PHTHALATES IN THE NICU

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In the Neonatal Intensive Care Unit: the preterm infants.

- **1/10 born** < 37 weeks, **15 million** babies each year
- Adverse outcome if **born < 32 weeks**

Cognitive impairment: **40%: x 2**

Motor impairment: **10-20%: x 10**

Behavior/Social impairment: **x 2-10**

Impact on neurodevelopment after preterm birth

Parents

Gestational age

Birthweight

Gender

Infections

Lung disease

Genetic

Pain

Developmental care

Sound/noise

Music/voice

Nutrition

Sleep

Environment

Neonatal Intensive Care Unit
NICU

Chemical presence:

Drugs
Cleaning solutions
Hand disinfection
Medical devices
Diapers
Nutrition

Neonatal Intensive Care Unit
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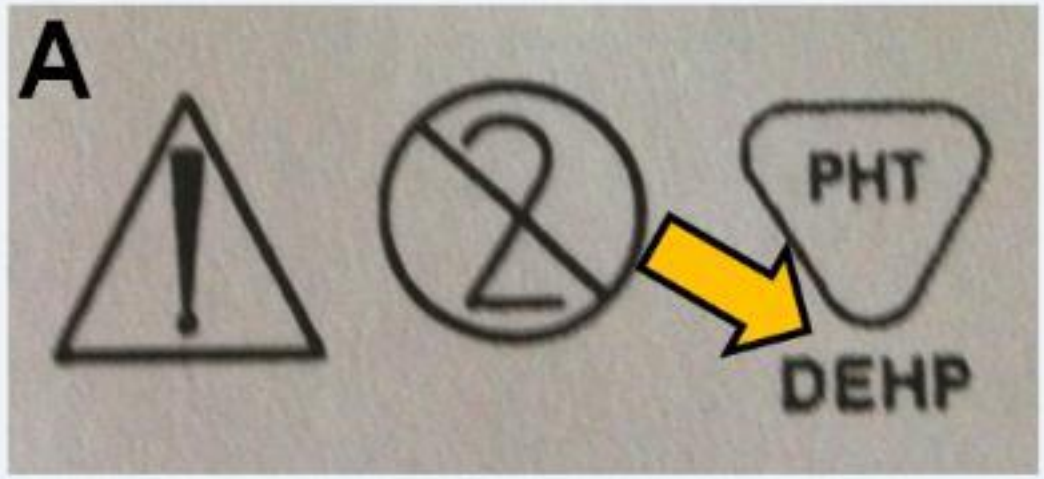
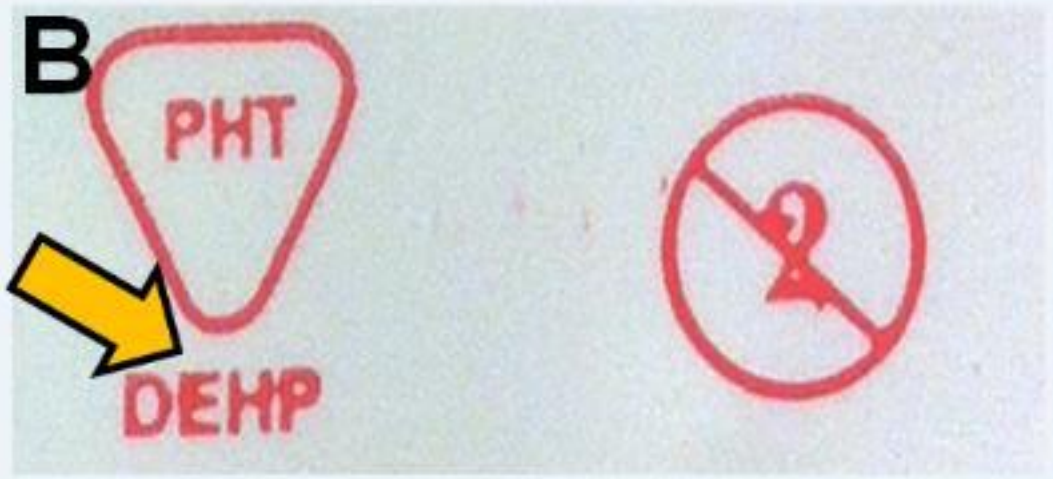
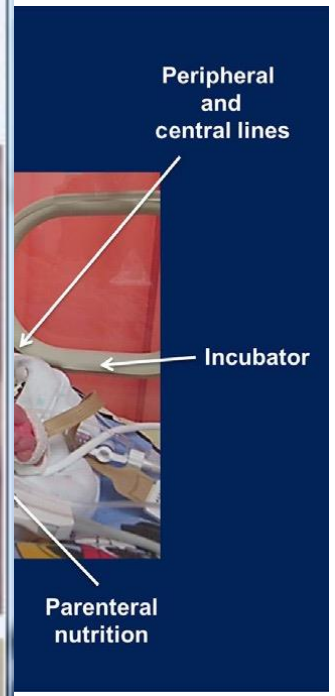

A
PHT
DEHP


B
PHT
DEHP

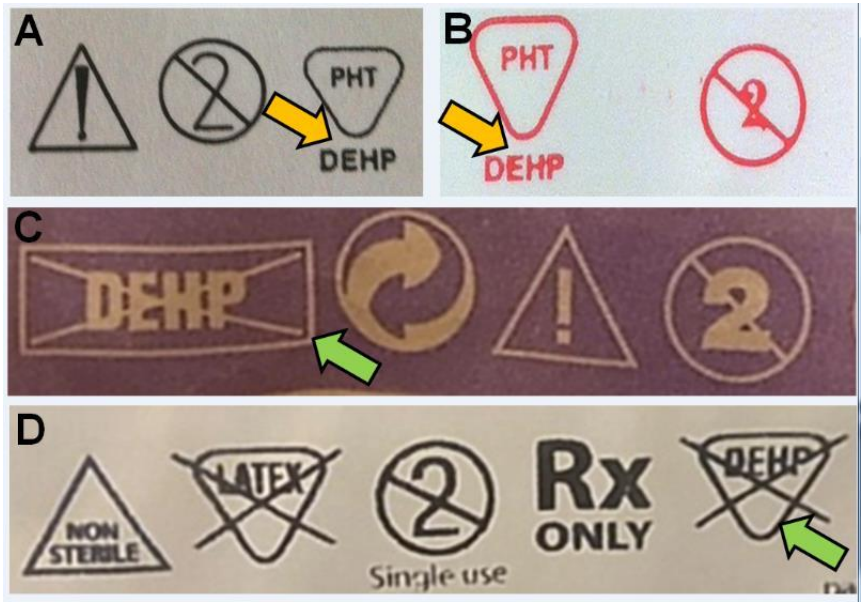

C
DEHP


D
NON STERILE
LATEX
Rx
ONLY
DEHP
Single use


Peripheral and central lines
Incubator
Parenteral nutrition

Phthalates in medical devices: the survey

- 2014-2017
- Systematic examination of all medical devices
- Contact with providers/industry



- Plasified devices (n=354):
  - **10% with DEHP**
  - **13% unknown**
- Mainly ventilation equipment

Fischer Fumeaux et al., Phthalate exposure in the neonatal intensive care unit, Arch. Ped 2014

Neonates and phthalates: what is known

- Publications
- **Doses:**
  - Leaching
  - Temperature, lipids
- **Procedures at risk**:
  - ECMO, transfusion
    - Long-term ventilation
- Crtically ill infant: up to 160’000 x the hepatotoxic limit , 4000x reproductive toxicity

Table 5. Estimated daily DEHP exposures for a critically ill 2-kg infant; hazard quotients calculated for each DEHP source using a reproductive ADI_{inf} of 0.0037 mg/kg per day, and liver toxicity ADI_{inf} of 0.0001 mg/kg per day.

Source	*Daily exposure, 2-kg infant[a] (mg/kg per day)*	*Hazard quotient (HQ)[b]*	
		Reproduction[c]	*Liver[d]*
Lipid emulsion	6.5	1757	65,000
PRBC	0.13[e]	40	1407
FFP	0.87[e]	235	8686
Platelets	0.18[e]	50	1840
Endotracheal tube	8.22[f]	2221	82,167
Feeding tube	0.33[g]	89	3300
Total	**16.3**	**4391**	**162,459**

Mallow EB et al, Journal of Perinatology **2014**

Neonates and phthalates: what is known

- **Animal models:** gestation, birthweight, behavior et…
- **Human epidemiology**
  - Prenatal exposure: association with
    - Gestational length
    - Birthweight
    - Endocrine disruption: males > females (Anogenital distance, spermatogenesis, endometriosis)
  - Postnatal exposure: possible association with
    - Bronchopulmonary dysplasia
    - Necrotising enterocolitis
    - Retinopathy of prematurity
    - Neurodevelopment?
  - Biological plausibility

Fischer et al, Phthalates in the NICU: Is it safe?, J. Paed. Child Health 2012

Phthalates, neonates and neurodevelopment

- Neurodevelopmental outcome after:
  - Preterm birth
  - Birth asphyxia
  - Antidepressant treatment
  - Migration
  - Congenital infections
  - …..

  - And phthalate exposure as well!

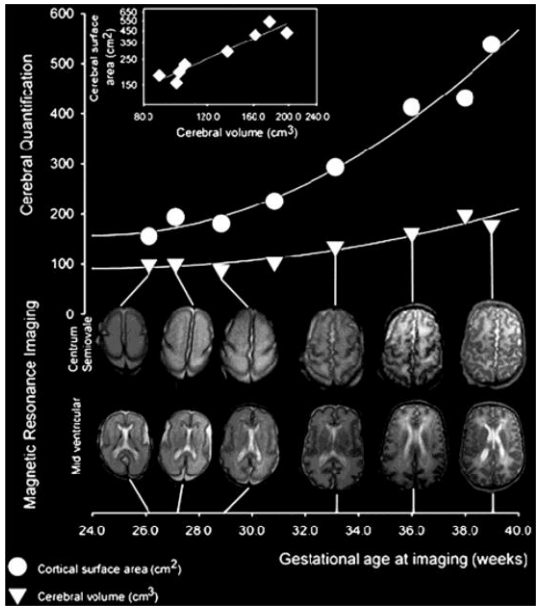
Increased risk of:
Autistic spectrum disorder
Hyperactivity +/- attention deficit

- Bias? Systematic error? Recruitment? Methodology?
- Administrative databases

Phthalates, neonates and neurodevelopment

- DOHAD: Developmental Origins of Health and Disease
- Brain: 400g-1.2 kg in 2 years
- Maturation
- Connections
- High lipid content
- Blood-brain barrier
- **Vulnerability**

- Biological plausibilty



Kugelman A. Pediatrics 2013

Phthalates, neonates and neurodevelopment

- Animal models:
  - cell damage, apoptosis
  - ↘ learning and spatial memory

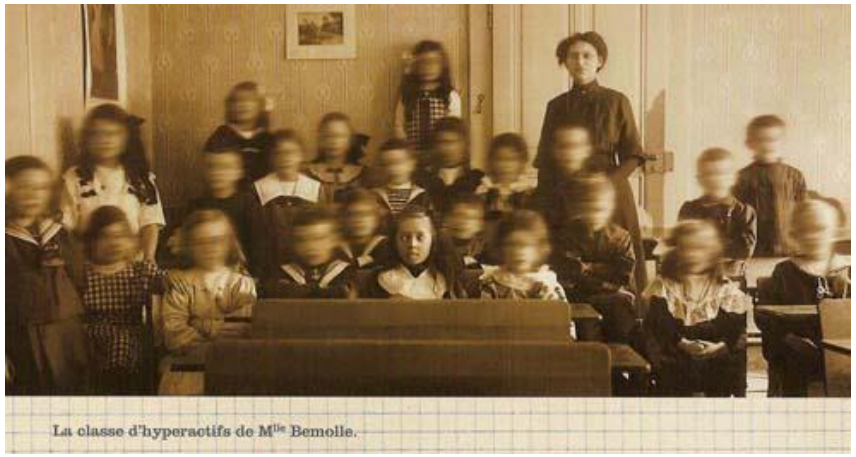
- Neonates
  - Term neonate possible association with maternal urinary
  - Preterm: *better* scores associated with infant urinary (???)

- Children:
  - Association between maternal urinary and cognition: conflicting results
  - Association between child urinary and cognition: possible negative association in prospective cohort

Stroustrup et al, NICU phthalate exposure and Infant neurobehavior, 2018

Phthalates, neonates and neurodevelopment

- Behavior/social
  - Clinical diagnoses
  - Questionnaires
- Possible association with child urinary
  - Conflicting results
- In summary:
  - Possible neurodetrimental effect
  - Mainly in boys
- Biological plausability
- Heterogeneity



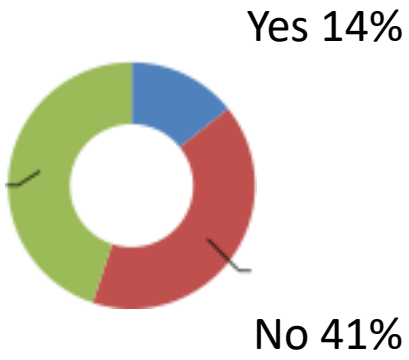
Bickle Graz et al, Phthalates and neurodevelopmental toxicity, 2015

Phthalates in the NICU: who knows?

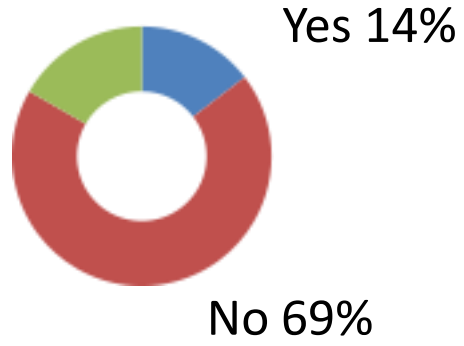
- Survey senior neonatologists level III NICU:
- France-Belgium-Switzerland
- Had heard about phthalates: 53%

MD + Phthalates?

Means to identify?

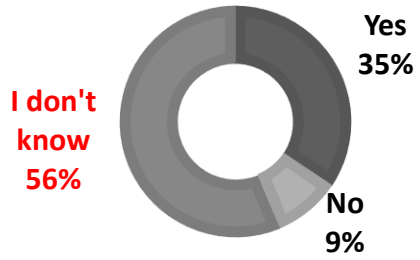


Limitation strategy

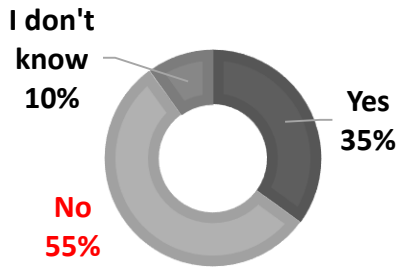


Doctors in Neonatology

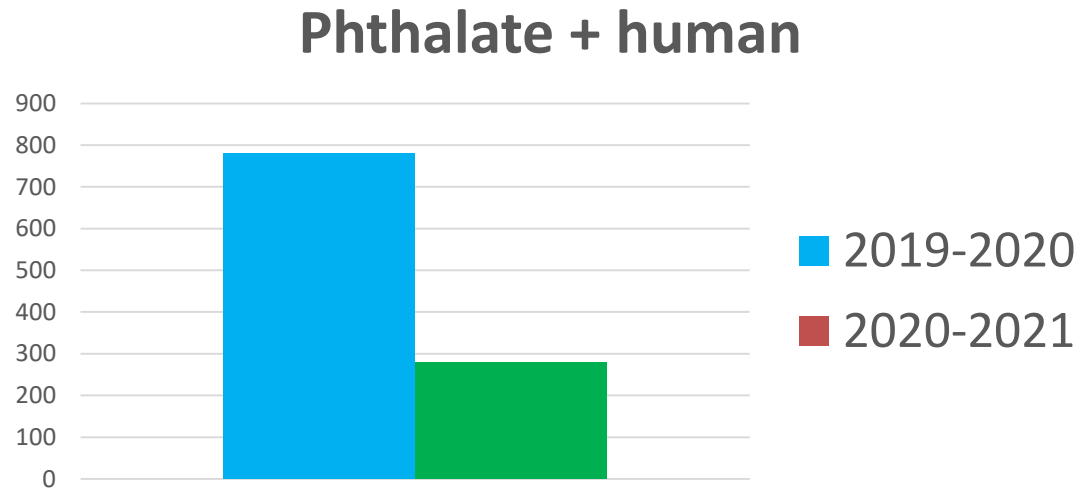
TO YOUR KNOWLEDGE, ARE THERE CURRENTLY MEDICAL DEVICES CONTAINING PHTHALATES IN YOUR UNIT?



FRANCE: ARE YOU AWARE OF THE LAW BANNING DEHP IN NEONATOLOGY FROM 1 JULY 2015?



Research ?



CoVID+ human 2020-2021: 69 000

Phthalates in the NICU: a survey. Bickle-Graz M, Tolsa J-F, Fischer Fumeaux CJ. Arch Dis Child Fetal Neonatal Ed 2020;**105**:F110– F111.

Take home

- Preterm/critically ill neonates: increased vulnerability :
  - Increased skin/bodyweight ratio
  - Immature metabolic pathways
  - Cocktail effect
- Long hospitalisation
- High doses, > toxicity levels
- Possible longterm effects
  - Neurodevelopment
  - Endocrine, lungs, eyes etc
- Neonatal specialists not aware

Questions:

Intensity of exposure and levels?

Intensity of exposure and outcome

Alternate and safe MD?

Biomonitoring with small volumes?

Let's do it!