Exposure to Plasticizers in the Neonatal Intensive Care Unit – a Case of Primum Non Nocere

PhD thesis presented on June 30, 2025, at the University of Antwerp, Antwerp, Belgium

Lucas Panneel [a,b]

PROMOTORS: Adrian Covaci [c], Philippe G Jorens [b,d], Antonius Mulder [a,b]

[a] Neonatal Intensive Care Unit, Antwerp University Hospital, Belgium
[b] Laboratory for Experimental Medicine and Pediatrics, University of Antwerp, Belgium
[c] Toxicological Centre, University of Antwerp, Belgium
[d] Department of Intensive Care Medicine and Clinical Pharmacology, Antwerp University Hospital, Belgium

lucas.panneel@uza.be

Keywords
Endocrine disrupting chemicals; Neonatal intensive care unit; Plastic medical devices; Respiratory outcome; Neurodevelopment

Introduction

Plasticizers are chemical compounds added to rigid plastics, such as plastic medical devices, to make them flexible, soft and to extend their lifetime. Phthalates, such as di-(2-ethylhexyl) phthalate (DEHP), are the best-known and most widespread group of plasticizers (1). Unfortunately, phthalates have been classified as endocrine disrupting chemicals and were restricted in the EU Medical Devices Regulation (EU MDR 2017/745) and gradually replaced by alternative plasticizers (2). The neonatal intensive care unit (NICU), an important environment for providing essential care to premature neonates, relies on invasive plastic medical devices. In addition, premature neonates hospitalized in the NICU are susceptible to potential toxic plasticizers, as exposure happens at a critical developmental period, while being at risk for long-term impaired respiratory and neurodevelopment (3).

Nutrition as a source of plasticizer exposure in neonates

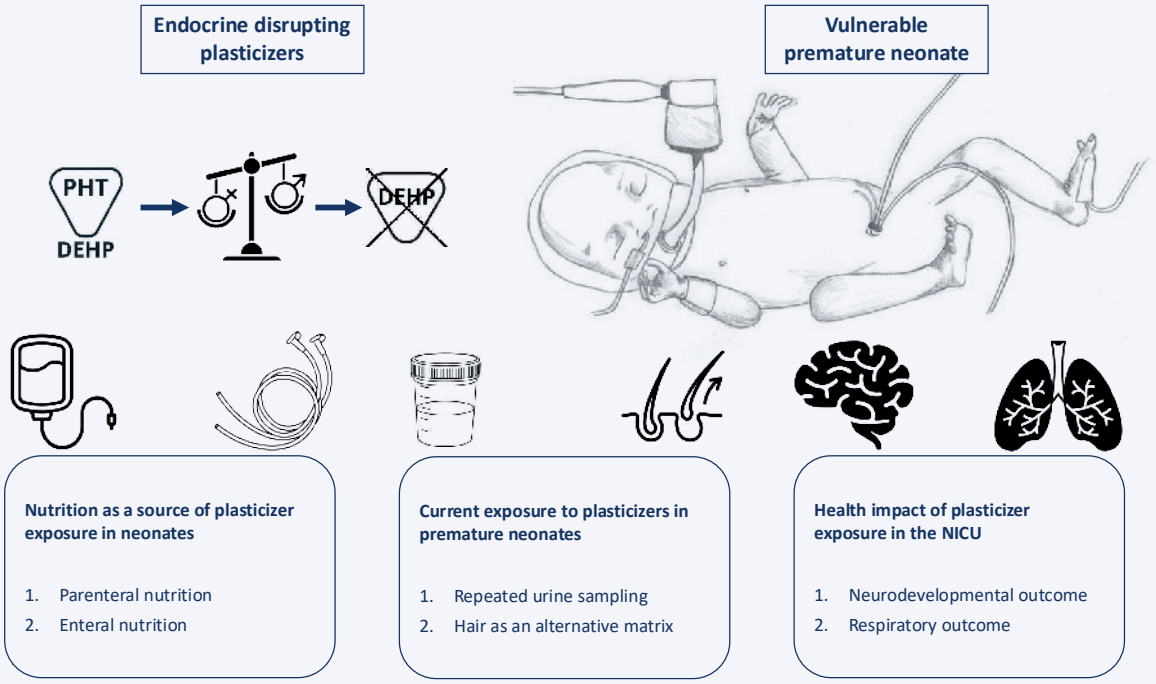
To start with, we demonstrated that DEHP and several alternative plasticizers are still present in relevant amounts in nutrition related products in the NICU of the Antwerp University Hospital, even though all devices were labelled by the manufacturers as DEHP-free (4, 5). Tris (2-ethylhexyl) trimellitate (TOTM) was identified as the main alternative plasticizer in plastic medical devices used for neonatal parenteral and enteral nutrition (4, 5). Interestingly, the low migration potential of TOTM provides opportunities to reduce exposure. Ex vivo simulation of parenteral nutrition administration showed that lipid emulsions contained high concentrations of DEHP and several alternative plasticizers (4). Nevertheless, concentrations were estimated to result in daily exposures below safe reference values (4). Concerning enteral nutrition, formula milk was shown to contain significantly higher levels of endocrine disrupting phthalates, compared to human milk collected from mothers of premature neonates in the NICU (5). Ex vivo simulation of preterm formula milk administration led to a phthalate exposure up to three times above the reference value (5).

Current exposure to plasticizers in premature neonates

In parallel, human biomonitoring was used to quantify whole-body exposure during clinical practice. Therefore, a prospective cohort (Clinicaltrials.gov identifier NCT05404815) was set up including premature neonates (n=132) born at <31 weeks gestational age and/or <1500 g birth weight in the Antwerp University Hospital. Urinary concentrations of plasticizers' biomarkers were measured weekly using liquid-chromatography coupled to tandem mass spectrometry, showing ongoing exposure of premature neonates to both phthalate and alternative plasticizers during their NICU stay (6). More immature children, especially receiving respiratory support and/or blood products, are at increased risk of exposure above "safe" levels. Time trend analysis showed increasing phthalate metabolite levels the first few days of life until four weeks postnatal. 57% had at least once during their NICU stay an estimated plasticizer exposure above the reference levels (6).

In addition, we described the first field study to detect biomarkers of exposure to phthalate and alternative plasticizers in neonatal hair samples (7). Our results showed that hair sampled from premature neonates after NICU stay contained significantly higher metabolite concentrations of both classic phthalates and alternative plasticizers, when compared to healthy control neonates and adults. In addition, continuous NICU exposure to non-invasive respiratory support and a gastric tube was correlated with increased concentrations in hair samples, indicating accumulation in this alternative matrix (7).

FIGURE: A premature neonate staying in a neonatal intensive care unit (NICU), exposed to a chemical-intensive environment during a critical period for brain and lung development.



Health effects of plasticizer exposure in the neonatal intensive care unit

Lastly, follow-up of the Plastic-NICU cohort was used up to study the correlation between neonatal exposure to both phthalates and alternative plasticizers, and clinical respiratory and neuro-developmental outcome at one-year of age (8). Neurodevelopmental outcome was assessed at 12 months corrected age using the validated Bayley Scales of Infant and Toddler Development-III (9). Respiratory outcome was assessed using a parent-completed questionnaire (10), assessing respiratory symptoms and respiratory-associated health-care utilization during the first year of life. To assess simultaneous exposure to different compounds, weighted quantile sum regression was used to address mixture effects (11).

We showed that exposure of premature neonates to specific plasticizer mixtures during NICU stay might be associated with neurodevelopment at 12 months corrected age (8). We found associations of increased levels of plasticizer mixtures, with worse fine motor and receptive communication skills on one hand, and better gross motor and expressive communication skills on the other hand. These seemingly conflicting results are in line with a systematic review showing that epidemiological studies in older populations are not entirely consistent either over different aspects of neurodevelopment (12). We hypothesized that the impact of perinatal phthalate exposure during a period of increased susceptibility, may follow a non-linear trajectory on different neurodevelopmental domains (12), and could potentially even accelerate specific neural networks (13). In addition, the used outcome measures at one year must be interpreted with caution, as the predictive validity for further neurodevelopment has been shown to be moderate (14).

Regarding the impact on neonatal lung development, experimental studies suggest that perinatal phthalate exposure can modify lung parenchyma both at structural (e.g., reduced gas exchange surface, and increased collagen deposition) and functional (e.g., alteration of type II pneumocyte function) levels (1). Indeed, our results show that NICU exposure to plasticizer mixtures was also associated with increased respiratory morbidity (increased odds for repeated airways infections, and respiratory-related healthcare visits) during the first year of life (8). Mixture analysis revealed that phthalates and alternative plasticizers were important contributors to the observed effects. Likewise, observational studies in non-NICU populations showed a similar strong positive association between prenatal or early childhood DEHP exposure and later asthma development, and eczema (1).

Future perspectives

Both ex vivo and in vivo studies showed that, despite changing regulations, DEHP is still present in neonatal intensive care medical devices, and labelling is insufficient to guarantee its absent. However, it should be noted that the sunset date, after which companies cannot market or use endocrine disrupting phthalates in medical devices, was postponed from 27 May 2025 to 1 July 2030 (Commission Regulation (EU) 2023/2482). Therefore, our first recommendation would be to not only draft regulations, but also to enforce implementation into practice.

Next, although environmental toxicologists have addressed the problem of plasticizer exposure for some time, the production and use of safe plastic medical devices also relies on physicians and hospitals asking for phthalate-free products. On a day-to-day basis, clinicians can try to use "DEHP-free" products where available, by examining the icon of DEHP absence/presence (≤/> 0.1 mass percent DEHP), which is obligatory on the package of all plastic medical devices present on the EU market. In addition, we recommend both physicians and hospital-purchasing departments to cooperate with legislative bodies and manufacturers to determine alternative strategies.

Alternative plasticizers have been used for over a decade based on acute toxicity in animal studies after enteral exposure.

Nevertheless, current oral reference values are not adequate for IV hazard assessment, given the IV exposure route results in higher bioavailability. Therefore, repeat dose toxicity studies after IV exposure should be performed to represent the parenteral route of exposure. Nevertheless, since the EU MDR does not describe a reference to guide manufacturers in the choice and amount to be integrated into plastic medical devices, we recommend providing legal and extralegal frameworks for the changing use of alternative plasticizers.

This thesis also recommended future research priorities. First, our biomonitoring studies highlighted that the assessment of factors influencing plasticizer leaching from respiratory support and the resulting direct airway exposure during clinical use, remain an important knowledge gap and potential starting point to reduce future exposure. As done for the enteral and parenteral leaching experiments, we would recommend starting from a clinical theoretical assumption, for example by collecting exhaled breath condensate during simulation experiments. Next, pharmacokinetic-pharmacodynamic approaches based on individual parameters as birth weight, creatinine excretion and postmenstrual age, might aid in more precise estimated daily intake interpretations. Lastly, to further study the associated health effects of neonatal plasticizer exposure, follow-up studies at older age are needed to confirm or disapprove the found associations at later developmental stages.

Conclusion

To conclude, this thesis highlights ongoing iatrogenic exposure of premature neonates to phthalates and alternative plasticizers in the NICU, despite the EU Medical Devices Regulation. It underscores the urgent need for targeted interventions to reduce exposure, enhance regulatory frameworks, and improve clinical practices. By addressing these gaps, the healthcare community can better safeguard this vulnerable population from potential long-term health impacts.

REFERENCES

1. Panneel L, Malarvannan G, Jorens PG, Covaci A, Mulder A. Plasticizers in the neonatal intensive care unit: A review on exposure sources and health hazards. Critical Reviews in Environmental Science and Technology. 2021;52(22):3947-72.
2. Den Braver-Sewradj SP, Piersma A, Hessel EVS. An update on the hazard of and exposure to diethyl hexyl phthalate (DEHP) alternatives used in medical devices. Crit Rev Toxicol. 2020;50(8):650-72.
3. Woods JCS, J. C. Lung Structure at Preterm and Term Birth. In: Jobe AHUoCW, J. A.; Abman, S. H., editor. Fetal and Neonatal Lung Development: Cambridge University Press; 2016. p. 126-40.
4. Panneel L, Cleys P, Breugelmans C, Christia C, Malarvannan G, Poma G, et al. Neonatal exposure to phthalate and alternative plasticizers via parenteral nutrition. International Journal of Pharmaceutics. 2023;631:122472.
5. Cleys P, Panneel L, Jorens PG, Mulder A, Covaci A. Neonatal Exposure to Phthalate and Alternative Plasticizers via Enteral Nutrition. Environmental Science & Technology. 2025.
6. Panneel L, Cleys P, Poma G, Ait Bamai Y, Jorens PG, Covaci A, et al. Ongoing exposure to endocrine disrupting phthalates and alternative plasticizers in neonatal intensive care unit patients. Environment international. 2024;186:108605.
7. Cleys P, Panneel L, Bombeke J, Dumitrascu C, Malarvannan G, Poma G, et al. Hair as an alternative matrix to assess exposure of premature neonates to phthalate and alternative plasticizers in the neonatal intensive care unit. Environmental research. 2023;236:116712.
8. Panneel L, Cleys P, Ait Bamai Y, Dewispelaere L, Laroche S, Van Hoorenbeeck K, et al. One year respiratory and neurodevelopmental outcome of premature neonates after exposure to plasticizers in the neonatal intensive care unit – A prospective cohort study. Environmental research. 2025;274:121266.
9. Michalec D. Bayley Scales of Infant Development: Third Edition. In: Goldstein S, Naglieri JA, editors. Encyclopedia of Child Behavior and Development. Boston, MA: Springer US; 2011. p. 215-.
10. Strippoli MP, Silverman M, Michel G, Kuehni CE. A parent-completed respiratory questionnaire for 1-year-old children: repeatability. Arch Dis Child. 2007;92(10):861-5.
11. Carrico C, Gennings C, Wheeler DC, Factor-Litvak P. Characterization of Weighted Quantile Sum Regression for Highly Correlated Data in a Risk Analysis Setting. J Agric Biol Environ Stat. 2015;20(1):100-20.
12. Radke EG, Braun JM, Nachman RM, Cooper GS. Phthalate exposure and neurodevelopment: A systematic review and meta-analysis of human epidemiological evidence. Environment international. 2020;137:105408.
13. Stroustrup A, Bragg JB, Andra SS, Curtin PC, Spear EA, Sison DB, et al. Neonatal intensive care unit phthalate exposure and preterm infant neurobehavioral performance. PLoS One. 2018;13(3):e0193835.
14. Luttikhuizen dos Santos ES, de Kieviet JF, Königs M, van Elburg RM, Oosterlaan J. Predictive value of the Bayley scales of infant development on development of very preterm/very low birth weight children: a meta-analysis. Early human development. 2013;89(7):487-96.