Exposure to plasticizers of premature newborns in Neonatal Intensive Care Unit

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Outline

Plasticizers in Medical Devices - background

Exposure assessment

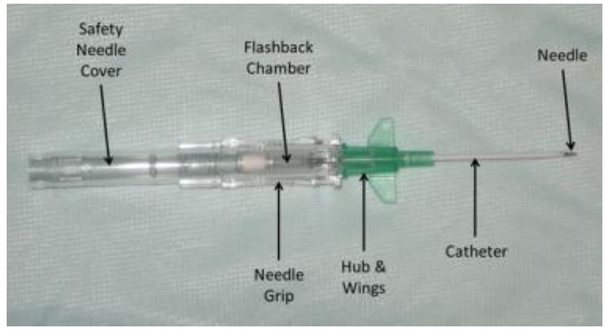
- Medical devices in NICU
- Urinary measurements

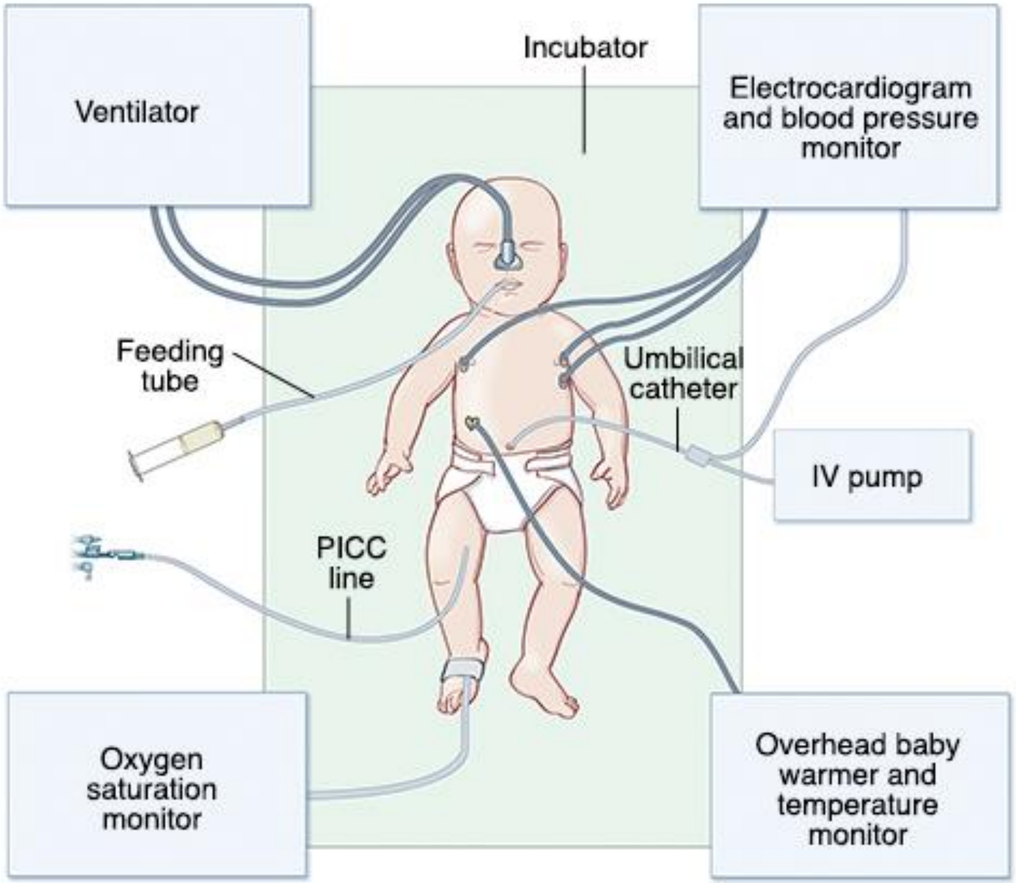
ICU

NICU

Background

Intensive care relies heavily on the use of soft and flexible **indwelling medical devices**, like intravenous catheters and cannulas, which are indispensable to administer medicines and parenteral feedin





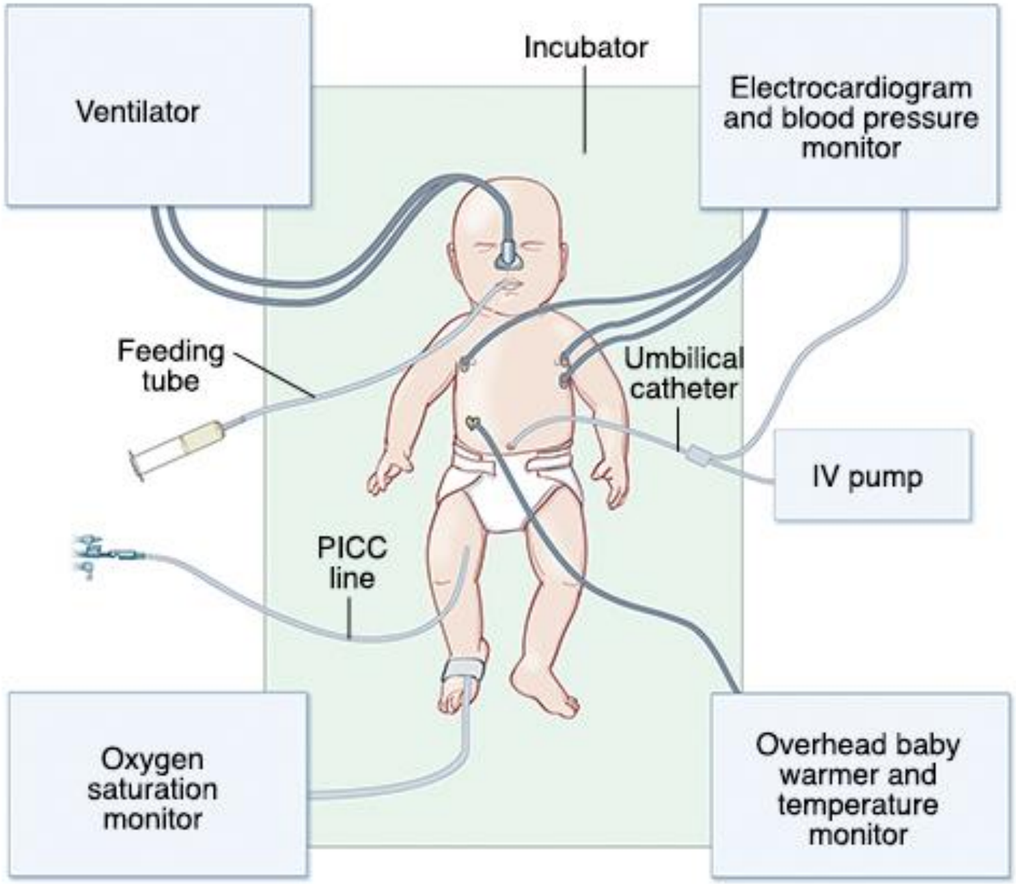
G. Malarvannan et al. Journal of Hazardous Materials 363 (2019) 64–72

Background

These devices are mostly made of PVC, an inherently rigid polymer.

To increase flexibility and softness, phthalates, and in particular **DEHP**, have been historically used as plasticizers (or softeners) for plastic indwelling medical devices.

DEHP is not chemically bound to plastics and can thus **leach from the medical devices during use**.



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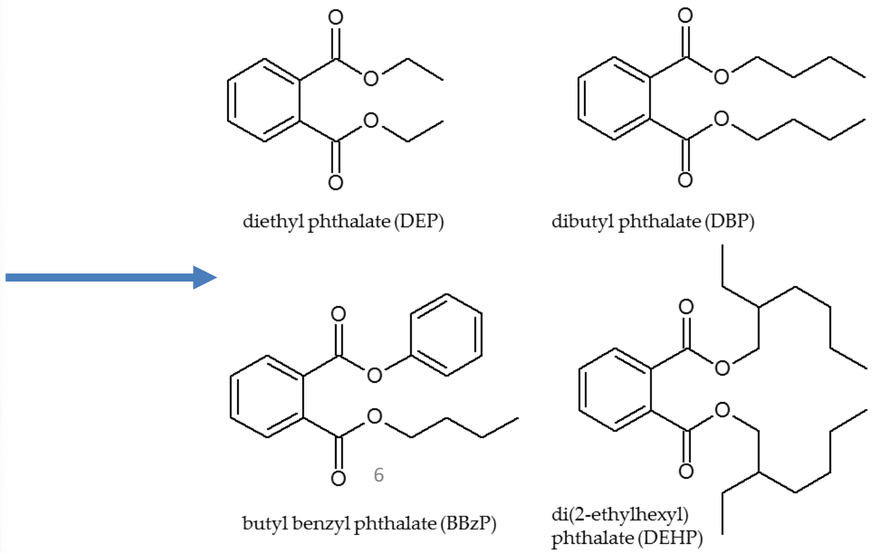
Background



Elasticity and durability

Phthalates (PHT)

- DEHP, BBzP, DBP

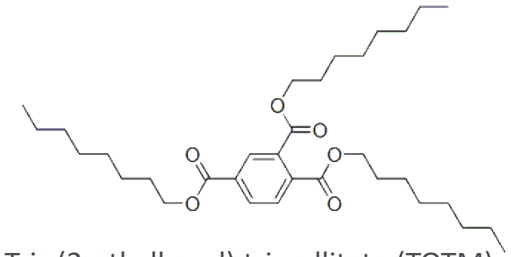
Adverse health effects

- Endocrine Disrupting Chemicals
- Carcinogenic, mutagenic or toxic for reproduction

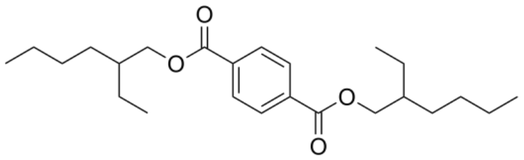
EU MDR 2017/45

- Justification and labelling
- COVID-delay → 26/05/2021

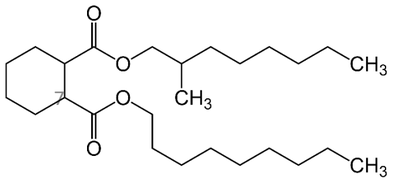
Background



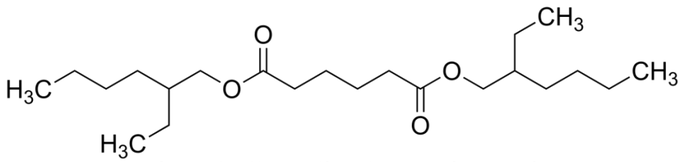
Tris (2-ethylhexyl) trimellitate (TOTM)



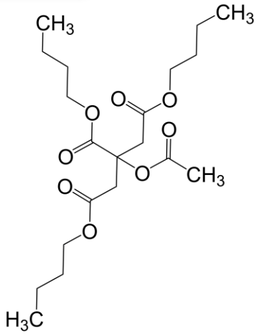
Di(2-ethylhexyl) terephthalate (DEHT)



1,2-Cyclohexane dicarboxylic acid diisononyl ester (DINCH)



Di(2-ethylhexyl) adipate (DEHA)



Acetyl tributyl citrate (ATBC)

Elasticity and durability

Phthalates (PHT)

- DEHP, BBzP, DBP

Adverse health effects

- Endocrine Disrupting Chemicals
- Carcinogenic, mutagenic or toxic for reproduction

EU MDR 2017/45

- Justification and labelling
- COVID-delay → 26/05/2021

Alternative Plasticizers (AP)

- TOTM, DEHT, DINCH, DEHA, ATBC
- Still insufficient toxicity data

Background

Plasticizer use is constantly evolving as there is **no reference** to guide manufacturers in the choice and amount to be integrated into their products.

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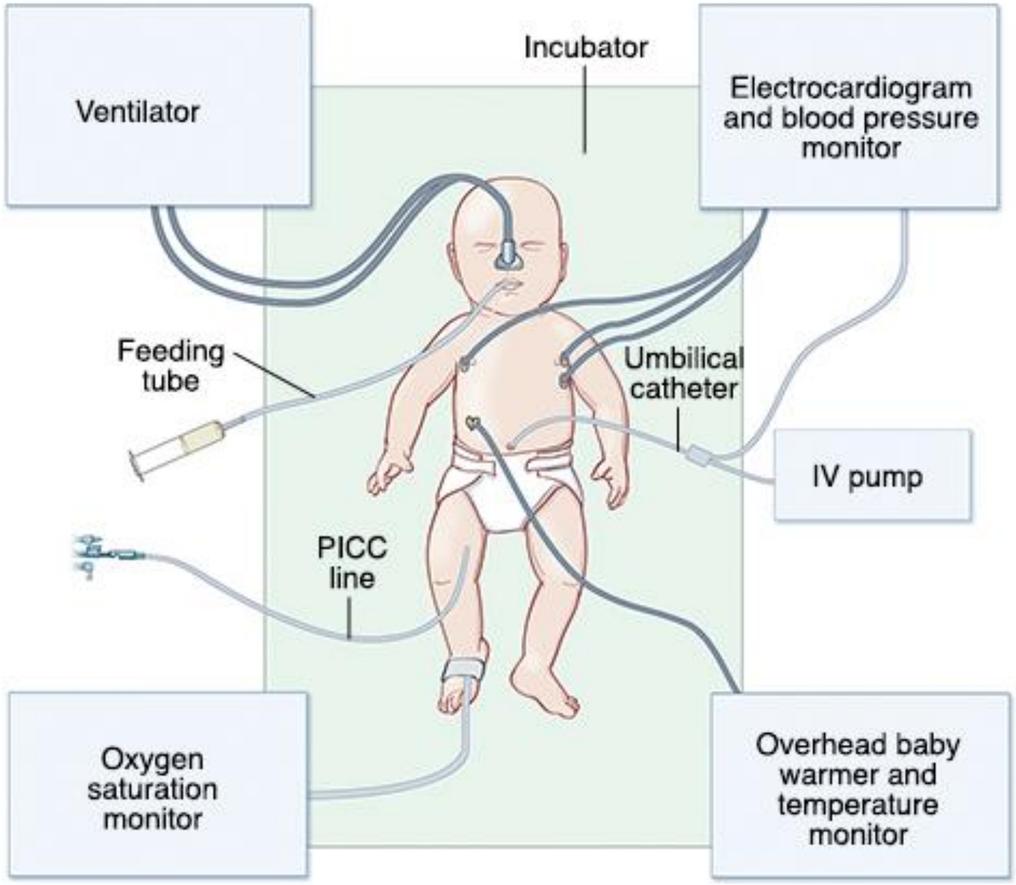
2019

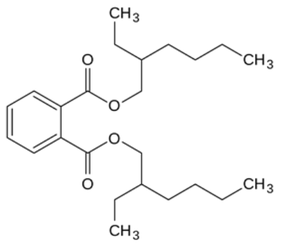
Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units

Govindan Malarvannan[a,*], Matthias Onghena[a], Sören Verstraete[b], Esther van Puffelen[c], An Jacobs[b], Ilse Vanhorebeek[b], Sascha C.A.T. Verbruggen[c], Koen F.M. Joosten[c], Greet Van den Berghe[b], Philippe G. Jorens[d], Adrian Covaci[a,*]



Exposure through medical devices – NICU project

2021



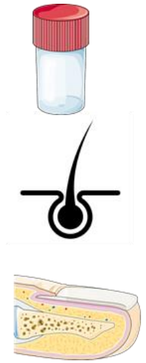
Plasticizers

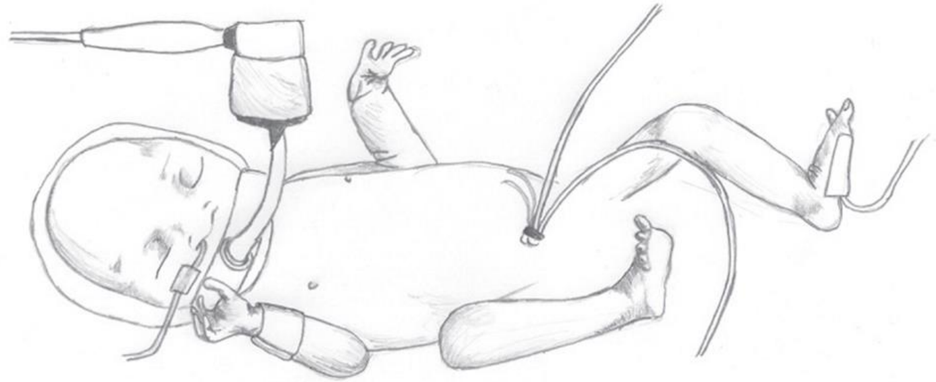
- Phthalates
- Alternative plasticizers

Biomonitoring

- Primary metabolites
- Secondary metabolites

→ Urine, Hair, Nails





Exposure sources

- Enteral nutrition → Gastro-intestinal
- Parenteral nutrition → Intravenous
- Blood products → Intravenous
- Respiratory support
  - Invasive
  - Non-invasive → Inhalational

Routes of exposure

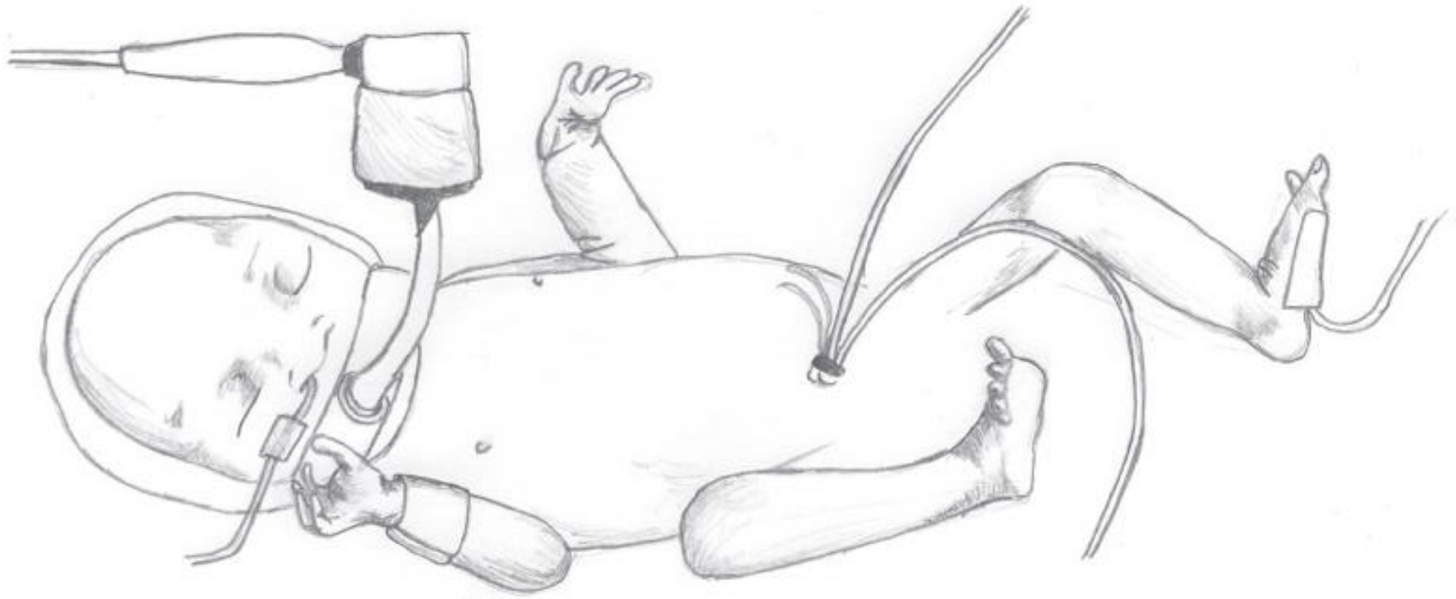
Health hazards

→ Neurobehavior, Psychomotor function, Cognition

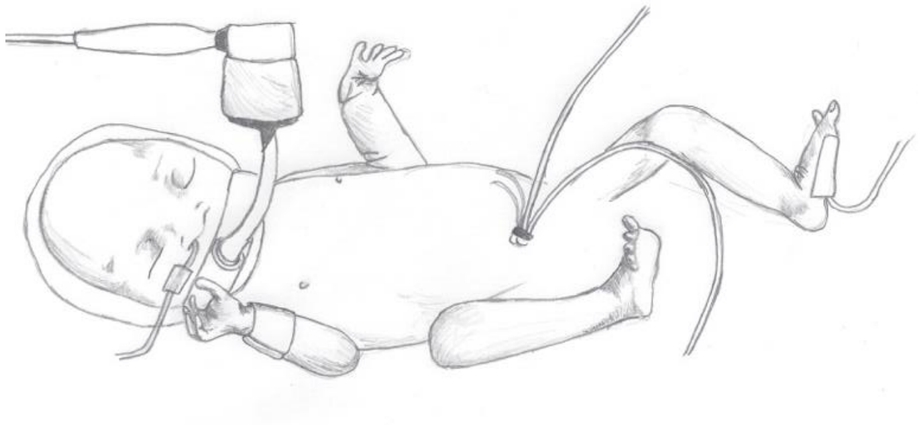
→ Airway inflammation, Impaired alveolarization, Asthma

Panneel, Covaci et al. Critical Reviews in Environmental Science and Technology https://doi.org/10.1080/10643389.2021.1970455

Neonatal Intensive Care Unit (PART 1)
Exposure assessment in neonates through the use of medical devices



NICU Project – part 1



Aim

- Characterize current phthalate and alternative plasticizer (AP) exposure in the NICU
- Identify the sources of exposure

Plastic medical devices in the NICU

- Respiratory support (invasive – non-invasive)
- Parenteral nutrition (lipid – nonlipid)
- Blood products

Parenteral nutrition

- Lipid: 20% soybean oil, olive oil, fish oil
- Crystalloid: glucose, proteins, electrolytes

Parenteral Nutrition

Clinical experiment design

Phase 1

- Quantification of 8 PHTs and 10 APs in plastic medical devices
  - 14 samples from 5 devices used in parenteral nutrition

Phase 2

- *Ex vivo* leaching
- Clinical theoretical assumption

- 2020-2021

Phthalates (PHTs)	Alternative plasticizers (APs)
DEHP	DEHT(P)
DMP	DINCH
DEP	TOTM
DiBP	THTM
DPP	DEHA
BzBP	ATBC
DIDP	ATEC
DINP	BTHC
	DIBA
	CDPHP

Parenteral Nutrition

Factors influencing leaching of DEHP from medical devices:

- **Temperature**: increasing temperature is associated with significantly increased DEHP levels

- **Nature of the infused solution**: greater leaching rates occurred when a lipid-containing solution passes through a PVC-infusion line rather than an aqueous solution, explained by the lipophilic nature of DEHP.

- **Flow rate**: the migration kinetic of DEHP is higher when drugs are infused at lower flow rates.

- **Contact time**: Contact time between the PVC matrix and the infused solution also seems an essential influencing factor in which the cumulative amount of DEHP increases with an increasing contact time.

- **Contact area**: leaching is proportional to the length of the tubing

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Parenteral Nutrition

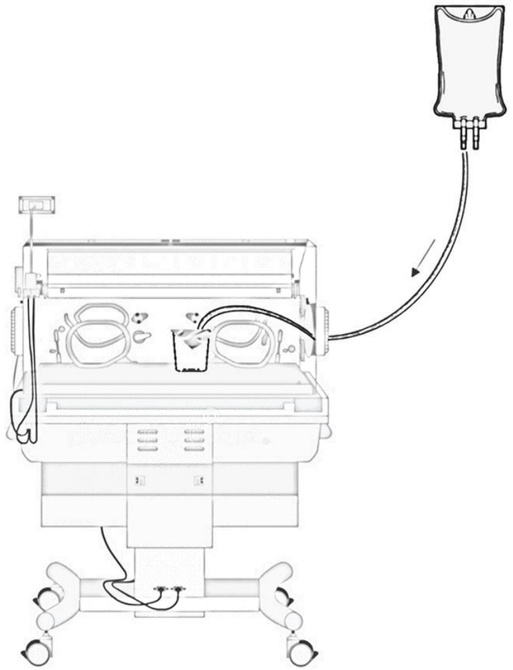
Clinical experiment design

Phase 1

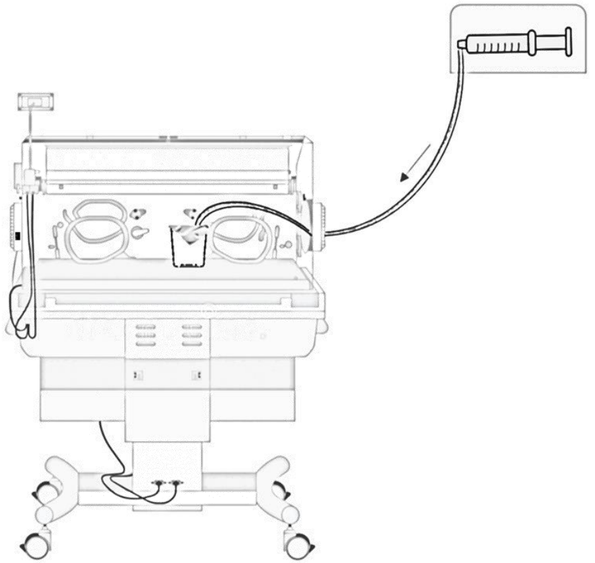
- Quantification of parent compounds (PHT and AP) in plastic medical devices

Phase 2

- *Ex vivo* leaching
- Clinical theoretical assumption
  - Incubator 34°C – humidity 80%
  - Weight 1 kg
  - Total fluid requirement of 120 mL/kg/d



Crystalloid solution



Lipid emulsion

Parenteral Nutrition

Clinical experiment design

Phase 1

- Quantification of parent compounds (PHT and AP) in plastic medical devices

Phase 2

- *Ex vivo* leaching
- Clinical theoretical assumption

Infused solution	Duration	Infusion rate (mL/h)	Time points	Repetitions	Total
Neolipid	24h	0.8 15	T0-T12-T24 (N = 3)	N = 3	**N = 9**
	12h	1.6	T0-T6-T12 (N = 3)	N = 3	**N = 9**
Neobin	24h	4.2	T0-T12-T24 (N = 3)	N = 3	**N = 9**
	12h	8.4	T0-T6-T12 (N = 3)	N = 3	**N = 9**
Total				**N = 12**	**N = 36**

Parenteral Nutrition

Analytical methods

Phase 1

Sample Preparation

- Sample: 100 mg
- Extraction in ethyl acetate:hexane (1:1)

Instrumental Analysis

- Agilent 6410 LC-ESI-MS/MS Triple Quad (parent compounds)
- Agilent 6890 GC-EI-MS (DEHP-DEHT)

QC

- 6 blank samples
- 6 spiked samples

Phase 2

Sample Preparation

- Crystalloid sample: 10 mL, lipid sample: 2.5 mL
- Extraction in ethyl acetate:hexane (1:1)
- SPE Florisil ENVI
- Elute ethyl acetate

Instrumental Analysis

- Agilent 6410 LC-ESI-MS/MS Triple Quad (parent compounds)
- Agilent 6890 GC-EI-MS (DEHP-DEHT)

QC

- 6 blank samples
- 9 spiked samples
  - 3 crystalloid matrix
  - 6 lipid matrix

Parenteral Nutrition

Results Phase 1

Circuit	Device	Sample part (100 mg)	Predominant plasticizers (% w/w, ≥0.1)			Compounds < 0.1 % w/w
			Compound 1	Compound 2	Compound 3	
Crystalloid	Infusion bag	1.1 Plastic bag	n/a	n/a	n/a	DEP > DEHA > ATEC > ATBC > DPP
		1.2 Outlet port	**TOTM (11.0)**	**DEHT (0.4)**	n/a	DEHP > ATBC
	Infusion set	2.1 Distal tube	**TOTM (12.1)**	**DEHT (3.5)**	**DEHA (0.5)**	DEHP
		2.2 Proximal tube	**TOTM (0.3)**	n/a	n/a	DEHT, DEHA, DnBP
		2.3 Drip Chamber	**TOTM (0.1)**	n/a	n/a	ATBC
		2.4 Pressure sensor disc	**ATBC (33.4)**	**DEHT (0.8)**	**DINCH (0.4)**	DEHA
	Extension set	3.1 Tube	**TOTM (10.8)**	**DEHT (0.7)**	**DEHP (0.2)**	DEHA > ATBC
		3.2 Needle-free connector	n/a	n/a	n/a	ATBC > DINCH > TOTM
		3.3 Filter (0.2 µm pores)	n/a	n/a	n/a	ATBC > CDPHP
Lipid	Syringe	4.1 Barrel	n/a	n/a	n/a	ATBC > TOTM
		4.2 Plunger seal	n/a	n/a	n/a	DINCH > ATBC > TOTM
	Extension set	5.1 Main tube	**ATBC (1.0)**	n/a	n/a	DEHA > DINCH, TOTM
		5.2 Filter (1.2 µm pores)	n/a	n/a	n/a	ATBC
		5.3 Pressure sensor disc	**ATBC (35.2)**	**DEHT (3.7)**	n/a	DEP > DEHA, DINCH, DEHP

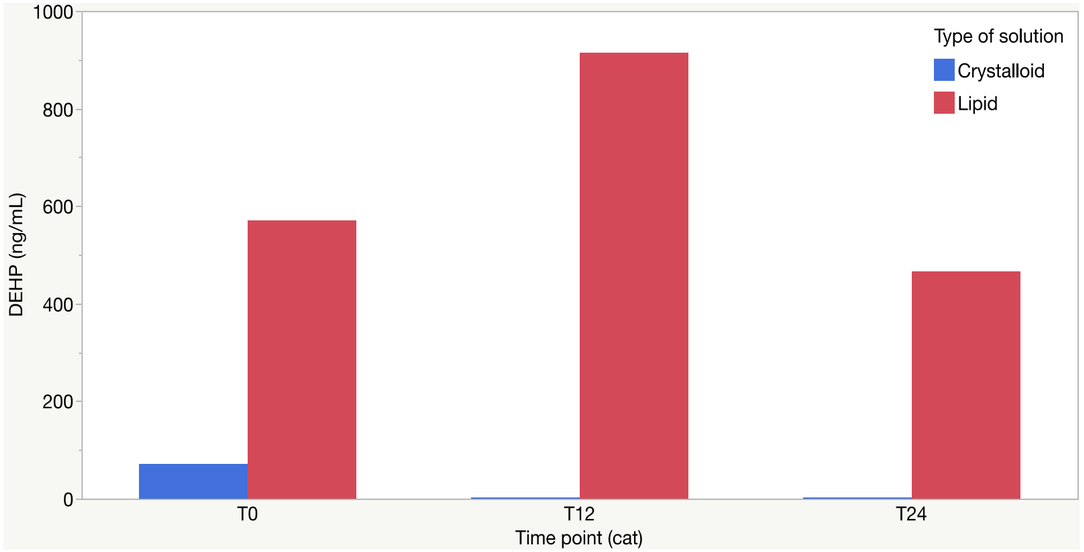
Parenteral Nutrition

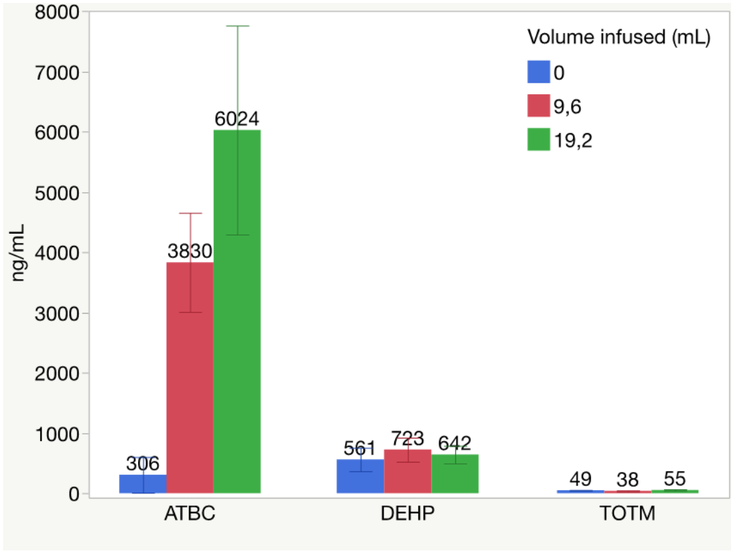
Results Phase 1

Circuit	Device	Sample part (100 mg)	Predominant plasticizers (% w/w, ≥0.1)			Compounds < 0.1 % w/w
			Compound 1	Compound 2	Compound 3	
Crystalloid	Infusion bag	1.1 Plastic bag	n/a	n/a	n/a	DEP > DEHA > ATEC > ATBC > DPP
		1.2 Outlet port	**TOTM (11.0)**	**DEHT (0.4)**	n/a	DEHP > ATBC
	Infusion set	2.1 Distal tube	**TOTM (12.1)**	**DEHT (3.5)**	**DEHA (0.5)**	DEHP
		2.2 Proximal tube	**TOTM (0.3)**	n/a	n/a	DEHT, DEHA, DnBP
		2.3 Drip Chamber	**TOTM (0.1)**	n/a	n/a	ATBC
		2.4 Pressure sensor disc	**ATBC (33.4)**	**DEHT (0.8)**	**DINCH (0.4)**	DEHA
	Extension set	3.1 Tube	**TOTM (10.8)**	**DEHT (0.7)**	**DEHP (0.2)**	DEHA > ATBC
		3.2 Needle-free connector	n/a	n/a	n/a	ATBC > DINCH > TOTM
		3.3 Filter (0.2 µm pores)	n/a	n/a	n/a	ATBC > CDPHP
Lipid	Syringe	4.1 Barrel	n/a	n/a	n/a	ATBC > TOTM
		4.2 Plunger seal	n/a	n/a	n/a	DINCH > ATBC > TOTM
	Extension set	5.1 Main tube	**ATBC (1.0)**	n/a	n/a	DEHA > DINCH, TOTM
		5.2 Filter (1.2 µm pores)	n/a	n/a	n/a	ATBC
		5.3 Pressure sensor disc	**ATBC (35.2)**	**DEHT (3.7)**	n/a	DEP > DEHA, DINCH, DEHP

Parenteral Nutrition

Results Phase 2



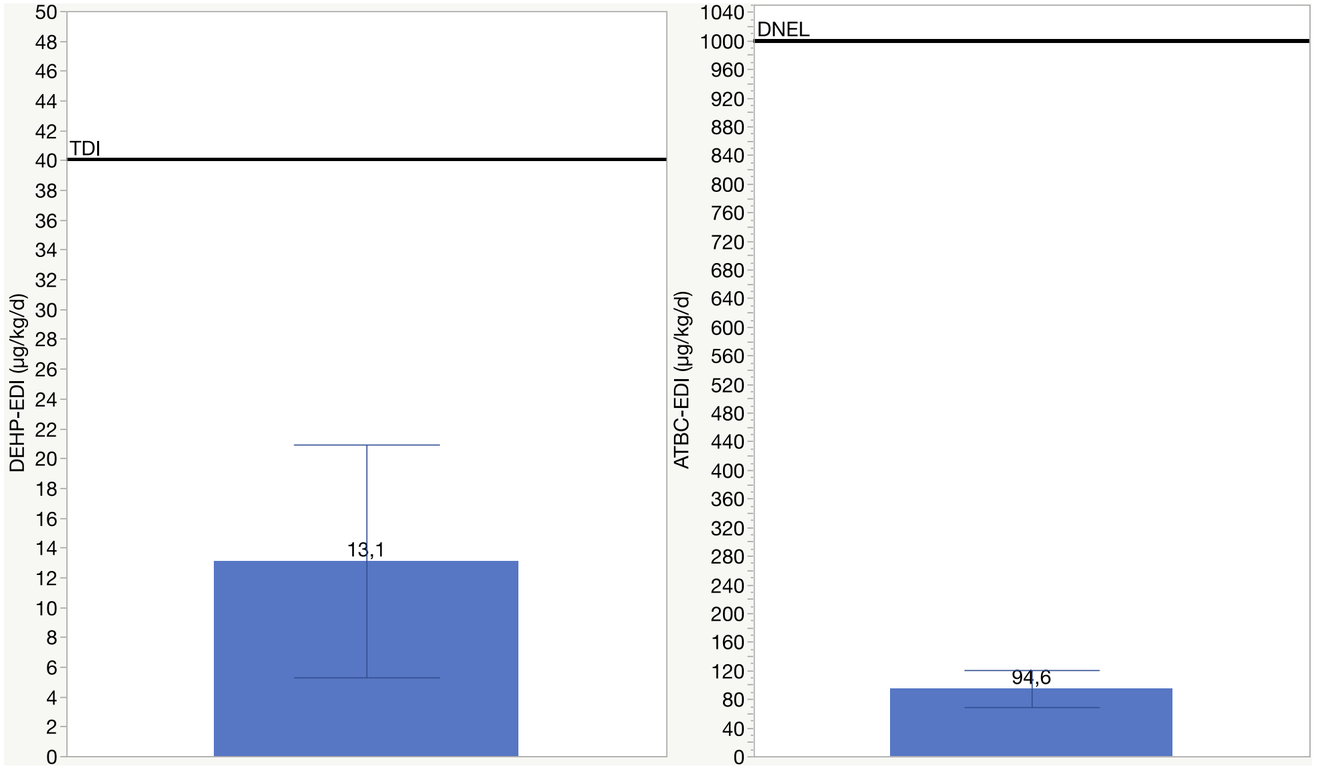


- Higher leachability with higher lipid content
- Trace amounts of DEHP in plastic medical devices
- Source is emulsion itself

- TOTM: low leachability (high molecular weight, hydrophobic)
- ATBC: high leachability (lower molecular weight, less steric hinderance)

Parenteral Nutrition

Estimated daily intake (EDI - 1 kg)



- $EDI\ (\mu g/kg/d) = \frac{concentration\ (ng/mL)\ X\ Volumeday\ (ml/d)}{body\ weight\ (kg)\ x\ 1000}$

- Tolerably Daily Intake (TDI) (SCENIHR – 2015)
- Derived No Effect Level (DNEL) (EPA – 2014)

- Hazard Quotiënt
  - DEHP: 0.26
  - ATBC: 0.09
  - *Faessler et al. (2017) HQ DEHP: 20*

Parenteral Nutrition

Conclusion

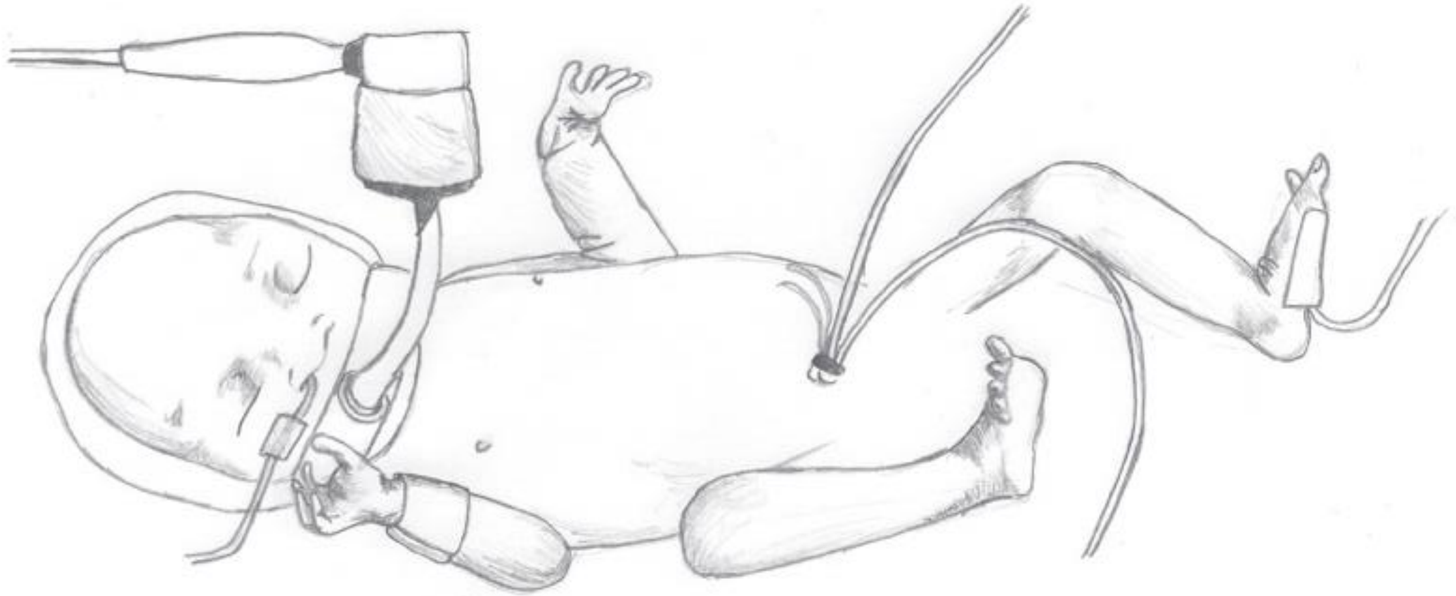
Conclusion

- Medical devices: ATBC and TOTM
- Lipid > crystalloid: DEHP, ATBC and TOTM
- Wide range of concentrations for PHT's & AP's

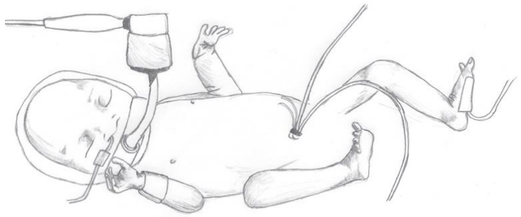
- High migration potential of ATBC
- Low migration potential of TOTM

- Hazard Quotiënt < 1
- Limitations!
  - Cumulative exposure
  - Animal studies
  - Immature metabolism and excretion
  - Bioavailability 100%

Neonatal Intensive Care Unit (PART 2)
– Exposure assessment in neonates through urinary excretion



NICU Neonate



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Day 1 → Day 2 → Day 3 → 1x/week

Neonatal Intensive Care Unit
Antwerp University Hospital

- **Pregnancy duration < 31 w / Birth weight < 1500 g** (n=54)
- Daily record of medical device use
- Urine sample collection
  - Cotton gauzes
  - NICU – baby: cf. time line
  - Control and mother: day 1

- **Control population – healthy neonates** (n=21)

- Total 476 samples

Sample collection → Sample preparation → Instrumental analysis → Data analysis → Statistical analysis

Analysis

Sample preparation (n=476)

- Extraction of phthalate metabolites (PHTm) and alternative plasticizers metabolites (APm)
  - 1 mL sample
  - SPE – OASIS MAX
  - 8 PHTms and 16 Apms
  - QC: interlaboratory ring test (HBM4EU/EQUAS)

Instrumental analysis

- Analysis with LC-MS/MS Agilent 6460 QqQ (PHTm) and 6495 QqQ (APm)
- LOQ range 0.2 to 0.4 ng/mL

Correction:

- Specific gravity: $Conc_{SG}$ = (1.024 / SG) x Conc
- Values under LOQ → LOQ x DF

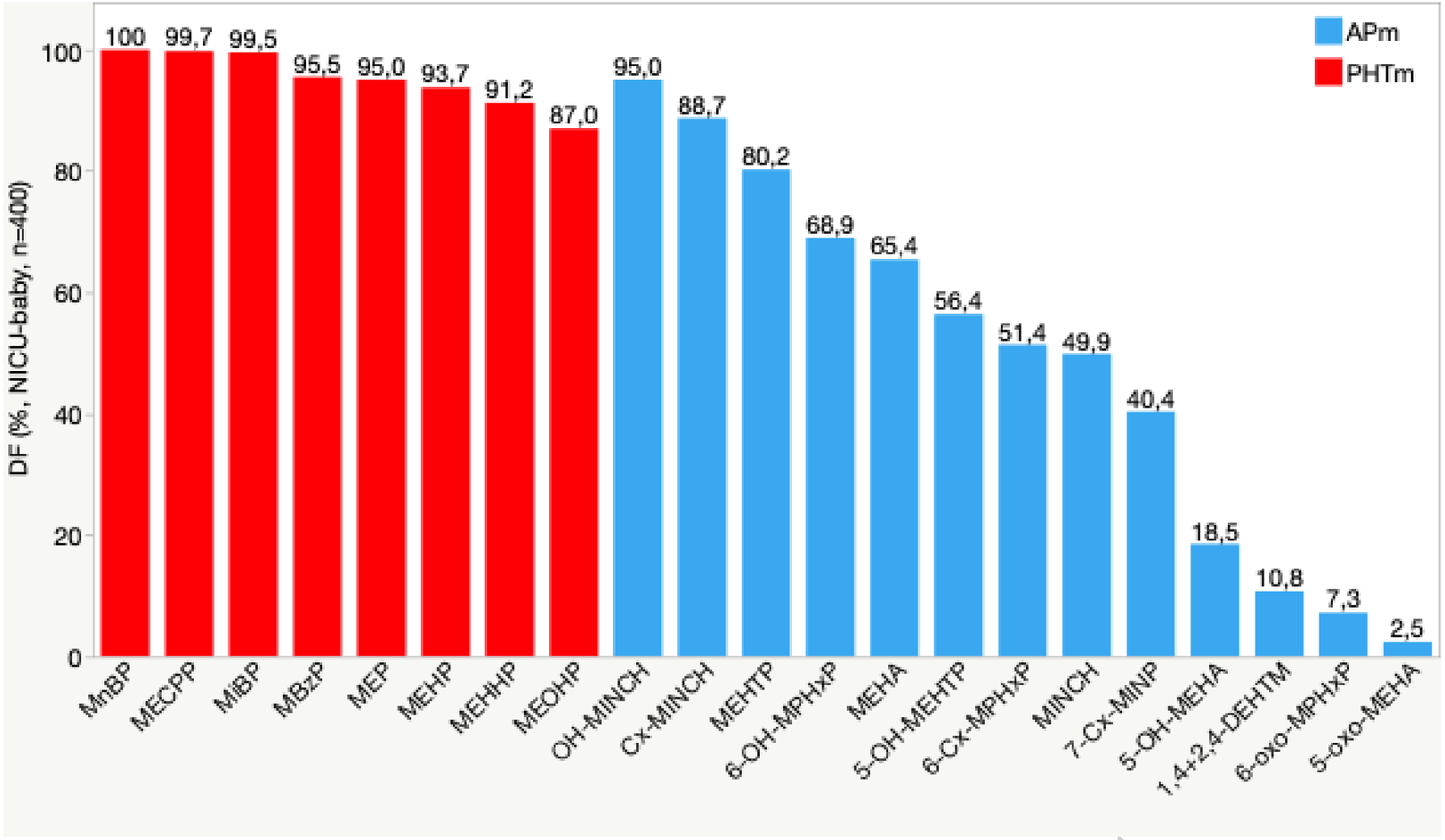
Sample collection | Sample preparation | Instrumental analysis | Data analysis | Statistical analysis

Descriptive Results

Detection Frequency

PHTm > 90%

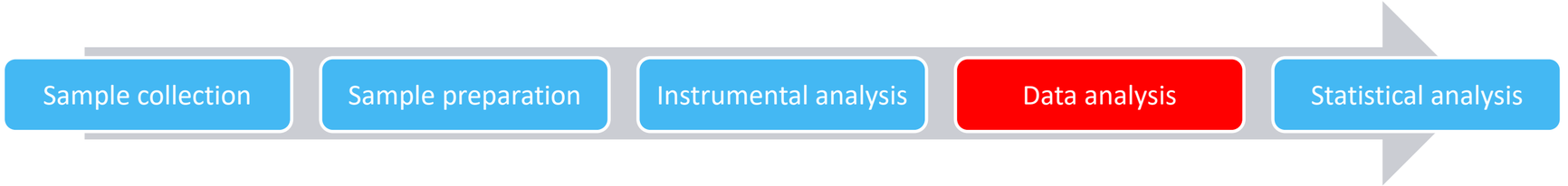
Half of APm < 50%



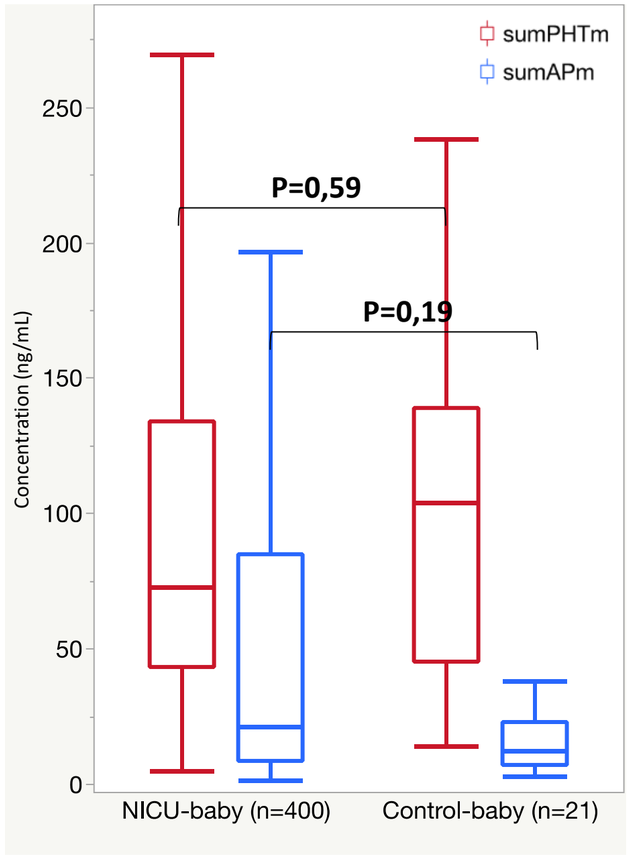
Sample collection | Sample preparation | Instrumental analysis | **Data analysis** | Statistical analysis

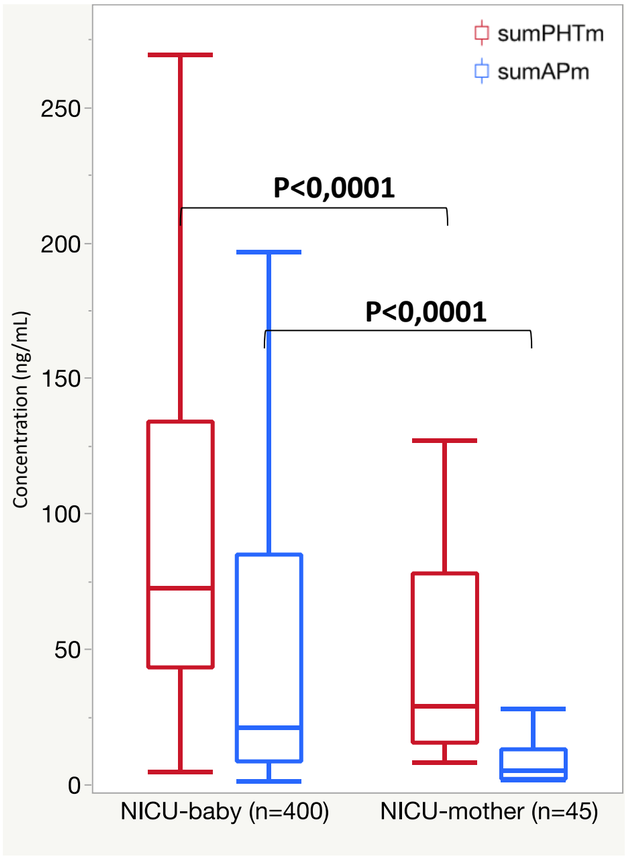
Descriptive Results

Reference	Population	Median MEHHP (ng/mL)	Median sum DEHP metabolites (ng/mL)	Median sumAPm (ng/mL)
Green et al. (2005), USA https://doi.org/10.1289/ehp.7932	Level III NICU > 3d (n = 81)	267	1203	n/a
Stroustrup et al. (2018), USA https://doi.org/10.1038/s41370-018-0069-2	Birth weight < 1500 g (n = 149)	11.8	95	n/a
Pinguet et al. (2019), France https://doi.org/10.1016/j.talanta.2019.01.115	NICU after 24 h exposure to medical devices (n = 104)	49.6	190	0.2
Current study (2021), Belgium	NICU <31 w or <1500 g (n = 400)	**1.2**	**26.7**	**20.8**



Statistical Results





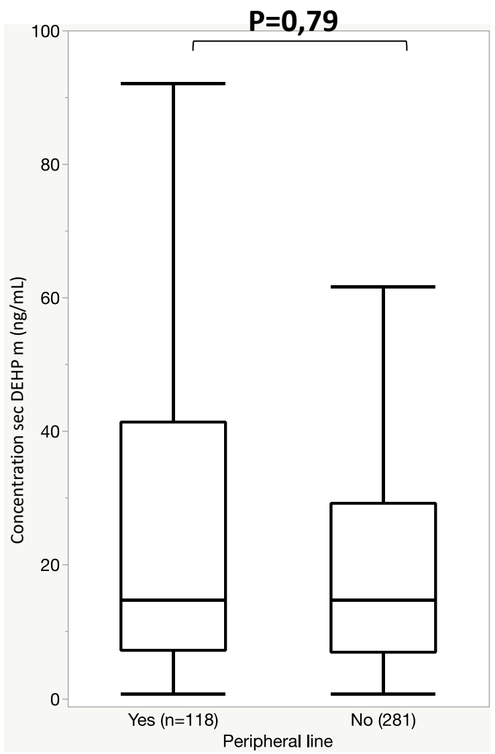
Wilcoxon Rank Sum Test

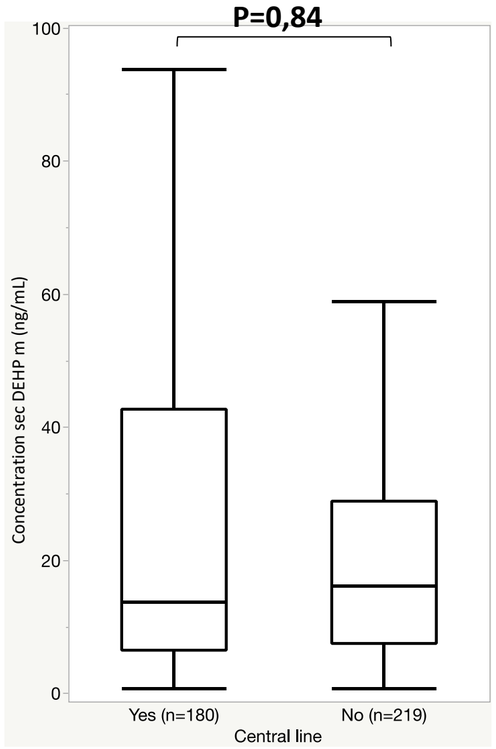
Sample collection | Sample preparation | Instrumental analysis | Data analysis | Statistical analysis

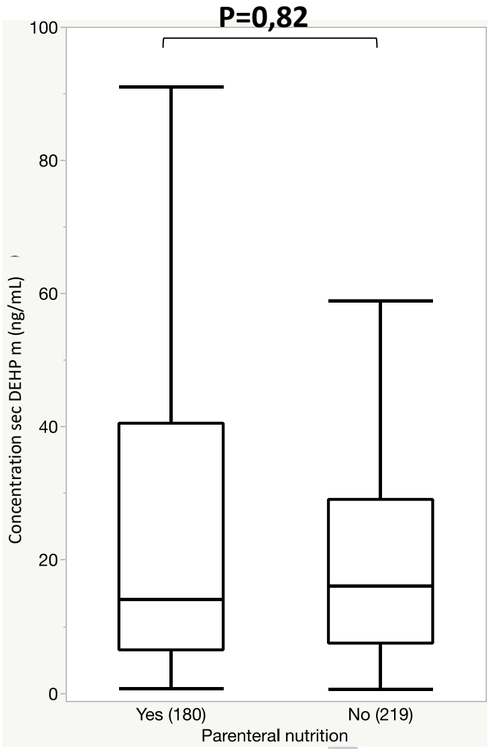
Statistical Results

Medical device exposure

- Binary exposure assessment
- 2-day window
- Sum Secondary DEHP metabolites
- Wilcoxon Rank Sum Test

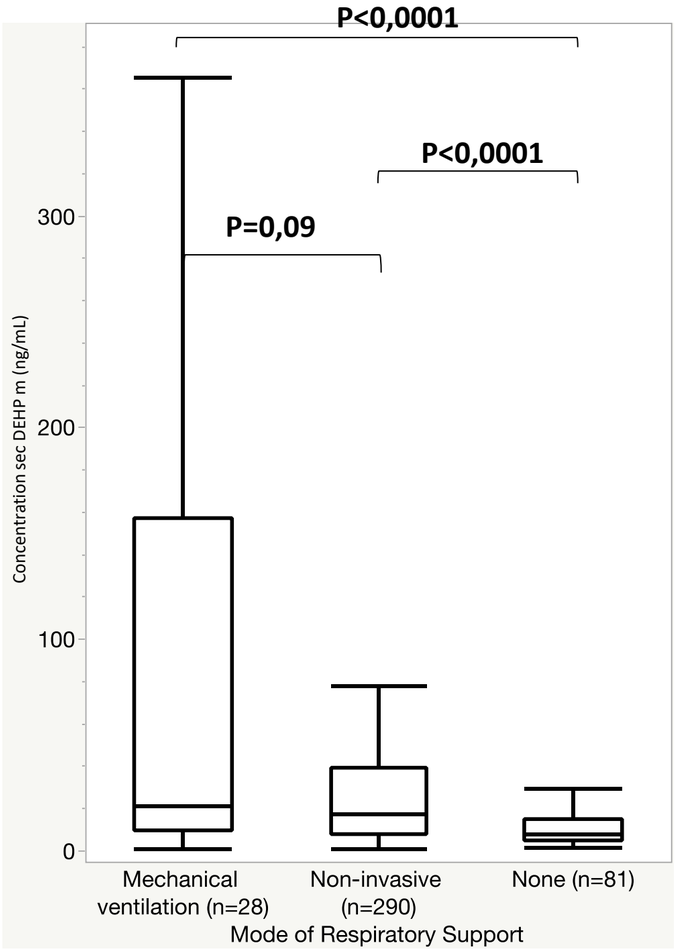






Sample collection | Sample preparation | Instrumental analysis | Data analysis | Statistical analysis

Statistical Results



Mechanical Ventilation

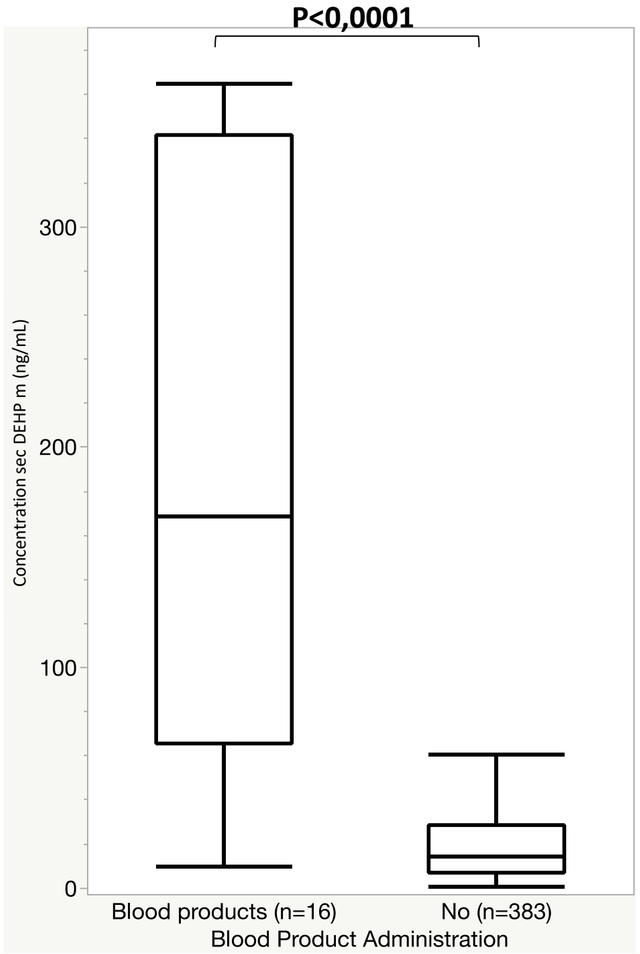
= respiratory support

Kruskal Wallis Test (Steel Dwass multiple comparisons)

Sample collection → Sample preparation → Instrumental analysis → Data analysis → Statistical analysis

Statistical Results

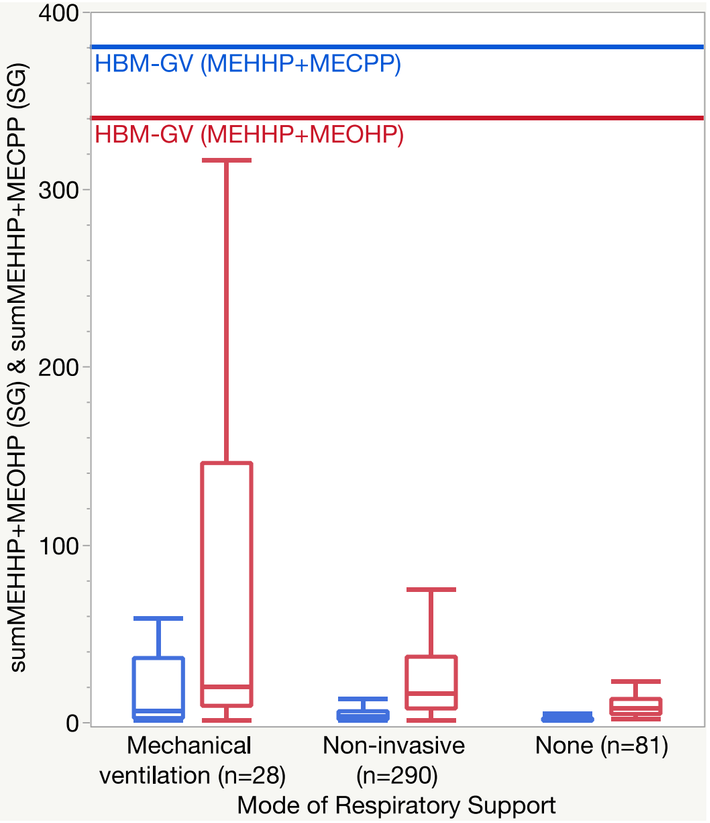
Use of blood products

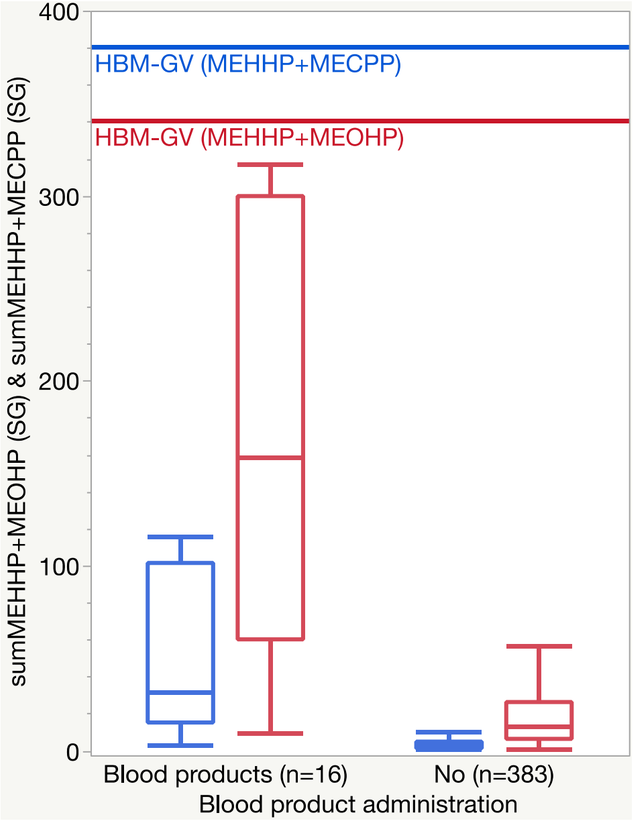


Wilcoxon Rank Sum Test

Sample collection | Sample preparation | Instrumental analysis | Data analysis | Statistical analysis

Risk Assessment - HBM-GV





Lange et al. 2021 → Human Biomonitoring Guidance Values (HBM-GV) (for DEHP)

CAVE: HBM-GV not appropriate < 6 years

- Lack of relevant toxicokinetic data
- General assumptions for urinary flow rates (0.02 L/kg/d for children)
- Only single substance risk assessment
- Used for exposure interpretation of a general population

Sample collection | Sample preparation | Instrumental analysis | Data analysis | Statistical analysis

Conclusions

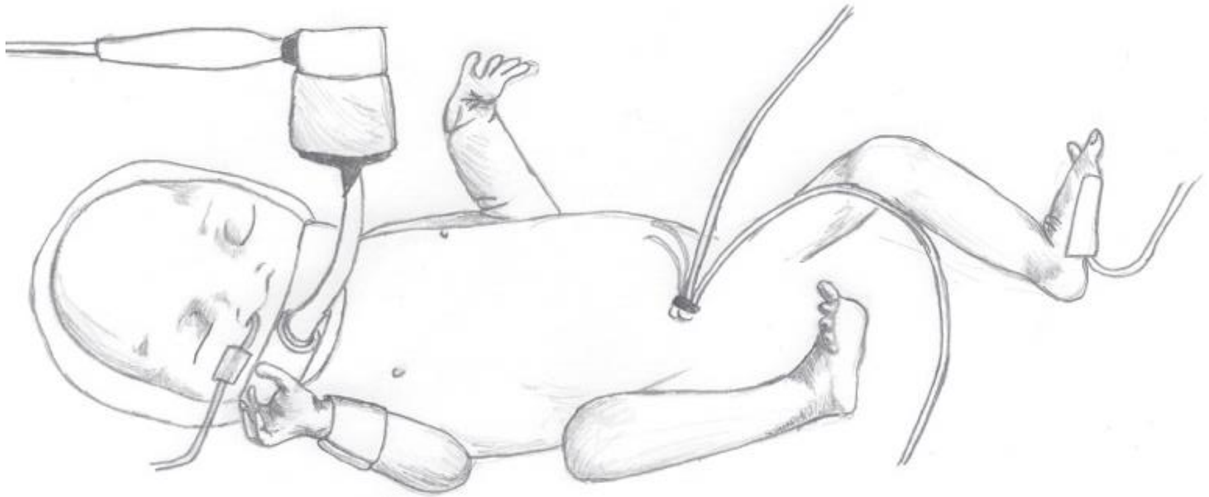
Plasticizer exposure NICU

- Positive evolution?
- Phthalates → alternative plasticizers

- Fragile population
  - (Invasive) respiratory support
  - **Blood products**

- Legislative changes
- Lack of toxicity data
- Health consequences?
  - Respiratory effects?
  - Neurobehavioural effect?

Follow-up to 1-4 years

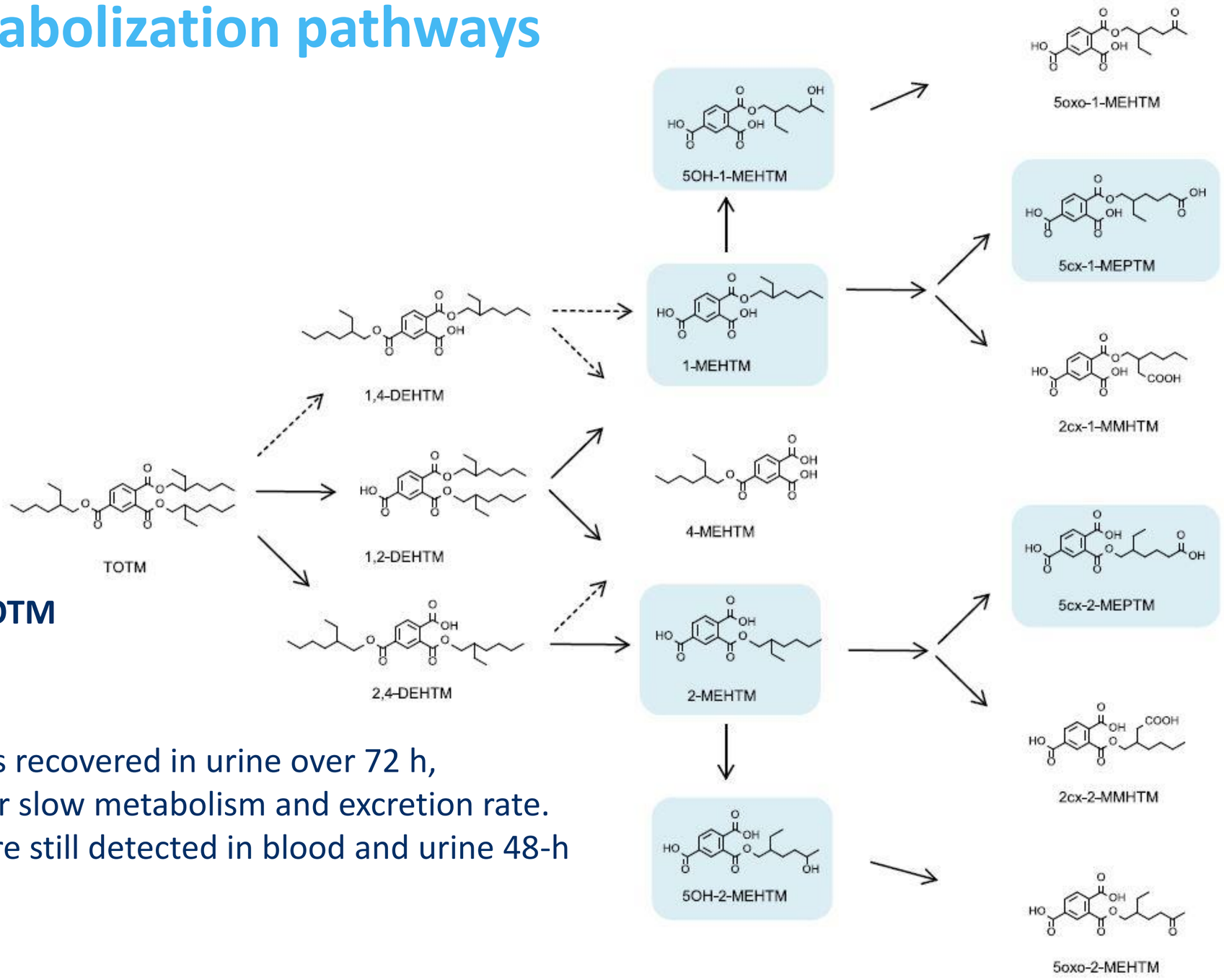


TOTM and ATBC metabolization pathways

ATBC

- 80% degradation after 1h in HLM
- Identification of metabolites not fully elucidated

TOTM



TOTM

~6% of the oral dose in humans was recovered in urine over 72 h,

- low resorption of TOTM and rather slow metabolism and excretion rate.
- TEHTM and some metabolites were still detected in blood and urine 48-h and 72-h post-exposure,

Intensive Care Unit

- Pediatric

- Adult

Phthalate and alternative plasticizers in pediatric ICU

Intensive Care Med
DOI 10.1007/s00134-015-4159-5

ORIGINAL

2015

S. Verstraete
I. Vanhorebeek
A. Covaci
F. Güiza
G. Malarvannan
P. G. Jorens
G. Van den Berghe

Circulating phthalates during critical illness in children are associated with long-term attention deficit: a study of a development and a validation cohort

Environment International 158 (2022) 106962

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

2021

Phasing out DEHP from plastic indwelling medical devices used for intensive care: Does it reduce the long-term attention deficit of critically ill children?

Ilse Vanhorebeek[a,*], Govindan Malarvannan[b], Fabian Güiza[a], Giulia Poma[b], Inge Derese[a], Pieter J. Wouters[a], Koen Joosten[c], Sascha Verbruggen[c], Philippe G. Jorens[d], Adrian Covaci[b], Greet Van den Berghe[a]

Journal of Hazardous Materials 363 (2019) 64–72

Contents lists available at ScienceDirect

Journal of Hazardous Materials

journal homepage: www.elsevier.com/locate/jhazmat

2019

Phthalate and alternative plasticizers in indwelling medical devices in pediatric intensive care units

Govindan Malarvannan[a,*], Matthias Onghena[a], Sören Verstraete[b], Esther van Puffelen[c], An Jacobs[b], Ilse Vanhorebeek[b], Sascha C.A.T. Verbruggen[c], Koen F.M. Joosten[c], Greet Van den Berghe[b], Philippe G. Jorens[d], Adrian Covaci[a,*]

Adult ICU

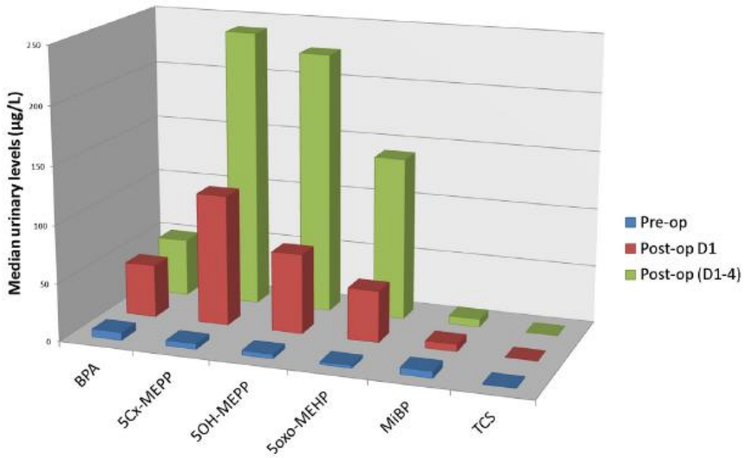


Fig. 1. Median urinary levels pre-operatively, postoperatively on day 1 (D), and pooled results of day 1 (D1)–day 4 (D4).

Environment International 81 (2015) 64–72

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

2015

Considerable exposure to the endocrine disrupting chemicals phthalates and bisphenol-A in intensive care unit (ICU) patients

Johan Huygh [a], Katrien Clotman [a], Govindan Malarvannan [b], Adrian Covaci [b], Tom Schepens [a], Walter Verbrugghe [a], Eveline Dirinck [c], Luc Van Gaal [c], Philippe G. Jorens [a,b,*]

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