenatal and postnatal. Prenatal exposure originates from maternal blood passing through the placenta, whereas postnatal exposure may be from human milk or other products containing parabens or BPA the mother uses.

Presumed sources of parabens in this study were pharmaceuticals such as respiratory stimulants (caffeine), antibiotics (gentamycin) and vitamins for parenteral administration, whereas potential sources of BPA were medical equipment containing plastic (intravenous cannulas, baby bottles, plastic bags used for storing parenteral nutrition solutions and medical equipment used for breathing support). In 2003, Calafat et al. measured urinary concentrations of parabens and BPA in approximately 40 premature infants who were divided into a low, medium, or high category based on intensity of use of medical equipment (high intensity category concentrations: BPA = 24.0 ng/mL, MeP = 340 ng/mL, PrP = 21.3 ng/mL). Duty et al. measured urinary BPA concentrations in 50 premature infants based on low or high exposure from medical devices (high intensity category concentration: BPA = 18.5 ng/mL). We measured higher first week median MeP concentrations (541 ng/mL), similar PrP concentrations (23.8 ng/mL) and lower median urinary BPA concentrations (11.3 ng/mL), compared with previous studies on premature infants with high exposure from medical devices. The cause of the high paraben

levels in our study is not clear. European plastic manufacturers no longer use BPA in plastic production which may explain lower exposure from medical equipment in recent studies (Testai, 2015). Other unrecognized sources may exist as some products contain parabens and BPA without enclosing/including it in the list of contents (Iribarne-Duran et al., 2019). Other possible sources of parabens and BPA were breast milk (Mikolajewska et al., 2015; Park et al., 2019), certain clothing (Freire et al., 2019), and parents/healthcare providers. All infants received breast milk, wore clothing to reduce heat loss, and were cared for by parents and healthcare providers. Data on these sources were not available.

Premature infants have much higher concentrations of certain parabens and BPA compared to term infants and older children. For example, the average MeP and PrP concentrations in premature infants (Calafat et al., 2009; present study) were 8–13 fold higher than in children between 3 and 12 years of age (Frederiksen et al., 2014; Larsson et al., 2014; Kang et al., 2016; Sakhi et al., 2018; CDC, 2019). Average BPA concentrations in premature infants (Calafat et al., 2009; Duty et al., 2013; present study) were 10 fold higher compared to children between 5 and 12 years of age (Frederiksen et al., 2014; Larsson et al., 2014; Covaci et al., 2015; Sakhi et al., 2018; CDC, 2019). We found high concentrations of parabens and BPA among infants born with low GAs. A case-control study suggested that risk of preterm birth could be associated with parabens (Aung et al., 2019), and Cantonwine et al. reported significantly elevated odds of spontaneous preterm birth with maternal BPA concentrations between 33 and 38 weeks of pregnancy (Cantonwine et al., 2015). Researchers in the USA reported higher BPA concentrations in infants born at lower GA (Calafat et al., 2009), and high BPA concentrations among VLBW infants (Duty et al., 2013).

Paraben levels dropped from the first to the fifth week of life in VLBW infants born before 28 weeks GA, possibly reflecting reduced need of pharmaceuticals containing parabens, whereas the opposite was observed for BPA. Most infants born before 28 weeks GA received gentamycin, caffeine, and parenteral vitamins the first week of life, all potential sources of parabens which could explain the high levels detected. At five weeks of age, the same infants rarely received antibiotics or vitamins, which could explain the reduced levels of parabens measured. Infants on antibiotics at this time received antibiotics without parabens. The increase in BPA concentrations from the first to the fifth week of life may reflect persistent use of breathing support containing BPA due to development of BDP. Moreover, infants born before 28 weeks GA received parenteral nutrition through central lines longer than infants born after 28 weeks GA. Intravenous cannulas and plastic bags used to provide parenteral nutrition the first weeks of life contained BPA, which could explain the cumulatively increasing BPA levels detected at five weeks of age.

Infants born at low GA have increased risk of developing LOS and BPD. These conditions require use of pharmaceuticals and medical equipment that may contain parabens and BPA, thereby increasing exposure (Calafat et al., 2009; Duty et al., 2013). However, infants developing LOS and BPD had non-significantly higher concentrations of BPA compared to infants without LOS and BPD. Infants with LOS and BPD received parenteral nutrition through central lines and were on respiratory support longer than infants without these diagnoses. The medical equipment used to provide parenteral nutrition and breathing support were potential sources of BPA, which may explain the higher levels of BPA detected in these infants. The lack of difference in paraben concentrations between infants with and without LOS was somewhat surprising because most infants with LOS received gentamycin, a broad-spectrum antibiotic containing parabens (MeP and PrP). This might partly be explained by the fact that the first urinary samples were collected before the infants were diagnosed with LOS. It was also surprising that we did not find any significant differences in urinary concentrations of parabens or BPA between infants with or without BPD, although infants with BPD were more exposed to parabens and BPA. A possible explanation may be that the urinary samples were collected before BPD was diagnosed (at 36 weeks gestation). Other explanations for the lack of differences in excipient concentrations among infants with or without LOS or BPD may be that the actual exposure was lower than expected, or that the rate of elimination was enhanced as a response to high excipient load. A more likely explanation may be lack of statistical power due to low number of infants in these subgroup analyses.

There were no significant correlations between parabens and BPA at any of the two time points, suggesting that parabens and BPA do not share the same exposure sources. However, mostly positive correlations were observed among different parabens, in accordance with previous studies among children from Norway (Sakhi et al., 2018), Greece (Myridakis et al., 2015) and the USA (Calafat et al., 2009).

Our study was not designed to evaluate the effects of excipient exposure in VLBW infants. We did not obtain specific information on maternal exposure, pre-screen pharmaceuticals, medical equipment or sampling devises for presence of parabens or BPA, nor did we calculate daily exposure. Furthermore, we did not adjust for creatinine, or urine dilution by specific gravity, as the collected urine volume was insufficient or too concentrated. The inclusion of participants to the original trial was terminated after inclusion of 50 infants due to a higher occurrence of LOS in the intervention group (Moltu et al., 2013); thus, we had a lower number of study participants than planned.

5. Conclusions

Urinary paraben and BPA concentrations were very high compared to term infants and older children. The Σ paraben concentration in this group of premature children was higher than the concentrations detected in previous studies on premature infants. Infants born at low GAs had significantly higher concentrations of parabens and BPA than infants born at a later GAs. Infants with LOS and BPD were treated with pharmaceuticals and medical devices containing parabens and BPA with non-significantly higher concentrations of BPA measured compared to infants without LOS and BPD.

CRediT author statement

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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.

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Corrigendum

Corrigendum to "High urinary concentrations of parabens and bisphenol A in very low birth weight infants" [Chemosphere 271 (2021) 129570]

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The authors regret that the printed version of the article above contained one error in Table 2. The correct and final version follows. The authors will apologize for any inconvenience this may cause.

Table 2 Urinary concentrations of paraben and bisphenol A (ng/mL) at two time points.

		1st week of life (n = 38)		5th week of life (n = 35 - 36)		1st week of life in infants with paired samples (n = 28)		5th week of life in infants with paired samples (n = 28)		
Analyte	Samples > LOQ (%)	Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	Min - Median - Max	Geometric mean (SD)	P-value [b]
MeP	100	13.5 - 541 - 4795	396 (4.01)	1.72 - 261 - 4269	187 (6.17)	13.5 - 437 - 4795	357 (4.15)	6.00 - 290 - 4269	217 (5.89)	*0.12*
EtP	97	0.04 - 0.87 - 5.32	0.78 (2.86)	0.04 - 1.19 - 614	2.05 (10.0)	0.04 - 0.67 - 5.32	0.69 (2.89)	0.04 - 1.65 - 614	2.43 (10.7)	**0.01**
PrP	100	0.51 - 23.8 - 640	23.7 (4.20)	0.14 - 11.9 - 358 [a]	11.9 (8.08)	0.51 - 21.1 - 640	18.7 (4.36)	0.41 - 12.8 - 358	15.0 (7.00)	0.52
BuP	70	0.04 - 0.21 - 2.80	0.17 (3.93)	0.04 - 0.35 - 122 [a]	0.52 (9.36)	0.04 - 0.16 - 2.80	0.16 (4.21)	0.04 - 0.35 - 122	0.68 (9.70)	***0.01***
Σ parabens	-	16.5 - 556 - 4908	438 (3.92)	1.94 - 284 - 5242 [a]	210 (6.09)	16.5 - 475 - 4908	392 (4.06)	7.15 - 294 - 5242	242 (5.81)	*0.19*
BPA	100	0.04 - 11.3 - 92.9	10.7 (3.88)	1.09 - 7.27 - 98.0	8.46 (3.03)	0.04 - 13.1 - 92.9	10.4 (4.26)	1.28 - 7.80 - 98.0	9.53 (2.91)	*0.40*

MeP = methylparaben; EtP = ethylparaben; PrP = propylparaben; BuP = butylparaben; Σ parabens = sum of parabens (calculated); BPA = bisphenol A; LOQ = limit of quantification = 0.05 ng/mL; min = minimum; max = maximum; SD = standard deviation; [a] n = 35. [b] Comparing geometric means from 1st and 5th week of life in infants with samples at both time points. P-values in italics are calculated using non-parametric tests.

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