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The link between DEHP exposure and neurocognitive outcome of critically ill children

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HCWH Europe, December 3, 2019

Critical illness in children

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Critical illness in children

Mechanical ventilation (endotracheal tube)

Renal replacement therapy

Cardiac assist device

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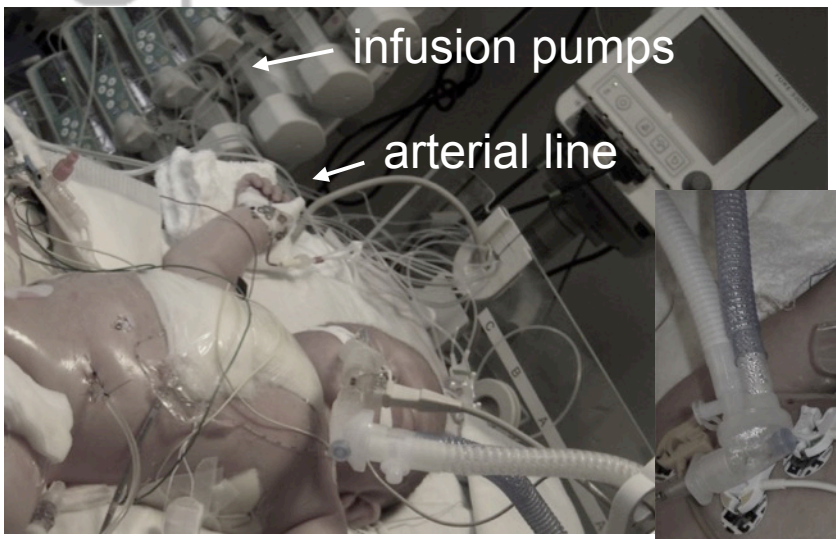
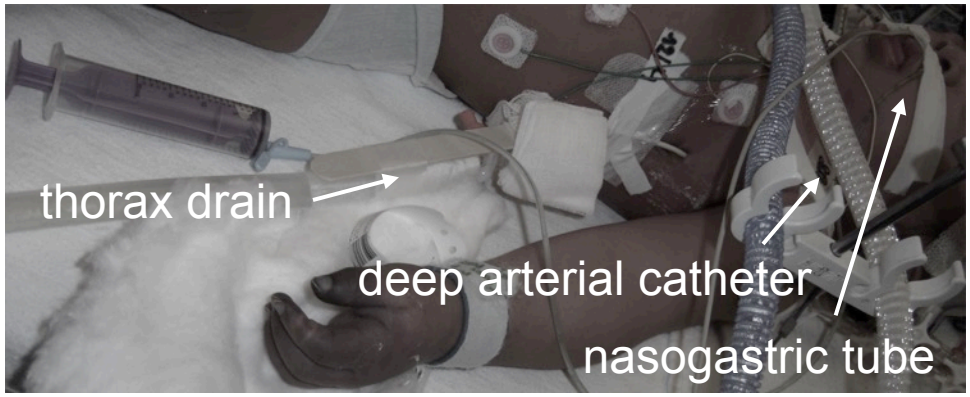
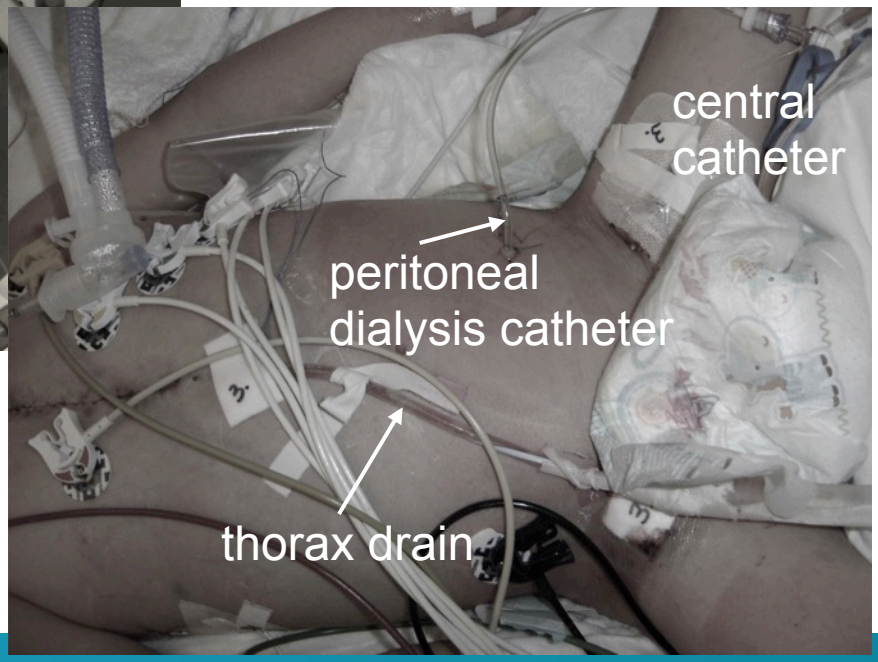
Critical illness in children

Intravenous nutrition







Critical illness in children

Major progress in intensive care medicine

SHORT-TERM

↑ Survival

↑ Recovery from the acute insult

LONG-TERM

Adverse consequences
years after hospital discharge …

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Developmental legacy of critical illness

Long-term impairment physical development

Long-term impairment neurocognitive development

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Mesotten et al. JAMA 2012
Verstraete et al. Lancet Resp Med 2019

Impaired neurocognitive development

- ⬇ Intelligence
- ⬇ Visual-motor integration
- ⬇ Attention
- ⬇ Motor coordination
- ⬇ Executive functions
- ⬇ Memory

- ⬆ Behavioral problems

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Mesotten et al. JAMA 2012
Verstraete et al. Lancet Resp Med 2019

Impaired neurocognitive development

- Intelligence
- Visual-motor integrati
- Attention
- Motor coord
- Execu
- M
- Behavioral problems

How can this legacy be explained?
Is this legacy modifiable?

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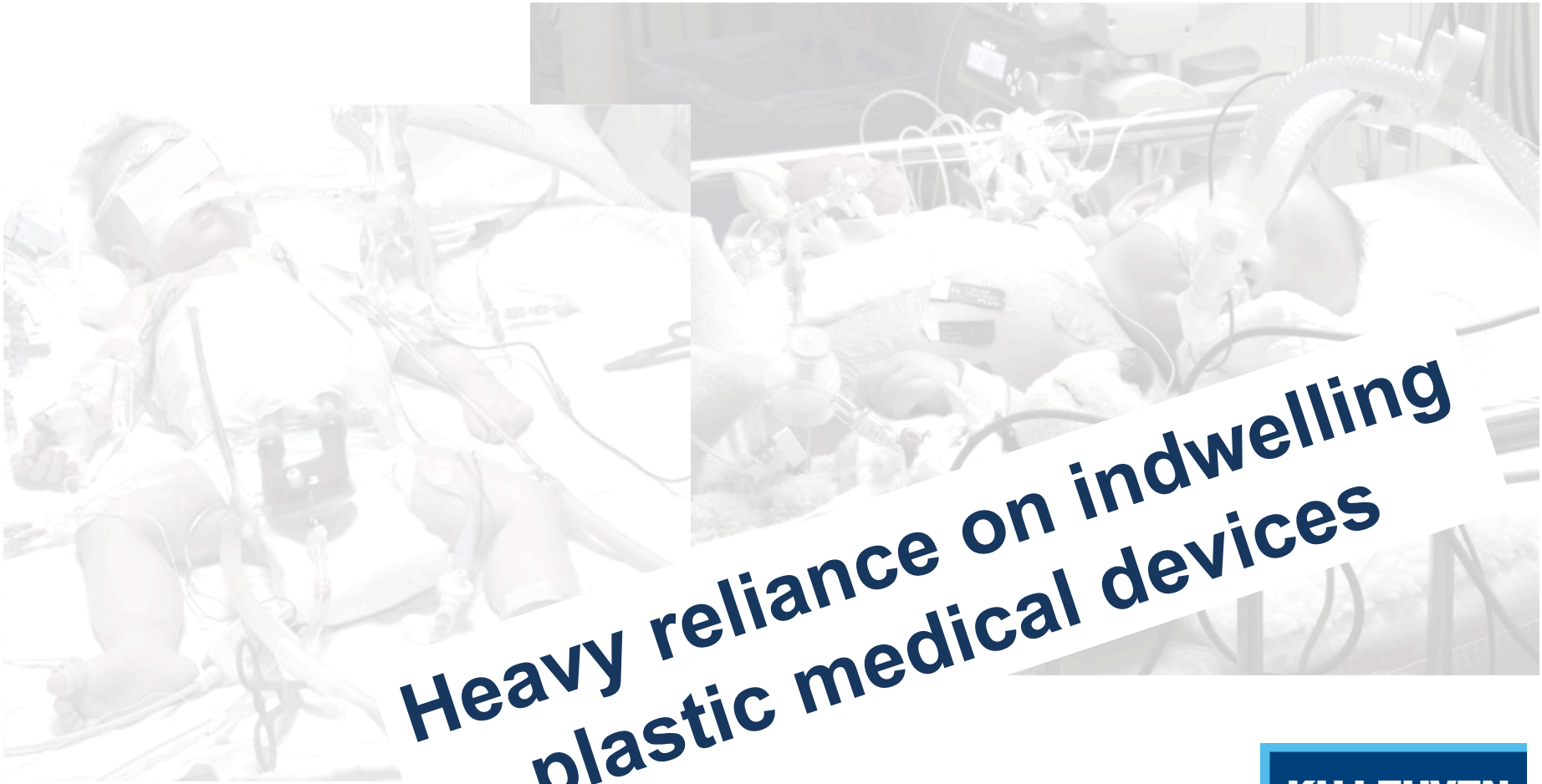
Mesotten et al. JAMA 2012
Verstraete et al. Lancet Resp Med 2019

Intensive care and plastic medical devices



Heavy reliance on indwelling plastic medical devices

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Softening indwelling plastic medical devices

- Plastic indwelling medical devices:

  - made smaller for use in small children
  - plastic made more soft and pliable with phthalates

- Phthalates

  - not chemically bound to the devices
  - gradually leach during use

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Chiellini et al. Int J Pharm 2011
Kastner et al. Sci Total Environ 2012

Di(2-ethylhexyl)phthalate (DEHP)

- One of the most widespread phthalates

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Concerns about potential toxicity of DEHP

- Chronic environmental exposure to DEHP
  - may compromise fertility
  - may compromise neurocognitive development
    - *in vitro* studies
    - studies in animal models
    - observational studies in humans

      ➡ increased prevalence of **ATTENTION DEFICIT** disorders in young children

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Chen et al. Toxicol Lett 2011; Tanida et al. Toxicol Lett 2009; Cho et al. Environ Health Persp 2010
Kim et al. Biol Psychiatry 2009; Chopra et al. Environ Res 2014; Park et al. Psychol Med 2015; Ku et al. Sci Total Environ 2020 …

Di(2-ethylhexyl)phthalate (DEHP)

- Prohibited in cosmetics

- Prohibited in materials in contact with food

- Banned from children's toys

- Still used to soften plastic medical devices!!!
  - significant exposure with long-term hemodialysis
  - long-term blood transfusions

Concerns about potential toxicity of DEHP

- Premature neonates
  - High urinary levels of DEHP metabolites
  - Inferred to originate from indwelling medical devices
- Adult critically ill patients
  - High urinary and serum levels of DEHP metabolites
  - Very high in patients on CVVH or ECMO

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Green et al. Environ Health Perspect 2005; Weuve et al. Environ Health Perspect 2006;
Frederiksen et al. Environ Health Perspect 2014; Huygh et al. Environ Int 2015

Hypothesis

High circulating DEHP metabolite levels are present in critically ill children treated in the PICU, contributing to the attention deficit and possibly other aspects of the long-term neurocognitive legacy

Leaching of DEHP from indwelling devices

Intravascular

Intravenous, central: catheters and accessories
Intravenous, peripheral: catheters and accessories
Arterial catheters and accessories
Blood transfusion sets and accessories
Parenteral nutrition

Extravascular

Endotracheal tubes
Gastric tubes
Chest tubes and accessories
Bladder catheters

All leached DEHP !

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Verstraete et al. Intensive Care Med 2016

Study participants

Neurocognitive Development of Children 4 Years After Critical Illness and Treatment With Tight Glucose Control

A Randomized Controlled Trial

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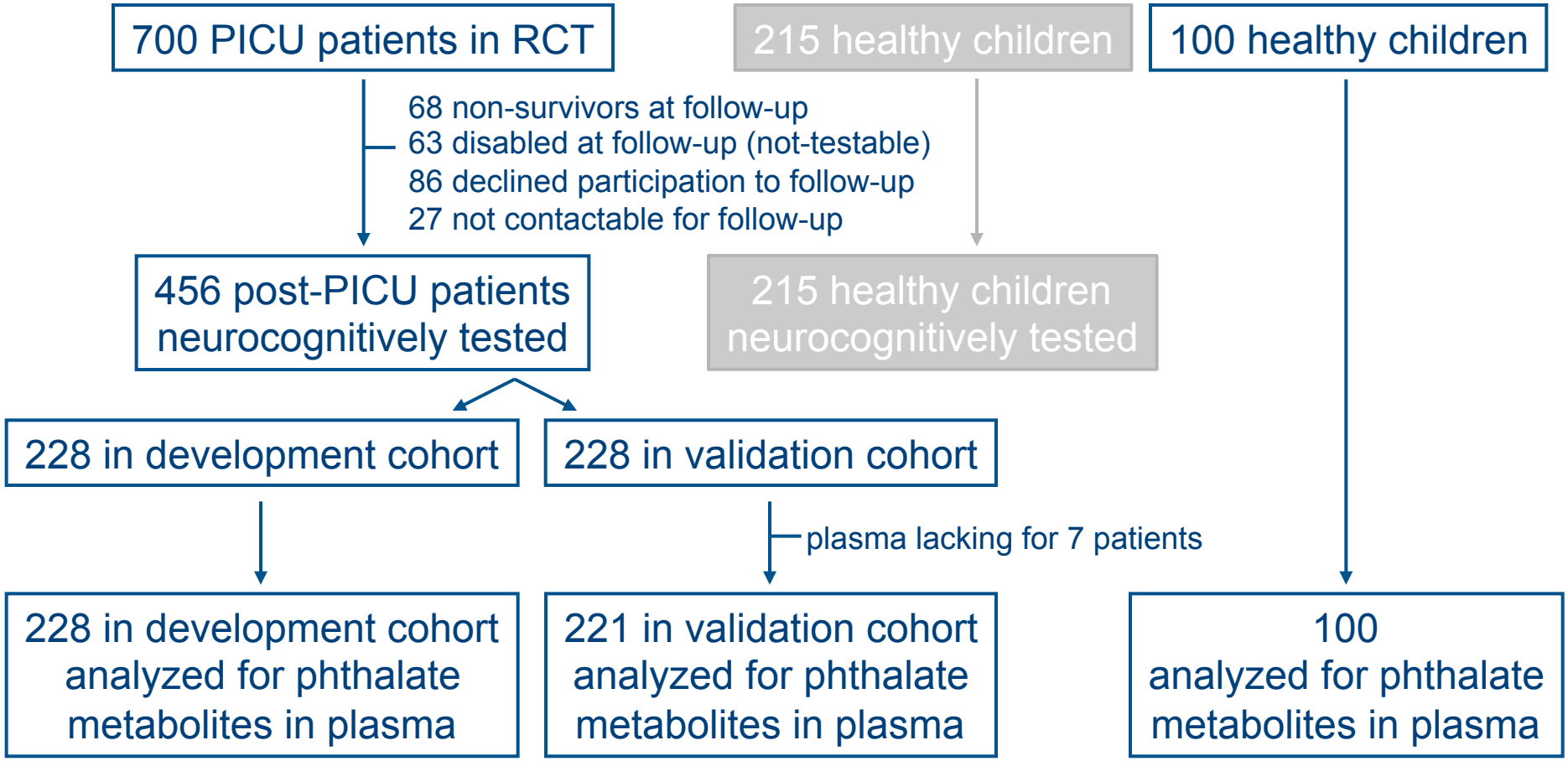
Study participants



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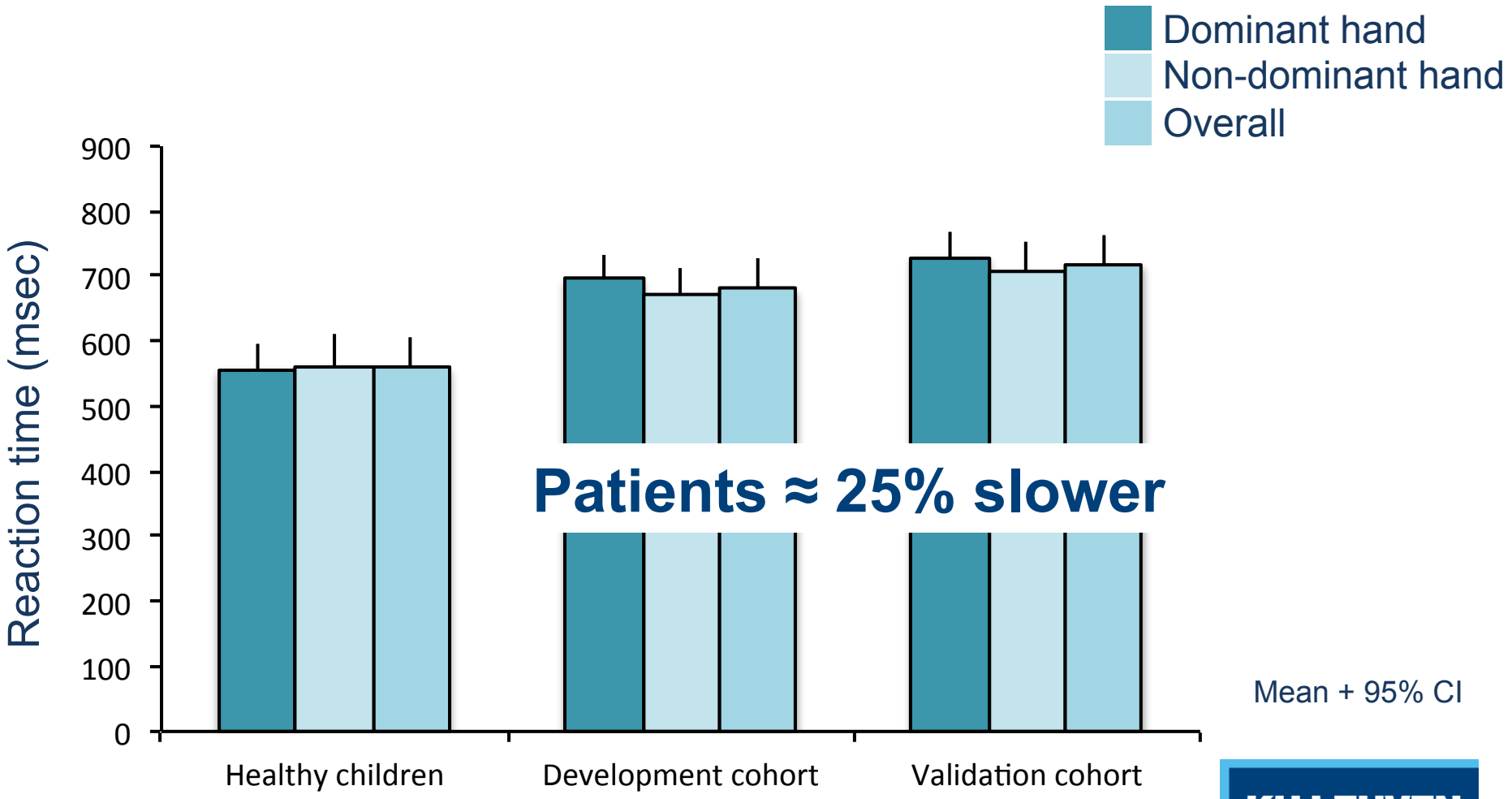
Attention deficit in critically ill children



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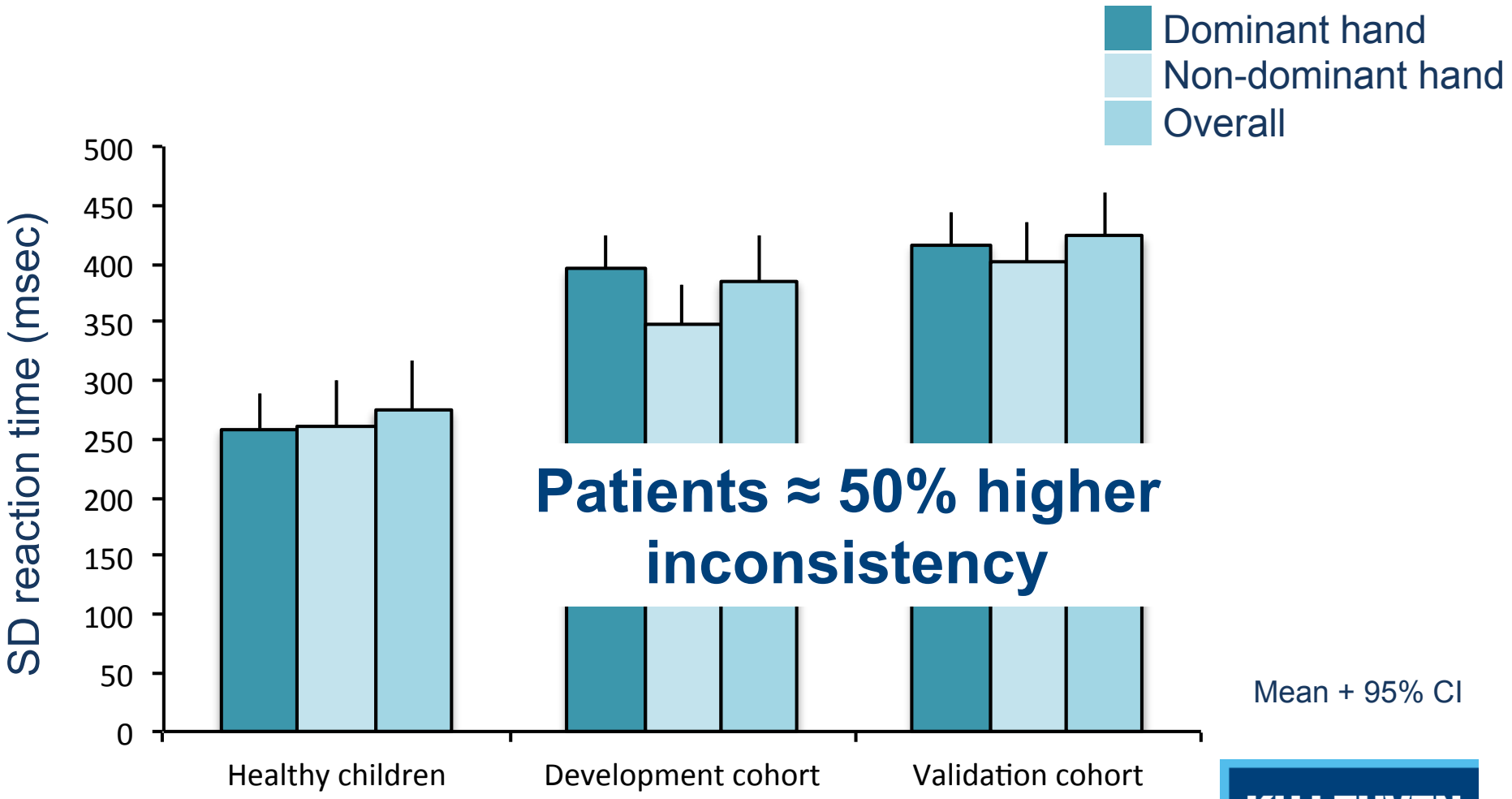
Verstraete et al. Intensive Care Med 2016

Attention deficit in critically ill children



DEHP exposure of critically ill children

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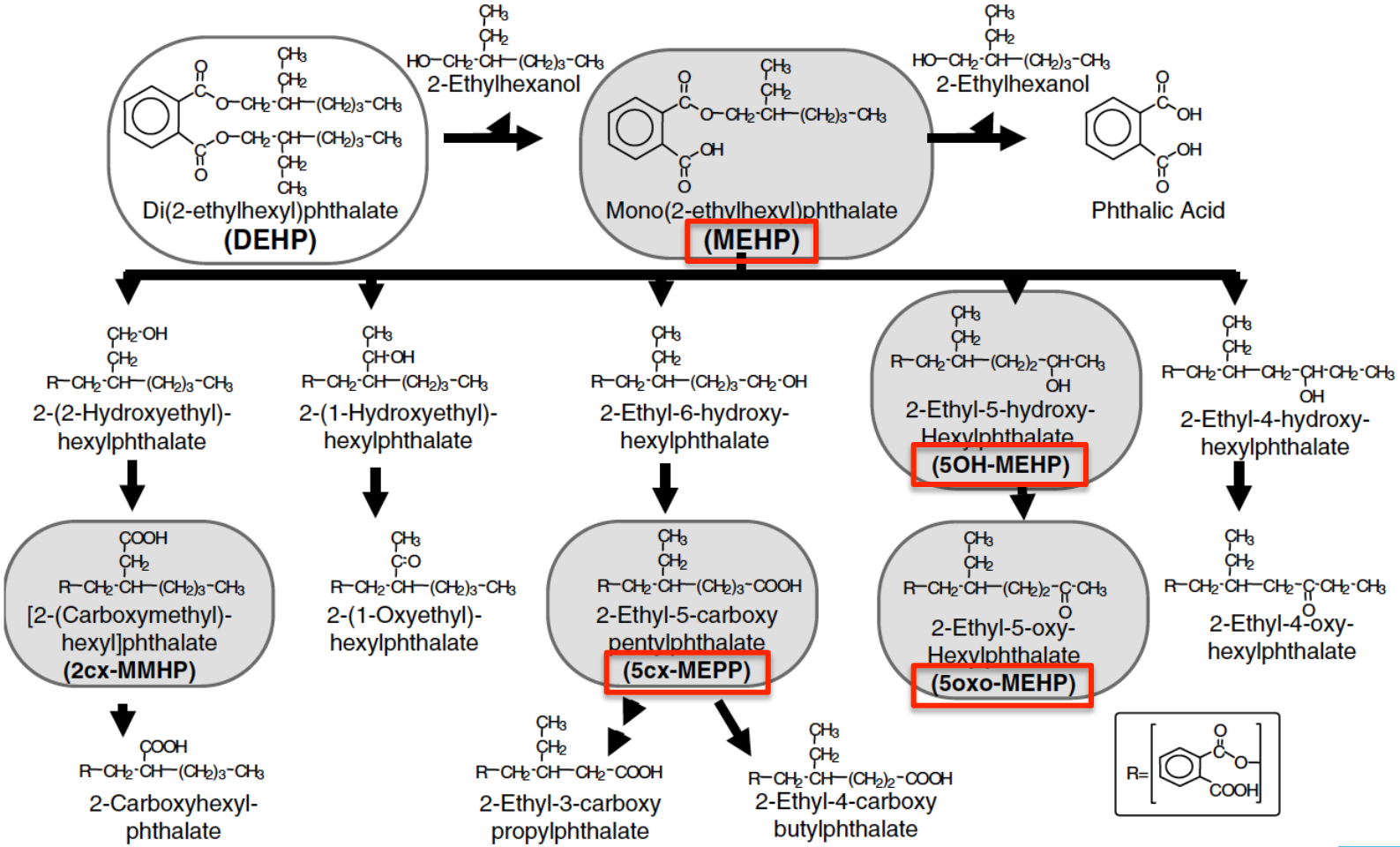
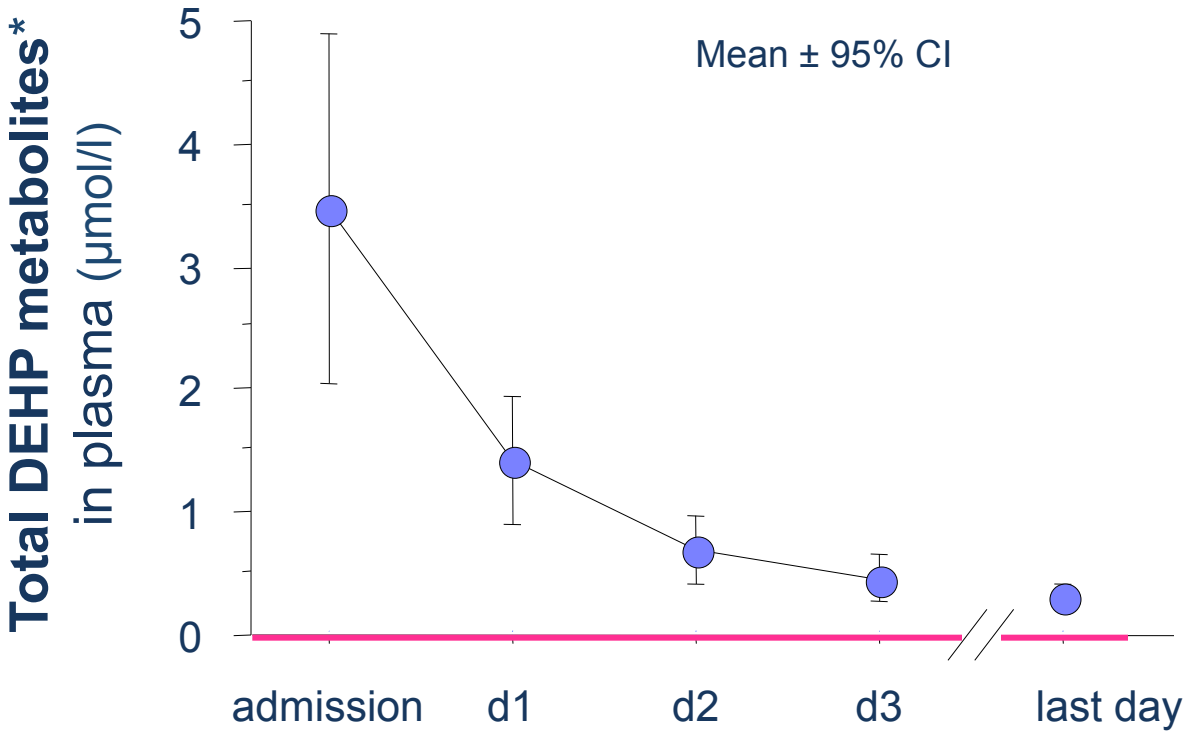
DEHP metabolism



Koch et al. Int J Androl 2006

DEHP metabolites in critically ill children



* [MEHP] + [5cx-MEPP] + [5OH-MEHP] + [5oxo-MEHP]

Critically ill children

Healthy children

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DEHP exposure and outcome of critically ill children

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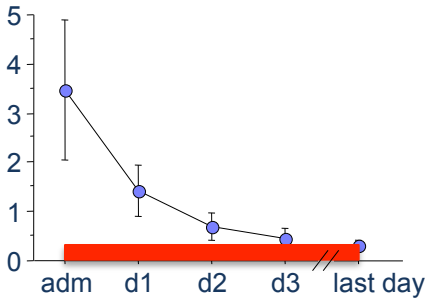
Measure of DEHP metabolite exposure

[circulating DEHP metabolites]
to which the brain is exposed

duration of exposure

eventual long-term
neurocognitive harm



"minimal" **phthalate exposure**
=
last day [phthalate] x PICU stay

Total DEHP metabolites
Total MEHP metabolites
MEHP
5cx-MEPP
5OH-MEHP
5oxo-MEHP

Development cohort

Multivariable regression analyses
400 bootstrap resamplings (stability)

Threshold for potential neurocognitive harm

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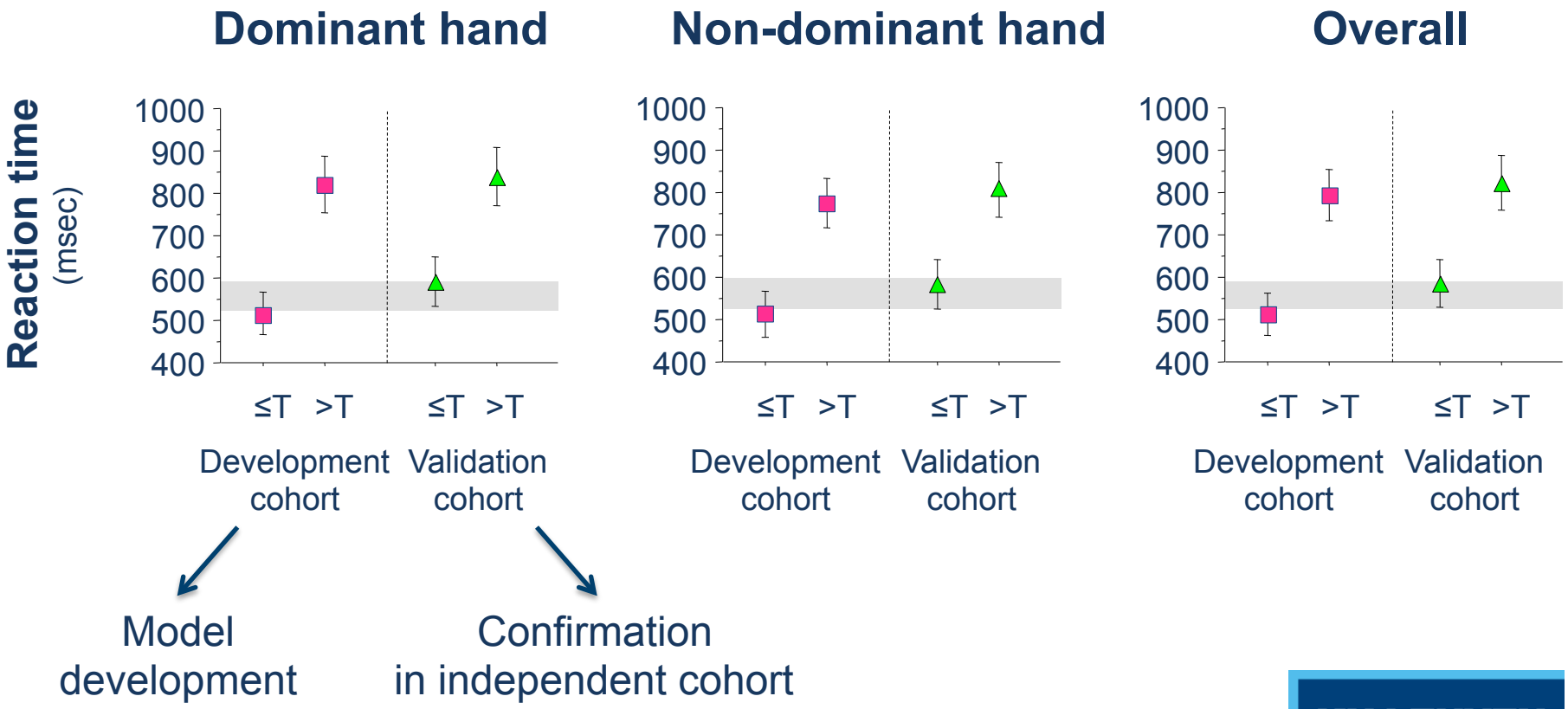
Threshold total DEHP metabolites and attention

Univariable analysis

Mean ± 95% CI



Verstraete et al. Intensive Care Med 2016

T : threshold

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Total DEHP metabolite exposure and attention deficit

Independent impact of **exceeding potentially toxic threshold**

Multivariable regression analysis *

	Development cohort		Validation cohort		
	Estimate	% of deficit	Estimate	% of deficit	Average %
Reaction time RT (msec)					
dominant hand	79.37	**57**	61.47	**36**	**46**
non-dominant hand	70.51	**65**	50.89	**35**	**50**
overall	74.37	**62**	57.59	**36**	**49**

Approximately half of the attention deficit statistically explained by exceeding the threshold of DEHP exposure

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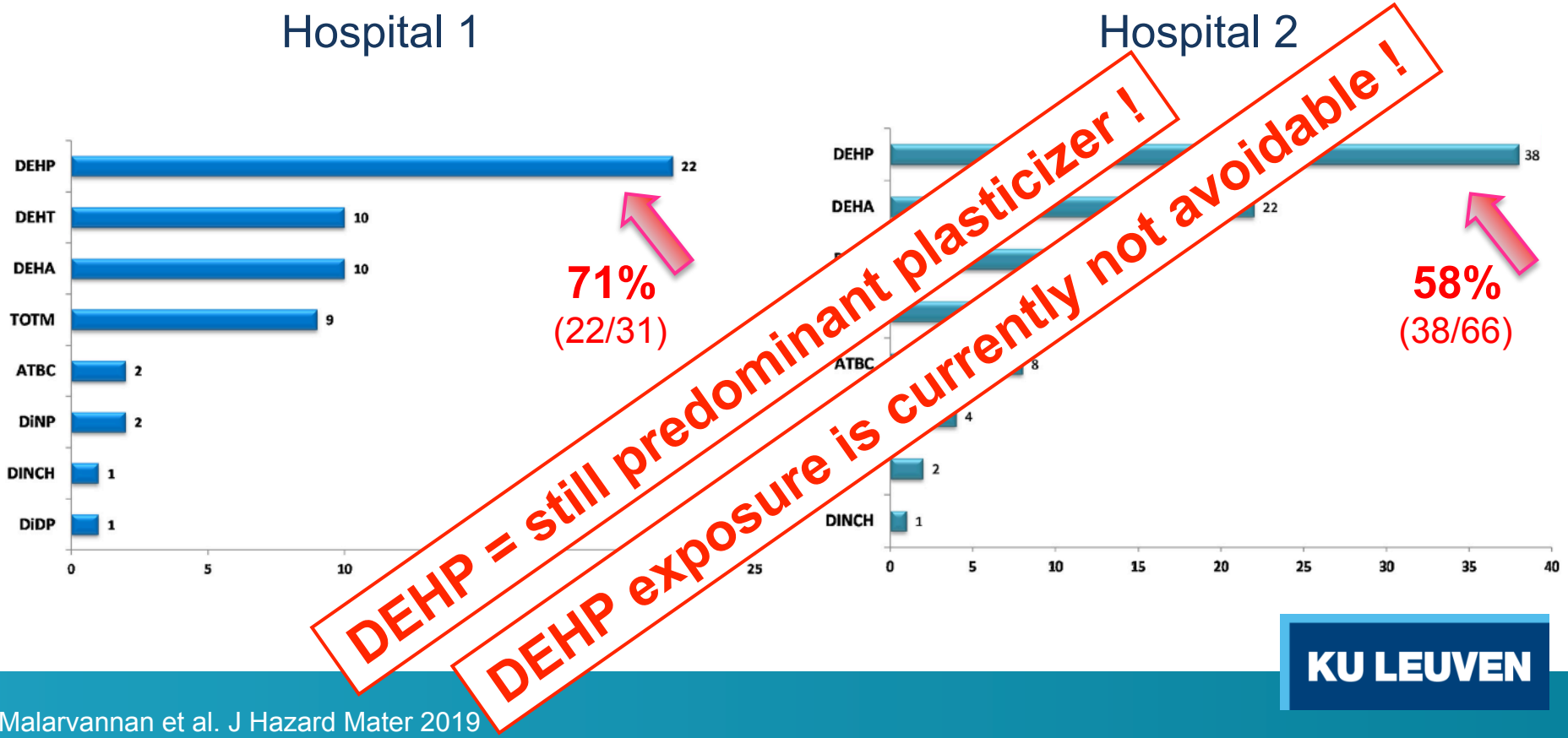
Verstraete et al. Intensive Care Med 2016

* Adjusted for baseline risk factors, duration of intensive care, surgery characteristics, clinical complications and treatments during ICU stay

Is DEHP exposure avoidable?

Plasticizers present in indwelling medical devices and essential accessories commonly used in the PICU of two academic hospitals



Malarvannan et al. J Hazard Mater 2019

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Conclusions

- Iatrogenic exposure to DEHP metabolites during intensive care was independently and robustly associated with the important attention deficit observed in children 4 years after critical illness
- Approximately half of the attention deficit was statistically explained by exceeding a certain threshold of DEHP exposure
- Whenever possible, medical devices with low DEHP release potential should be used
- A large proportion of indwelling medical devices still contains DEHP and hence, exposure to DEHP and its metabolites is currently unavoidable

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