EDITORIAL

Dealing with phthalates in medical devices: a case of *primum non nocere* (first do no harm)?

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Introduction

Is it possible that we are, inadvertently, harming the long-term health and development of patients receiving intensive care unit (ICU) therapy in infancy? How would we know? What constitutes evidence of harm? What experiment would convince practitioners, toxicologists and public health experts? Would we be able to change some aspect of our practice to prevent such harm?

In a recent article in *Intensive Care Medicine*, Verstraete et al. [1] report an association between “Iatrogenic exposure to circulating phthalates during treatment in intensive care and attention deficit observed 4 years after pediatric critical illness” in 449 previous recruits to a randomized controlled trial [2]. These results have the potential to become a major focus of controversy and alarm. To better understand how intensivists are to use this information in ICU practice, in this editorial we consider the following: (1) our current understanding of potential phthalate toxicity; (2) the history of research underpinning the study of Verstraete et al. [1] and its characteristics; (3) current regulations on di(2-ethylhexyl)phthalate (DEHP) in medical devices.

Phthalate exposure

Phthalates are chemical plasticizers used in the production of soft plastics, such as polyvinyl chloride (PVC). DEHP is used to make PVC softer and more pliable and to extend its lifetime. In laboratory animal toxicity studies, certain phthalates, such as DEHP, can act as carcinogens and can also cause fetal death, malformations and

reproductive toxicity—although these effects are seen only at levels far in excess of normal human exposure.

In humans, most exposure to DEHP comes from oral intake in our diet [3, 4], which has been estimated to range from 1 to 30 µg/kg body weight/day (µg/kg/day); for infants and children, the 95th percentile is approximately 6–17 µg/kg/day (see: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_047.pdf). The tolerable daily intake (TDI) for DEHP is approximately 48 µg/kg/day based on the no observed adverse effect level (NOAEL) of 4.8 mg/kg/day for reproductive toxicity in rats that incorporates a safety factor of 100. Phthalates such as DEHP are regulated by legislation; for example, the European Parliament prohibits the use of certain categories of phthalates, including DEHP, in toys and childcare articles intended for children aged <3 years (<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV:l32033>).

DEHP is present in plastics used in medical devices, especially in bags and infusion tubing for intravenous solutions and feeding. In adults, DEHP exposure resulting from blood transfusion can reach up to approximately 10,000 µg/kg/day in trauma patients and in those undergoing extracorporeal membrane oxygenation (ECMO). Premature babies on the ICU can be exposed to DEHP at levels similar to the NOAEL (4.8 mg/kg/day) for reproductive toxicity. Neonatal ECMO may result in DEHP exposure totaling 35,000 µg/kg over 10 days (approx. 3500 µg/kg/day) [5].

The study cohort

In 2009, Vlasselaers et al. [2] reported results from a prospective, randomized controlled study of intensive insulin therapy for targeting age-adjusted normoglycemia in critically ill infants/children, and its effect on short-term

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outcome. A total of 700 critically ill patients were enrolled in this study, of whom 45 % were aged <1 year. Among these children, 74 % underwent cardiac surgery for congenital heart disease and a further 11 % underwent complicated or high-risk surgery or trauma. Forty-two percent received parenteral nutrition, and the median ICU length-of-stay was 3 days. In 2012, Mesotten et al. [6] reported the neurocognitive developmental follow-up of 456 subjects (65 %) from the original cohort [1]. These children had on average a 15-point reduction in intelligence quotient 4 years post-ICU treatment [6, 7]. Findings for the Amsterdam Neuropsychological Tasks System (a measure of attention, motor coordination and executive function) were also abnormal. In this recent study of Verstraete et al. [1], neurocognitive outcome was assessed in 449 children (64 % of the 700 critically ill patients recruited to the original study) in relation to the plasma DEHP concentration during the original period of critical illness [2]; 89 % of the children included in this 2016 study had undergone cardiac or other surgery or treatment for trauma. Therefore, follow-up analyses [1, 6] involved predominantly post-surgical cases (approx. 89 %), with approximately 50 % of the patients aged <1 year at enrollment.

Before the relationship between DEHP exposure and subsequent neurocognitive outcome can be considered, readers need to be aware of inherent confounding—i.e. the reasons an infant needs ICU care are inherently likely to result in cognitive impairment of the sort present described herein (Table 1) [8–10]. Thus, multiple, interrelated factors are associated with neurocognitive outcomes in the post-ICU population with congenital heart disease. The question which needs to be carefully

considered is whether phthalates should be added to this list, or is the “harmful” association with DEHP exposure reported by Verstraete et al. [1] related to factors such as duration of cardiopulmonary bypass and ICU length-of-stay and, consequently, the need for repeated exposure to blood transfusion and blood product bags, or to parenteral nutrition. Furthermore, the method used by these authors to compile their data on DEHP exposure, namely, the product of the plasma concentration on the last day of ICU admission and the ICU length-of-stay [1], means it cannot be related to the TDI and NOAEL for DEHP.

Regulation of DEHP in medical devices

In 2015 the European Commission adopted an updated report (http://ec.europa.eu/health/scientific_committees/emerging/docs/scenih_r_o_047.pdf), which concluded that there is insufficient evidence to suggest that DEHP-containing medical devices constitute a health risk to patients, whilst recognizing that the use of such devices (essential for survival in ICU) may result in high DEHP exposure. Consequently, the report recommends that materials with low DEHP release potential should be used whenever possible and that replacement of DEHP with other materials should be considered, once lack of toxicity and safety are proven.

Toxicology, pediatric critical care practice and *primum non nocere*

Phthalate (mainly DEHP) exposure has been associated with impairment of neurobehavioral development in infants and children in epidemiological studies over the last 6 years, with a focus mainly on attention deficit

Table 1 Perioperative factors associated with adverse neurodevelopmental outcome in infants undergoing cardiac surgery

Factors associated with neurocognitive outcomes in the post-ICU population with congenital heart disease		
Patient	Surgical and anesthetic	Postoperative
Race	Sedative/analgesic selection	Low regional cerebral oxygen saturation
Sex	Prolonged deep hypothermic circulatory arrest	Inotrope score
Birth weight	Duration of aortic cross-clamping	Use of extracorporeal membrane oxygenation (ECMO)
Gestational age	Duration of surgery	Cardiac arrest
Chromosomal anomalies	Cumulative exposure to volatile anesthetics in the first year	Erythropoietin administration
Apolipoprotein E (APOE) genotype (ε2 allele)	Cumulative exposure to opioids in the first year	Care protocols
Structural brain immaturity	Cumulative exposure to benzodiazepines in the first year	Total length of stay in the intensive care unit (ICU)
Specific type of congenital heart disease lesion		Early oral feeding
Maternal education and intelligence		Number of days receiving chloral hydrate
		Cumulative dose of benzodiazepines
		Rehabilitation

hyperactivity disorders [11–15]; the DEHP exposure in such studies was orders of magnitude lower than those encountered in ICU. Readers should keep in mind that DEHP exposure in non-ICU children derives mainly from diet, raising the possibility of confounding with dietary factors.

The report by Verstraete et al. [1] is the first of its kind in pediatric critical care. The results reported by these authors may lend support to the notion that there is a developmental vulnerability or critical period for exposure to DEHP, with neurocognitive deficit more likely to be associated with younger, critically ill children. However, the subject of the study also impinges on another expanding field of literature, the developmental neurotoxic effects of anesthetic agents [16–18]. Almost 90 % of the population studied by Verstraete et al. [1] received general anesthesia, making it impossible to disentangle neurocognitive associations with DEHP exposure from those associated with cumulative exposure to volatile anesthetics and benzodiazepines [8].

Returning to the question posed at the start of this editorial—it is possible that healthcare providers involved in primary care in the ICU may, inadvertently, harm the long-term health and development of patients receiving ICU therapy in infancy. However, whether such harm is due to exposure to DEHP, to volatile anesthetics or to unmeasured factors, or indeed to an interaction between the multiplicity of known perturbations to homeostasis in a vulnerable, genetically predetermined population, it is not possible to say. We need more studies like the one performed by Verstraete et al. [1] in which large populations of infants and children are followed-up post-ICU. We also need to shift focus. If DEHP is banned in the manufacture of toys, why do we use it in medical devices for children? Is it beneficial and do these benefits outweigh potential risks? If it is not beneficial, then we should consider it an unwanted substance, providing we have alternative non-toxic plasticizers with which to replace it. Of course, these questions raise the issue of whether we have sufficient safety/toxicity data on any replacements, which will also need large population-based studies of the type available in the report by Verstraete et al. [1].

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