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CIRCULATING PHTHALATES DURING CRITICAL ILLNESS IN CHILDREN ARE ASSOCIATED WITH LONG-TERM ATTENTION-DEFICIT

A study of a development and a validation cohort

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Short running title: Plastic softeners and neurocognitive outcome of critically ill children

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Abstract

Purpose Environmental phthalate exposure has been associated with attention-deficit disorders in children. We hypothesized that in children treated in the pediatric intensive care unit (PICU), circulating phthalates leaching from indwelling medical devices contribute to their long-term attention-deficit.

Methods Circulating plasma concentrations of di(2-ethylhexyl)phthalate (DEHP) metabolites were quantified in 100 healthy children and 449 children who had been treated in PICU and were neurocognitively tested 4 years later. In a development patient cohort (N=228), a multivariable bootstrap study identified stable thresholds of exposure to circulating DEHP metabolites above which there was an independent association with worse neurocognitive outcome. Subsequently, in a second patient cohort (N=221), the observed independent associations were validated.

Results Plasma concentrations of DEHP metabolites, that were virtually undetectable [0.029(0.027-0.031) $\mu\text{mol/l}$] in healthy children, were 4.41(3.76-5.06) $\mu\text{mol/l}$ in critically ill children upon PICU admission ($P<0.001$). Plasma DEHP metabolite concentrations decreased rapidly but remained 18-times elevated until PICU discharge ($P<0.001$). After adjusting for baseline risk factors and duration of PICU stay, and further for PICU complications and treatments, exceeding the potentially harmful threshold for exposure to circulating DEHP metabolites was independently associated with the attention-deficit (all $P\leq 0.008$) and impaired motor coordination (all $P\leq 0.02$). The association with the attention-deficit was confirmed in the validation cohort (all $P\leq 0.01$). This phthalate exposure effect explained half of the attention-deficit in post-PICU patients.

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.

Trial registration [clinicaltrials.gov Identifier NCT00214916](https://clinicaltrials.gov/Identifier/NCT00214916)

Key words: PICU, critical illness, sepsis, phthalate, attention, neurocognitive development, plasticizers

Take-home message: Critically ill children have very high circulating levels of phthalate metabolites, explained by leaching indwelling medical devices, and these high levels are independently associated with the important attention-deficit observed 4 years later.

140-character Tweet: Exposure to plastic softeners released from indwelling medical devices is associated with long-term attention-deficit in children

Introduction

Children who have been critically ill at young age suffer from a substantial neurocognitive deficit when assessed years after admission to the pediatric intensive care unit (PICU) [1-5]. This neurocognitive legacy comprises, besides lower scores for intelligence, visual-motor integration, memory and behavior, also an important deficit in executive functions, motor coordination and attention [1]. The degree of this impairment is not negligible as for example the intelligence deficit is 15 IQ points and the attention-deficit is about 40% larger than that reported for children with attention-deficit disorders [1, 6]. Until recently, this neurocognitive legacy was considered the consequence of the illness and thus not modifiable. However, recent studies support the notion that it can be, at least partially, diminished by altering medical care. For example, changing the surgical technique for correcting congenital heart defects and preventing hyperglycemia during intensive care have shown to reduce the neurocognitive impairment [1, 7, 8]. Nevertheless, the neurocognitive legacy of critical illness in children is likely multifactorial [9].

Intensive medical care relies heavily on indwelling medical devices, made smaller for use in children and made soft and pliable by incorporating chemical plastic softeners such as phthalates. Phthalates are not chemically bound to these devices and thus can gradually leach during use [10]. One of the most widespread phthalates, di(2-ethylhexyl)phthalate (DEHP), has been banned from children's toys but is still used to soften medical devices. When DEHP leaches from the plastic into the circulation, it is hydrolyzed to mono(2-ethylhexyl)phthalate (MEHP). Further metabolism of MEHP occurs mainly in the liver and includes 6-hydroxylation, with formation of 2-ethyl-5-carboxy-pentylphthalate (5cx-MEPP), and 5-hydroxylation to 2-ethyl-5-hydroxy-hexylphthalate (5OH-MEHP) and subsequent conversion to 2-ethyl-5-oxo-hexylphthalate (5oxo-MEHP) [11]. These metabolites are eliminated via the urine [11]. A few small observational studies have reported high urinary levels of DEHP metabolites in premature neonates inferred to originate from indwelling medical devices [12-14].

In recent years, concerns have been expressed about potential toxicity for fertility and development of phthalate exposure via the food-chain and via long-term hemodialysis, long-term blood transfusions and repeated use of extracorporeal oxygenation in children [15-18]. *In vitro* studies, animal studies and observational reports in humans suggest that chronic exposure to DEHP may deleteriously affect neurocognitive development [19-23]. Specifically, a toxic effect on dopaminergic neurons was suggested to contribute to an increased incidence of attention-deficit disorders in young children exposed to environmental phthalates [24, 25]. However, it is unclear whether any phthalate leaching from routinely used medical devices during the short time that children are being treated in PICUs plays a causal role in the neurocognitive legacy of pediatric critical illness [18].

We hypothesized that high circulating phthalate 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. To test this hypothesis, concentrations of DEHP metabolites were quantified in plasma samples obtained during PICU stay from children who were tested for neurocognitive development 4 years later [1, 26] and compared with healthy children. In a development cohort, stable potentially harmful threshold levels of exposure to circulating DEHP metabolites were first identified with a multivariable bootstrap approach. Subsequently, the observed independent associations between phthalate exposure during PICU stay and the neurocognitive test results were validated in a second cohort.

Methods

Study population: development and validation cohort

In this study, 449 critically ill infants and children (0–16 years upon PICU admission) who had been enrolled in a randomized controlled trial on blood glucose control in PICU [26], of whom plasma was available and who underwent neurocognitive testing at 4 years follow-up [1], were included (Figure_1a). For comparison with plasma concentrations of DEHP metabolites resulting from environmental exposure, 100 healthy children with comparable age and gender were sampled immediately after IV catheterization for minor elective surgery (Figure_1a, eMethods_1). For the full study protocol we refer to the original articles and electronic supplementary protocol. The study was approved by the institutional ethical review board (ML2586) and performed in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent for blood sampling/analyses and neurocognitive testing was obtained from the parents/legal guardians and/or the child when 18 years or older at follow-up.

Given the inevitably observational study design, we *a priori* decided to chronologically divide the study population in two (Figure_1a). This was done to first identify any independent associations between exposure to circulating DEHP metabolites during PICU stay and the neurocognitive test results 4 years later in a development cohort and to subsequently validate the findings in a second cohort (see statistical analyses).

Measurement of plasma concentrations of phthalate metabolites, identification of phthalate-leaching devices and definition of “phthalate exposure” during PICU stay

Blood samples were taken upon PICU admission and daily at 6 a.m. until discharge, with plasma stored at -80°C. *Plasma concentrations* of 4 DEHP metabolites (MEHP, 5OH-MEHP, 5cx-MEPP, and 5oxo-MEHP) were quantified with high-performance liquid-chromatography tandem-mass-

spectrometry (Agilent 6410 Triple-Quad LCMS; Agilent, Santa Clara, California) [27] (eMethods_2, eTable_1).

Leaching experiments excluded any contamination with DEHP from the containers used to collect and store the plasma. Leaching experiments were also performed to assess which of the indwelling devices used in these patients were actively leaching DEHP when placed in DEHP-free saline for 18h at room temperature [28]. The number and type of indwelling medical devices used per child during 24h preceding sampling was noted.

We assumed that plasma DEHP metabolite concentrations would be highest upon PICU admission and lowest on the last PICU day. This assumption was based on the fact that many patients were admitted after exposure to extracorporeal circuits for surgery [29], and on the number of indwelling medical devices that typically diminishes throughout PICU stay, taking into account the half-life of the metabolites (between 5-15h) [11]. We first confirmed the inferred time course, by measuring plasma concentrations on day 1, 2, and 3 in a subset of 25 children from the development cohort. Subsequently, plasma concentrations of the DEHP metabolites were measured upon admission and on the last day for all patients. The available evidence suggests that both the concentration of circulating DEHP metabolites to which the brain is exposed and the duration of this exposure determine any eventual long-term neurocognitive harm [19] within a concept of “threshold” toxicity [15]. Therefore, we decided to consider the product of the last day plasma concentration and duration of PICU stay as that exposure to circulating phthalates during PICU stay that was minimally present for each patient, further referred to as the phthalate “*exposure*”. This was done for the sum of all DEHP metabolites, for each of the individual DEHP metabolites and for the sum of the 3 MEHP metabolites [11]. The latter was considered necessary to exclude bias originating from any artifactual *ex vivo* hydrolysis of DEHP [11].

Neurocognitive testing

Experienced pediatric psychologists (blinded to phthalate exposure) used validated, internationally recognized tests with adequate normative data to quantify performance for a broad range of neurocognitive functions [1]. The neuropsychological test battery comprised age range-specific tests measuring attention, motor coordination, inhibitory control and cognitive flexibility (Amsterdam Neuropsychological Tasks), general intellectual functioning (Wechsler Intelligence Quotient scales), visual-motor integration (Beery-Buktenica Developmental Test), verbal and visual-spatial learning and memory (Children's Memory Scale), and behavior (Child Behavior Checklist) (eMethods_3) [1]. These tests have been extensively used to quantify neurocognitive development in various pediatric populations [30, 31].

Statistical Analyses

Data are presented as means and 95% confidence intervals, medians and interquartile ranges or numbers and proportions. Differences between plasma concentrations of DEHP metabolites in critically ill and healthy children, and among patients with increasing numbers of indwelling medical devices, were compared with Wilcoxon rank-sum test. The latter analysis was subsequently corrected for markers of liver and kidney function.

The primary study aim was to assess, in a multivariable regression analysis adjusting for other risk factors, the presence of an independent association between “exposure” to the total circulating DEHP metabolites during PICU stay and the attention-deficit 4 years later, in the development *and* the validation patient cohort. Secondary study aims were similar analyses for the other neurocognitive outcomes, and for the individual DEHP metabolites and the sum of MEHP metabolites.

First, in the development cohort, the “exposure”/concentration values were evaluated as potential harmful thresholds for neurocognitive development, via a minimum P-value approach in multivariable regression analyses [32], adjusted for the following risk factors (eMethods_4, eFigure_1): age at PICU admission, gender, race [33], geographic and linguistic origin, history of malignancy or

diabetes, prior to PICU admission presence of a syndrome/illness *a priori* defined as affecting neurocognitive development, socioeconomic status of the parents, type and severity of critical illness, blood glucose management and duration of PICU stay. The stability of the identified thresholds was evaluated via 400 bootstrap resamplings per neurocognitive outcome (eMethods_4, eFigures_2-3). Each child received a dichotomized label according to whether or not these potentially harmful thresholds were exceeded. *Second*, the *significance and effect sizes of exceeding the identified potentially harmful thresholds* of phthalate “exposure” in the multivariable regression models, adjusted for other risk factors as described above, were determined for the development cohort and, to exclude findings by chance, repeated for the validation cohort. *Third, as a sensitivity analysis*, the multivariable models were further adjusted for extracorporeal circulation, aortic clamp times and “Risk-Adjusted Classification for Congenital Heart Surgery” (RACHS) score and for complications occurring during PICU stay, including new infections, duration of antibiotic and corticosteroid use, organ failure as reflected by peak levels of plasma creatinine and bilirubin, duration of hemodynamic/ventilatory support, treatment with hypnotics and cumulative doses of benzodiazepines and opioids [34]. In addition, it was also assessed whether any of the documented independent associations with the attention-deficit observed for “exposure” to the circulating DEHP metabolites in the validation cohort were also present for the raw plasma concentrations.

Statistical analyses were performed with Matlab 2014b® (The MathWorks, Natick, MA) and JMP® version 11.0.0 (SAS Institute, Inc, Cary, NC). Two-sided P-values of 0.05 or less were considered to indicate statistical significance. No corrections for multiple comparisons were done.

Results

Demographic and medical characteristics and neurocognitive test results of patients in the development and validation cohorts and of healthy children are presented in Table_1 and eTable_2.

In healthy children, total DEHP metabolites in plasma were virtually undetectable [0.029 (0.027-0.031) $\mu\text{mol/l}$], with just detectable levels of some individual DEHP metabolites in only 15 children. Mean plasma concentrations of DEHP metabolites were 4.41 (3.76-5.06) $\mu\text{mol/l}$ upon PICU admission in the development cohort and 3.42 (2.98-3.87) $\mu\text{mol/l}$ in the validation cohort, and thus 152-times and 118-times higher than in healthy children ($P<0.0001$) (Figure_1b,c), decreasing subsequently with time (Figure_1b). The lowest plasma concentrations of the total DEHP metabolites were found on the last PICU day, which were still 18- and 17-times higher than in healthy children ($P<0.0001$, Figure_1b,c).

During the 24h preceding PICU discharge, children were instrumented with 1-12 indwelling medical devices, of which up to 5 were intravascular. All these indwelling devices and/or the essential accessories for using them (eTable_3) were shown to leach DEHP *ex vivo*. Plasma concentrations of DEHP metabolites were always elevated irrespective of the number of indwelling medical devices and significantly increased by reduced kidney function (eFigure_4a).

The multivariable bootstrap analysis of the development cohort identified all stable threshold levels of exposure to circulating DEHP metabolites as potentially harmful for neurocognitive development (eTable_4, Figure_2). These thresholds were between the 25th percentile and the median of the distribution (Table_2).

The multivariable linear regression analyses of the development cohort, adjusted for baseline risk factors and duration of PICU stay, revealed that exceeding the potentially harmful threshold for “exposure” to circulating DEHP metabolites was independently and highly significantly associated only with the attention-deficit and with the impaired motor coordination (Table_2, eTable_5). The

independent association with the attention-deficit, and part of the association with impaired motor coordination, were reproduced in the validation cohort (Table_3, eTable_5). Similar findings were obtained for the “exposure” to the sum of the 3 circulating MEHP metabolites, to MEHP and most robustly, to 5oxo-MEHP (Table_2-3, eTable_5). These independent associations remained highly significant after further adjustment for extracorporeal circulation and aortic clamp times as well as for occurrence of new infections, organ failure, use of vital treatments during PICU stay and treatment with hypnotics, benzodiazepines and opioids (Table_2-3, eTable_5). Adjusting for number of indwelling devices did not change the results (eTable_6). In the subgroup of patients who required intensive care after cardiac surgery, further adjustment for RACHS score [35] did not alter any of the findings (eTable_7). Although in about 20% of patients last day DEHP metabolite concentrations were slightly higher than upon PICU admission, explained by baseline sampling before full instrumentation, sensitivity analyses confirmed that this did not cause bias (eMethods_5, eTable_8-9). The calculated estimates, reflecting the size of the effects on attention of exceeding the potentially harmful threshold, were the equivalent of about 50% of the differences between post-PICU patients and healthy children (eTable_10).

The sensitivity analyses performed on the raw data of the plasma concentrations revealed that the briefly, but substantially, elevated plasma concentrations of DEHP metabolites upon PICU admission were not significantly associated with the attention-deficit or any of the other neurocognitive test results (data not shown). However, on the last PICU day, the sum of the plasma concentrations of the 3 MEHP metabolites was also significantly associated only with the attention-deficit (eTable_11-13). This potentially harmful threshold could be reached even with minimal instrumentation of the patients (eFigure_4b).

Discussion

Critically ill children revealed very high circulating levels of DEHP metabolites throughout PICU stay, whereas these were virtually undetectable in healthy children. All indwelling medical devices and/or essential accessories showed to actively leach DEHP. Exceeding the potentially harmful threshold of exposure to circulating DEHP metabolites, identified by a multivariable bootstrap study of the development cohort, was found to be independently associated with the attention-deficit and to a lesser extent with the motor coordination deficit documented 4 years after PICU admission. These independent associations were largely confirmed in the validation cohort, even after further adjustment for PICU morbidities and treatments. This phthalate exposure effect statistically explained about half of the attention-deficit in post-PICU patients. By comparison with the attention-deficit reported for children with attention-deficit disorders, the effect size of phthalate exposure during pediatric critical illness was large [6].

As hypothesized, a large part of the attention-deficit in post-PICU patients could be statistically explained by exceeding a threshold of exposure to circulating DEHP metabolites, composed of the minimal plasma concentrations and time in PICU that these concentrations were present, and not by the extremely high plasma concentrations that were only briefly present upon PICU admission. This further supports the notion that phthalates leaching from a single run of extracorporeal support in children may not be a concern. However, these data are in line with experimental studies suggesting that both level and duration of exposure to phthalates determine their toxicity [15, 19]. The potentially harmful threshold could be reached even with minimal indwelling instrumentation of the children and thus, with the currently used material, appears unavoidable. Although the daily amount of phthalates that leached from these routinely used medical devices (which could not be quantitatively assessed) may well have been below the previously identified minimal dose that may evoke toxicity to the gonads [17], alterations in kidney and liver function may have augmented circulating levels (regardless of number of indwelling

devices) and increased the risk of exceeding a threshold that is potentially harmful to early life brain development.

It was striking that the phthalate exposure was specifically associated with attention and to a lesser extent motor coordination, but not the other aspects of the neurocognitive legacy. This corroborates epidemiological studies [21, 36, 37] suggesting a rather selective toxic effect of DEHP exposure on the biological substrate of the attention function. Attention is determined by neuronal networks involving connections between cerebellum, thalamus and frontoparietal cortex [38]. The exact brain areas vulnerable to the neurodevelopmental toxicity of phthalates related to the attention-deficit remain unclear. Degeneration of midbrain dopaminergic nuclei and an effect on dopamine transporters may play a role [39] as aberrations in the dopaminergic system are involved in the pathophysiology of attention-deficit disorders [40].

As compared with previous epidemiological studies, this study has some strengths. First, the timing and duration of the iatrogenic exposure to circulating phthalates related to the indwelling devices was accurately defined. Second, more than one measurement was done per child, reducing risk of inaccurate classification of exposure as may occur with single-spot urine samples [16]. Third, the current study used a development and a validation cohort, the latter to reduce the risk of observations by chance. The strikingly similar results in these two cohorts specifically for the association between phthalate exposure and the attention-deficit strongly supports that these associations are reproducible and biologically meaningful. Fourth, highly standardized tests were used to quantify attentional performance and other neurocognitive functions, whereas other studies drew conclusions based only on responses to questionnaires provided by teachers, parents or guardians [37].

This study also has limitations, most importantly that it was not a randomized controlled intervention trial and hence cannot provide proof of causality. However, unlike in animal models, deliberate random exposure of humans to potentially toxic phthalates is not possible for obvious ethical reasons. Also, with the currently used material, it is impossible to include a post-PICU control-group of

patients who were not exposed to phthalate-leaching indwelling devices during intensive care. There is some evidence for causality generated via studies in animal models [25]. We adjusted the analyses for dominant premorbid predestinators of neurocognition as well as for severity of the critical illness and its treatments. Although we cannot exclude residual confounding, the reproducibility of the current results in two patient cohorts underscores the robustness of the findings. One can only speculate about underlying molecular mechanisms in which epigenetic alterations may play a role [16].

In conclusion, a robust and reproducible independent association was found between the iatrogenic exposure to circulating phthalates during treatment in intensive care and the attention-deficit observed 4 years after pediatric critical illness. These data underscore a recent suggestion by the European Commission to use, whenever possible, medical devices with low phthalate release potential.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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Figure legends

Figure 1. Plasma phthalate concentrations in critically ill and healthy children

Panel A shows the CONSORT flow diagram of the study participants. We included two cohorts of healthy children. A first cohort of 215 children was recruited for neurocognitive testing at the time of neurocognitive follow-up of the critically ill children (grey shading) [1]. A second cohort was included for quantification of plasma concentrations of the DEHP metabolites. Panel B shows the time course of the DEHP metabolite concentrations in 25 critically ill children, with quantification of the respective concentrations upon admission to the PICU (Adm), day 1 (d1), day 2 (d2), day 3 (d3) and last day in the PICU (LD). Panel C shows the DEHP metabolite concentrations upon admission and the last PICU day for the patients in the development (N=228) and the patients in the validation cohort (N=221). Inserts show the last day plasma concentrations at a higher magnification. Total DEHP metabolite concentrations are calculated as the sum of MEHP and its metabolites 5cx-MEPP, 5OH-MEHP and 5oxo-MEHP, total MEHP metabolite concentrations are calculated as the sum of 5cx-MEPP, 5OH-MEHP and 5oxo-MEHP. Concentrations in matched healthy children were mostly below the quantification limit of the assay and are represented by thick dark grey lines upon the x-axis of the graphs. Data of the critically ill children are presented as means and 95% confidence intervals. Mean plasma concentrations of DEHP metabolites in the critically ill children from the development and validation cohorts were at least 152-times and 118-times higher upon PICU admission and at least 18- and 17-times higher on the last PICU day than those in healthy children. Tighter matching of the 100 healthy children with 100 critically ill children by propensity score matching for age and gender (eMethods_1) yielded similar results, with 111-times and 8-times higher plasma DEHP concentrations in the critically ill children upon PICU admission and on the last PICU day.

Figure 2. Univariate illustration of the alertness test results for patients who did and those who did not exceed the potentially harmful thresholds of exposure to circulating phthalate levels that were identified via multivariable bootstrap analysis

Measures of alertness are presented for patients in the development and the validation cohorts who had a total circulating DEHP metabolite exposure above and below the potentially harmful threshold (T), the latter identified with multivariable bootstrap analysis of the development cohort. Similar data are shown for the exposure to the sum of the 3 circulating MEHP metabolites and to 5oxo-MEHP. Data are presented as means and 95% confidence intervals. The size of the effect of exposure to these phthalates and the level of significance were determined with multivariable analysis after corrections for other risk factors as shown in Tables 2 and 3.

Tables

Table 1. Demographics and patient PICU outcomes

	Development cohort N=228	Validation cohort N=221	Healthy children N=100
Baseline characteristics			
Male gender, no. (%)	123 (54.0)	133 (60.2)	58 (58.0)
Age at sampling (years), mean (95% CI)	3.4 (2.9-4.0)	3.3 (2.7-3.8)	4.2 (3.5-4.9)
Height at sampling (%), mean (95% CI) ^a	45.6 (41.6-49.6)	44.4 (40.4-48.4)	47.5 (40.4-54.7)
Weight at sampling (%), mean (95% CI) ^a	44.4 (40.4-48.5)	41.6 (37.7-45.5)	52.7 (46.6-58.8)
Caucasian race, no. (%) ^b	219 (96.1)	200 (90.5)	93 (93.0)
Exclusively European, no. (%)	210 (92.1)	192 (86.9)	
Exclusively Dutch language, no. (%)	185 (81.1)	175 (79.2)	
Socioeconomic status, mean (95% CI) ^c	35 (33-37)	35 (33-37)	
Pre-existing syndrome, no. (%) ^d	58 (25.4)	66 (29.9)	
History of malignancy, no. (%)	5 (2.2)	8 (3.6)	
History of diabetes, no. (%)	2 (0.9)	0 (0.0)	
Randomization to strict glycemic control, no. (%)	105 (46.1)	112 (50.7)	
Diagnostic category, no. (%)			
Cardiac surgery for congenital heart defects	178 (78.1)	183 (82.8)	
Complicated/high risk surgery or trauma	25 (11.0)	16 (7.2)	
Neurological medical disorders	5 (2.2)	3 (1.4)	
Infectious medical diseases	9 (4.0)	4 (1.8)	
Other medical disorders	8 (3.5)	10 (4.5)	
Solid organ transplants	3 (1.3)	5 (2.3)	
PeLOD score first 24 hrs, mean (95% CI)	9 (8-10)	10 (9-11)	
PICU Outcomes			
ICU stay (days), mean (95% CI)	5.1 (4.3-5.8)	4.9 (4.0-5.8)	
Duration mechanical ventilation (days), mean (95% CI)	3.6 (3.0-4.2)	3.6 (2.9-4.4)	
Peak creatinine (mg/dl), mean (95% CI)	0.65 (0.62-0.68)	0.66 (0.59-0.73)	
Peak bilirubine (mg/dl), mean (95% CI)	1.42 (1.16-1.67)	1.43 (1.06-1.80)	
Hemodynamic support (days), mean (95% CI)	3.1 (2.6-3.6)	3.0 (2.4-3.6)	
Corticosteroid treatment (days), mean (95% CI)	0.3 (0.1-0.4)	0.8 (0.3-1.4)	
Infection, no. (%)	68 (29.8)	62 (28.1)	
Antibiotics (days), mean (95% CI)	3.3 (2.8-3.8)	3.6 (2.9-4.3)	

^a Height and weight, expressed as percentiles of population norms, were calculated with the anthropometric calculators for normal children, based on the World Health Organization Growth Charts for Canada (version 2015/02/24), and for children with syndromes known to affect height and weight (version 2014/09/25) (<http://www.bccchildrens.ca/Services/SpecializedPediatrics/Endocrinology/DiabetesUnit/ForProfessionals/AnthropometricCalculators.htm>).

Patients and healthy children were not matched for height and weight, as a growth delay is part of the long-term legacy of critical illness in children.

^b Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnic and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.³⁸

^c Socioeconomic status of the patient's parents was calculated with a modified version of the Hollingshead 7-point scale of educational level and the 9-point scale of occupational level. More points are given to higher educational or occupational level. Status score of an individual parent is calculated by adding the occupation value x 5, and the education value x 3. The average of the paternal and maternal score is used as the socioeconomic status score of the patient's family. A score of 66 is the highest possible score.

^d A prerandomization syndrome or illness a priori defined as affecting neurocognitive development.

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score.

Table 2. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the development cohort (n=228)

Phthalate exposure ^a	Neurocognitive functions affected, as determined by a multivariable bootstrap approach ^b	Potentially harmful threshold ($\mu\text{mol/l} \times \text{days}$) ^{c,d}	Model adjusted for baseline characteristics and duration of PICU stay			Model further adjusted for extracorporeal circulation, aortic clamp time and in-PICU complications and treatments		
			R ² of the model	Estimate [95% CI]	P value	R ² of the model	Estimate [95% CI]	P value
Total DEHP^e 0.78 (0.34-2.66) ($\mu\text{mol/l} \times \text{days}$) ^g	Attention and motor coordination							
	<i>Alertness (msec)^h</i>							
	Reaction time dominant hand	>0.551	0.57	78.26 [37.75;118.76]	0.0002	0.59	79.37 [34.84;123.90]	0.0006
	Reaction time nondominant hand	>0.551	0.55	64.94 [27.61;102.27]	0.0007	0.59	70.51 [30.66;110.36]	0.0006
	Reaction time overall	>0.551	0.60	71.44 [35.39;107.49]	0.0001	0.63	74.37 [35.40;113.35]	0.0002
	<i>Inconsistency of alertness (msec)ⁱ</i>							
	SD reaction time dominant hand	>0.551	0.51	55.81 [21.17;90.46]	0.001	0.51	51.48 [12.98;89.97]	0.009
	SD reaction time nondominant hand	>0.551	0.43	43.16 [9.84;76.47]	0.01	0.47	47.68 [11.83;83.53]	0.009
	SD reaction time overall	>0.551	0.55	53.91 [24.03;83.79]	0.0005	0.57	53.42 [20.62;86.21]	0.001
	<i>Motor coordination (No. of taps in 10s)^j</i>							
	No. of unimanual taps							
	Dominant hand	>0.551	0.76	-1.10 [-2.20;-0.01]	0.04	0.77	-1.34 [-2.52;-0.16]	0.02
	Nondominant hand	>0.551	0.76	-1.31 [-2.32;-0.29]	0.01	0.78	-1.24 [-2.31;-0.16]	0.02
	No. of valid synchronous taps	>0.551	0.66	-2.19 [-3.40;-0.97]	0.0005	0.67	-2.35 [-3.68;-1.03]	0.0006
MEHP Metabolites^f 0.47 (0.22-1.80) ($\mu\text{mol/l} \times \text{days}$) ^g	Attention and motor coordination							
	<i>Alertness (msec)^h</i>							
	Reaction time dominant hand	>0.365	0.58	84.05 [41.57;126.52]	0.0001	0.59	88.58 [41.61;135.56]	0.0003
	Reaction time nondominant hand	>0.365	0.55	67.94 [28.72;107.17]	0.0008	0.59	74.16 [32.00;116.33]	0.0006
	Reaction time overall	>0.365	0.60	76.07 [38.25;113.89]	0.0001	0.63	81.54 [40.38;122.70]	0.0001
	<i>Inconsistency of alertness (msec)ⁱ</i>							
	SD reaction time dominant hand	>0.365	0.51	61.87 [25.59;98.14]	0.0009	0.52	61.74 [21.19;102.28]	0.003
	SD reaction time nondominant hand	>0.365	0.44	50.73 [15.88;85.57]	0.004	0.48	52.50 [14.65;90.36]	0.006
	SD reaction time overall	>0.365	0.56	61.78 [30.60;92.96]	0.0001	0.57	61.73 [27.19;96.27]	0.0005
	<i>Motor coordination (No. of taps in 10s)^j</i>							
	No. of valid synchronous taps	>0.365	0.65	-2.05 [-3.33;-0.77]	0.001	0.66	-2.16 [-3.57;-0.75]	0.003
MEHP 0.23 (0.10-0.68) ($\mu\text{mol/l} \times \text{days}$) ^g	Attention and motor coordination							
	<i>Alertness (msec)^h</i>							
	Reaction time dominant hand	>0.157	0.56	58.79 [18.29;99.28]	0.004	0.58	57.95 [14.07;101.82]	0.009
	Reaction time nondominant hand	>0.157	0.55	56.24 [19.25;93.24]	0.003	0.59	60.27 [21.21;99.33]	0.002
	Reaction time overall	>0.157	0.59	57.19 [21.24;93.15]	0.002	0.61	58.33 [19.98;96.69]	0.003
	<i>Motor coordination (No. of taps in 10s)^j</i>							
	No. of valid synchronous taps	>0.157	0.66	-2.53 [-3.72;-1.34]	0.00004	0.68	-2.73 [-4.00;-1.45]	0.00004

Table 2. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the development cohort (n=228) (continued)

5cx-MEPP 0.39 (0.17-1.24) ($\mu\text{mol/l} \times \text{days}$) ^g	Memory <i>Verbal-auditory</i> Working memory, repeating numbers backward (up to 19 numbers) ^k	>0.379	0.34	-0.95 [-1.67;-0.22]	0.01	0.43	-0.75 [-1.64;0.13]	0.09
5oxo-MEHP 0.03 (0.01-0.12) ($\mu\text{mol/l} \times \text{days}$) ^g	Attention and motor coordination <i>Alertness (msec)^h</i> Reaction time dominant hand Reaction time nondominant hand Reaction time overall <i>Inconsistency of alertness (msec)ⁱ</i> SD reaction time dominant hand SD reaction time nondominant hand SD reaction time overall <i>Motor coordination (No. of taps in 10s)^j</i> No. of unimanual taps Dominant hand No. of valid synchronous taps	>0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.024	0.57 0.57 0.60 0.51 0.44 0.55 0.76 0.64	82.72 [34.77;130.66] 92.93 [50.07;135.79] 87.12 [44.88;129.37] 64.82 [24.07;105.56] 56.30 [17.62;94.97] 62.34 [27.19;97.50] -1.89 [-3.17;-0.61] -1.76 [-3.12;-0.41]	0.0008 0.00003 0.00007 0.002 0.004 0.0006 0.004 0.01	0.59 0.61 0.63 0.52 0.48 0.57 0.77 0.66	88.28 [35.89;140.66] 107.79 [62.64;152.93] 96.98 [51.73;142.23] 63.76 [18.74;108.78] 69.11 [27.89;110.32] 67.80 [29.55;106.05] -2.16 [-3.53;-0.78] -1.95 [-3.46;-0.45]	0.001 0.000005 0.00003 0.005 0.001 0.0006 0.002 0.01

^a "Exposure" was defined as the product of the last day concentrations in $\mu\text{mol/l}$ and the number of days exposed in PICU.

^b Only the neurocognitive functions that were significantly associated with the phthalate exposures as identified by bootstrapping are listed.

^c identified via bootstrap resampling.

^d Threshold values are rounded to three decimals.

^e Exposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^f Exposure to the sum of 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^g Distribution of metabolite exposures within the patient cohort ($\mu\text{mol/l} \times \text{days}$). Data are median (interquartile range).

^h For reaction times, higher scores reflect worse performance. Mean scores for the healthy children are 558 (95% CI 521-595) (range 230-1557) for the dominant hand reaction time, 562 (95% CI 524-600) (range 223-1532) for the nondominant hand reaction time and 560 (95% CI 524-600) (range 227-1428) for the overall reaction time.¹

ⁱ For inconsistency of alertness, higher scores reflect worse performance. Mean scores for the healthy children are 259 (95% CI 229-290) (range 24-1004) for the dominant hand, 262 (95% CI 232-292) (range 19-982) for the nondominant hand and 275 (95% CI 246-304) (range 29-861) for the overall SD, standard deviation.¹

^j For motor coordination, higher scores reflect better performance. Mean scores for the healthy children are 36 (95% CI 34-38) (range 10-66) for dominant hand unimanual taps, 32 (95% CI 30-33) (range 8-79) for nondominant hand unimanual taps and 22 (95% CI 20-24) (range 0-52) for valid synchronous taps.¹

^k For numbers within verbal-auditory memory, higher scores reflect better performance. Mean scores for the healthy children are 11 (95% CI 10-11) (range 3-18) for working memory (repeating numbers backward).¹

Table 3. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the validation cohort (n=221)

Phthalate exposure ^a	Neurocognitive functions from the development cohort, significantly affected in validation cohort ^b	Best threshold (μmol/l ×days) ^c of development cohort	Model adjusted for baseline characteristics and duration of PICU stay			Model further adjusted for extracorporeal circulation, aortic clamp time and in-PICU complications and treatments		
			R ² of the model	Estimate [95% CI]	P value	R ² of the model	Estimate [95% CI]	P value
Total DEHP ^d 0.72 (0.34-2.19) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.551	0.54	58.30 [17.88;98.72]	0.004	0.60	61.47 [19.87;103.07]	0.004
	Reaction time nondominant hand	>0.551	0.56	47.92 [10.58;85.27]	0.01	0.61	50.89 [11.94;89.85]	0.01
	Reaction time overall	>0.551	0.58	54.43 [17.44;91.43]	0.004	0.63	57.59 [19.39;95.80]	0.003
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.551	0.45	55.76 [18.1;93.43]	0.003	0.53	55.10 [16.62;93.58]	0.005
	SD reaction time nondominant hand	>0.551	0.45	30.15 [-6.15;66.44]	0.10	0.49	30.20 [-8.50;68.90]	0.12
	SD reaction time overall	>0.551	0.52	44.36 [11.54;77.17]	0.008	0.56	43.98 [9.58;78.38]	0.01
	Motor coordination (No. of taps in 10s) ⁱ							
	No. of unimanual taps							
	Dominant hand	>0.551	0.63	-0.83 [-2.14;0.49]	0.21	0.65	-0.78 [-2.18;0.61]	0.26
Nondominant hand	>0.551	0.63	-1.57 [-2.84;-0.30]	0.01	0.66	-1.63 [-2.96;-0.29]	0.01	
	No. of valid synchronous taps	>0.551	0.57	-1.09 [-2.37;0.19]	0.09	0.61	-1.46 [-2.80;-0.13]	0.03
MEHP metabolites ^e 0.53 (0.23-1.42) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.365	0.54	45.05 [4.77;85.33]	0.03	0.59	44.64 [2.71;86.57]	0.03
	Reaction time nondominant hand	>0.365	0.56	44.23 [7.25;81.21]	0.01	0.60	46.46 [7.52;85.40]	0.01
	Reaction time overall	>0.365	0.57	45.99 [9.21;82.76]	0.01	0.62	47.06 [8.67;85.45]	0.01
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.365	0.45	45.46 [7.97;82.95]	0.01	0.52	42.42 [3.71;81.13]	0.03
	SD reaction time nondominant hand	>0.365	0.45	27.33 [-8.57;63.23]	0.13	0.49	25.90 [-12.74;64.53]	0.18
	SD reaction time overall	>0.365	0.51	38.16 [5.58;70.74]	0.02	0.56	35.73 [1.22;70.23]	0.04
	Motor coordination (No. of taps in 10s) ⁱ							
	No. of valid synchronous taps	>0.365	0.57	-0.63 [-1.90;0.63]	0.32	0.49	-1.00 [-2.34;0.34]	0.14
	MEHP 0.18 (0.09-0.53) (μmol/l×days) ^f	Attention and motor coordination						
Alertness (msec) ^g								
Reaction time dominant hand		>0.157	0.54	45.57 [5.83;85.31]	0.02	0.59	40.09 [-1.01;81.20]	0.05
Reaction time nondominant hand		>0.157	0.55	35.62 [-1.07;72.32]	0.05	0.60	32.92 [-5.46;71.31]	0.09
Reaction time overall		>0.157	0.57	41.30 [4.88;77.71]	0.02	0.62	37.30 [-0.48;75.07]	0.05
Motor coordination (No. of taps in 10s) ⁱ								

Table 3. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the validation cohort (n=221) (continued)

	No. of valid synchronous taps	>0.157	0.58	-1.77 [-3.00;-0.53]	0.005	0.62	-1.60 [-2.90;-0.31]	0.01
5cx-MEPP 0.39 (0.17-1.24) ($\mu\text{mol/l} \times \text{days}$) ^f	Memory <i>Verbal-auditory</i> Working memory, repeating numbers backward (up to 19 numbers) ^j	>0.379	0.28	0.26 [-0.50;1.03]	0.49	0.45	0.63 [-0.19;1.46]	0.12
5oxo-MEHP 0.03 (0.02-0.10) ($\mu\text{mol/l} \times \text{days}$) ^f	Attention and motor coordination <i>Alertness (msec)^g</i> Reaction time dominant hand Reaction time nondominant hand Reaction time overall <i>Inconsistency of alertness (msec)^h</i> SD reaction time dominant hand SD reaction time nondominant hand SD reaction time overall <i>Motor coordination (No. of taps in 10s)ⁱ</i> No. of unimanual taps Dominant hand No. of valid synchronous taps	>0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.031 >0.024	0.58 0.58 0.60 0.49 0.46 0.55 0.63 0.56	100.67 [59.92;141.41] 73.85 [35.51;112.20] 88.60 [51.10;126.11] 91.91 [53.8;130.03] 48.76 [11.11;86.41] 74.64 [41.32;107.96] -0.93 [-2.30;0.45] -0.35 [-1.73;1.04]	0.000002 0.0002 0.000006 0.000004 0.01 0.00001 0.18 0.62	0.64 0.63 0.66 0.56 0.50 0.59 0.65 0.61	108.20 [66.91;149.49] 83.31 [43.91;122.71] 96.82 [58.71;134.93] 87.75 [48.93;126.56] 51.40 [11.57;91.24] 74.42 [39.74;109.10] -0.77 [-2.23;0.69] -0.30 [-1.76;1.16]	0.0000006 0.00004 0.000001 0.00001 0.01 0.00003 0.29 0.68

^a "Exposure" was defined as the product of the last day concentrations in $\mu\text{mol/l}$ and the number of days exposed in PICU.

^b Neurocognitive functions, that were significantly associated with the phthalate exposure in the development cohort, were tested in the validation cohort. Only the remaining functions that were also significantly associated with the phthalate exposure in the validation cohort are listed.

^c Threshold values are rounded to three decimals.

^d Exposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5-OH-MEHP.

^e Exposure to the sum of 5cx-MEPP, 5oxo-MEHP and 5-OH-MEHP.

^f Distribution of metabolite exposures within the patient cohort ($\mu\text{mol/l} \times \text{days}$). Data are median (interquartile range).

^g For reaction times, higher scores reflect worse performance. Mean scores for the healthy children are 558 (95% CI 521-595) (range 230-1557) for the dominant hand reaction time, 562 (95% CI 524-600) (range 223-1532) for the nondominant hand reaction time and 560 (95% CI 524-600) (range 227-1428) for the overall reaction time.¹

^h For inconsistency of alertness, higher scores reflect worse performance. Mean scores for the healthy children are 259 (95% CI 229-290) (range 24-1004) for the dominant hand, 262 (95% CI 232-292) (range 19-982) for the nondominant hand and 275 (95% CI 246-304) (range 29-861) for the overall SD, standard deviation.¹

ⁱ For motor coordination, higher scores reflect better performance. Mean scores for the healthy children are 36 (95% CI 34-38) (range 10-66) for dominant hand unimanual taps, 32 (95% CI 30-33) (range 8-79) for nondominant hand unimanual taps and 22 (95% CI 20-24) (range 0-52) for valid synchronous taps.¹

^j For numbers within verbal-auditory memory, higher scores reflect better performance. Mean scores for the healthy children are 11 (95% CI 10-11) (range 3-18) for working memory (repeating numbers backward).¹

Figures

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ELECTRONIC SUPPLEMENTARY MATERIAL

CIRCULATING PHTHALATES DURING CRITICAL ILLNESS IN CHILDREN ARE ASSOCIATED WITH LONG-TERM ATTENTION-DEFICIT

A study of a development and a validation cohort

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eMethods 1.	Propensity score matching of critically ill and healthy children
eMethods 2.	Sample preparation, analysis and QA/QC for DEHP metabolites in plasma
eMethods 3.	Tests and questionnaires to assess neurocognitive functions
eMethods 4.	Bootstrap selection of significant and stable potentially harmful thresholds for circulating DEHP metabolites
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eReferences

SUPPLEMENTARY ONLINE METHODS

eMethods 1. Propensity score matching of critically ill and healthy children

For comparison with plasma concentrations of DEHP metabolites resulting from environmental exposure, 100 healthy children with overall comparable age and gender as the total cohorts of critically ill children were sampled immediately after IV catheterization for minor elective surgery. To match age and gender more tightly, we subsequently performed a propensity score matching with one-to-one nearest neighbor matching with use of a caliper of 0.1, where propensity scores were estimated by logistic regression with age and gender as covariates (R-3.1.0 under SPSS version 23.0.0.0). The 100 control children were thus matched with 100 critically ill children. The age was 4.2 $\pm$ 3.3 years in the healthy children versus 3.8 $\pm$ 3.3 years ($p=0.3$) in the critically ill children and there were 58% male children in the healthy control group versus 61% in the critically ill group ($p=0.6$). We also compared the plasma DEHP metabolite concentrations for these propensity score matched critically ill and healthy children.

eMethods 2. Sample preparation, analysis and QA/QC for DEHP metabolites in plasma

Sample preparation and analysis

The sample preparation protocol for analysis of the DEHP metabolites was applied on 0.25 ml plasma fortified with 25 ng of each of the ^{13}C -labeled DEHP metabolites (see eTable 1A). To ensure deconjugation of DEHP metabolites, 25 μl of β -glucuronidase-arylsulphatase (from *Helix Pomatia*, corresponding to ≈ 1 IU enzyme per ml of plasma) (Merck, Darmstadt, Germany) and 1 ml of phosphate buffer solution (pH=6) were added to the plasma and the mixture was kept at 37°C for 90 min. The samples were further diluted with 1 ml of MilliQ water and extracted using Oasis MAX (60 mg/3 ml, Waters, Milford, MA). Afterwards, the sorbent bed was washed with MilliQ water containing 5% NH_4OH , followed with MilliQ water and dried under vacuum. Elution of DEHP metabolites was performed using 6 ml of MeOH containing 2% formic acid. The eluate was evaporated to dryness and reconstituted in 100 μl acetonitrile. The extract was filtered through centrifugal filters of 0.45 μm pore size (VWR International) and injected into a LC(ESI)-MS/MS system (liquid chromatograph 1200 series coupled to a 6410 Triple Quad mass spectrometer, Agilent, CA). Additional instrumental conditions employed for the analysis of DEHP metabolites are given in eTable 1B. All solvents used in the analyses (MeOH, acetonitrile) were of gradient grade for liquid chromatography and were obtained from Merck (Darmstadt, Germany). Formic acid (98-100%) was from Merck and NH_4OH (aqueous solution of 28-30%) was bought from Sigma-Aldrich. All glassware was soaked for 12 h in an alkali solution (diluted RBS T 105, pH 11–12) and, after washing, glassware was rinsed with water and dried overnight at 400°C. Prior to use, glassware was rinsed with acetonitrile.

Quality assurance/ Quality control (QA/QC)

For implementation and to ensure reliability of the data obtained for the DEHP metabolites targeted in this study, several validation parameters (calibration linearity, accuracy, precision, and method limits of detection (LOD) and quantification (LOQ)) were further tested (eTable 1C) and various QA/QC measures were taken during sample preparation.

Multi-level calibration curves in the linear response interval of the detector were created for the quantification, and good correlation ($r^2 > 0.998$) was achieved. Since the error on the measurements for calibrations should not increase with the concentration, the homoscedasticity was checked by plotting the residual error as function of the concentration. Calibration curves were accepted if errors showed a random distribution or if the occurring errors were not significant in comparison to the obtained results.

The identification of analytes was based on the relative retention times (RRTs) to the internal standards used for quantification, ion chromatograms and intensity ratios of the monitored transitions/ions. A deviation of the ion intensity ratios within 20% of the mean values obtained for calibration standards was considered acceptable.

The internal QA/QC was performed by regular analyses of procedural blanks (3 blanks per batch of 20 samples), random injection of standards, spiked samples (2 different concentration levels) and solvent blanks. The external quality control scheme was assessed through participation to inter-laboratory comparison exercises GERMAN EQUAS 2012, 2013 and 2014, for which the obtained concentrations of DEHP metabolites in urine deviated with less than 20% from the consensus values (eTable 1D).

Concentrations below the LOQ (2 ng/ml) were assigned a value of 1.9 ng/ml. Concentrations were measured in ng/ml and converted to $\mu\text{mol/l}$ for statistical analysis.

eMethods 3. Tests and questionnaires to assess neurocognitive functions

Extensively validated tests and questionnaires were used to evaluate a broad range of neurocognitive functions, as previously described [1], including attention, motor coordination, inhibitory control and cognitive flexibility, general intellectual functioning, visual-motor integration, verbal and visual-spatial learning and memory, as well as behavior.

Three computerized tasks of the Amsterdam Neuropsychological Tasks (ANT) system were used to quantify attention/alertness, motor coordination, and executive functions [2, 3]. Alertness was evaluated by the mean of the reaction time (msec) to 32 visual stimuli and the inconsistency of alertness by the standard deviation of the 32 reaction times. Reaction times for the dominant and nondominant hands and overall reaction time were recorded. Motor coordination was evaluated by the “Tapping Task”, which counts the number of taps in 10 seconds for the dominant hand, the nondominant hand, bimanual alternating taps and bimanual synchronous taps. Inhibitory control and cognitive flexibility are calculated by the difference in reaction time and in number of errors between tests of increasing demand in the “Response Organization Objects” test [3, 4].

Total IQ, verbal IQ, and performance IQ were scored with the Wechsler Preschool and Primary Scale of Intelligence-Revised (4-5 years) [5], Wechsler Intelligence Scale for Children-3rd Edition (6-16 years) [6], and Wechsler Adult Intelligence Scale-3rd Edition (17 years or older) [7], adapted for the Dutch language. The Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition (all ages) [8] was used to evaluate visual-motor integration.

Specific verbal-auditory memory and nonverbal, visual-spatial memory functions were assessed with tasks from the Children’s Memory Scale (CMS, 5-16 years) [9]. Memory span and verbal working memory were assessed with a CMS test where numbers had to be repeated forward or backward, respectively. Proportion of correct responses (range 0-1) in the age-adjusted CMS pictures, word pairs and dots test were recorded. In the CMS pictures test, picture locations have to be recalled as a measure for visual-spatial memory span. The CMS word pairs and dots tests measure verbal-auditory (correctly completed word pairs in 3 learning trials) and nonverbal, visual-spatial learning (correctly recalled dot locations in 3 learning trials), immediate memory (correctly recalled word pairs or dot locations), delayed memory (correctly recalled word pairs or dot locations after delay of 25-35 minutes), and recognition (correctly recognized word pairs after delay of 25-35 minutes). Age-adjusted versions of the Child Behavior Checklist, filled out by the parents or the child’s legal guardian, scored internalizing, externalizing, and total behavioral problems [10, 11].

eMethods 4. Bootstrap selection of significant and stable potentially harmful thresholds for circulating DEHP metabolites

In an initial visual exploratory analysis, we compared neurocognitive test results for the patients in the development cohort according to the quartiles of total exposure to circulating DEHP metabolites in univariable analysis (illustrated in eFigure 1 for alertness), as well as with a “lowess smoother” (data not shown). The results of these analyses suggested that there may be a threshold above which this exposure may be harmful for neurocognitive functions and provided the rationale for the identification of a threshold for potential harm in multivariable analyses [12].

Subsequently, unique exposure/concentration values in the development cohort were evaluated independently as a potential threshold for neurocognitive developmental harm. The stability of the identified thresholds was evaluated via bootstrap resampling of multivariable regression models. Bootstrapping is a computational technique introduced by Efron et al. [13] to estimate any statistic of a population from a small sample, and used in assessing the (in)stability of multivariable models [14]. Specifically, we made use of the 0.632 variant of the bootstrap method [15], which is the preferred technique to assess stability in datasets comprising less than approximately 250 patients [16]. The following methodology was used to identify the potentially harmful thresholds for plasma concentrations or exposures to each of the different DEHP metabolites considered combined or separately.

From the dataset comprising all exposure/concentration values of a given metabolite for the patients in the development cohort, 400 so-called “bootstrap sample” datasets were generated. The original development dataset consists of values from 228 patients; and each bootstrap sample is generated by random sampling with replacement so that it also contains 228 values. The probability that a bootstrap sample is identical to the original dataset is extremely low.

With the exception of a subset of the extreme values, each unique possible value for a given exposure/concentration in every bootstrap replica was evaluated as a possible cut-off for potential harm with respect to a neurocognitive test. These values were dichotomized as $>$ (greater-than) or $\leq$ (less-than or equal-to) the cut-off, and entered as a covariate in a multivariable regression analysis as described in the statistical analysis section. The exposure/concentration values that dichotomized the bootstrap replica into less than 10 patients per group (approximately 10% of the values) were not considered as possible cut-offs. The model was adjusted for the following risk factors: age at PICU admission, gender, race, geographic and linguistic origin, history of malignancy or diabetes, prior to PICU admission presence of a syndrome or illness a priori defined as affecting neurocognitive development, socioeconomic status of the parents, type and severity of the critical illness, blood glucose management and the duration of PICU stay.

The best cut-off for the bootstrap sample was identified via a minimum P-value approach in a multivariable model [17], and the overall model performance (highest R^2) was used to decide in case of a tie with respect to P-values [12]. The combined results from all bootstrap replicas produced a distribution of best cut-offs with their corresponding P-values. The bootstrap approach better assesses the variation in the cut-offs obtained across the resampled datasets [18]. For further evaluation we retained only the cases where: a) the median P-value was <0.05 and b) the variation of the cut-off distribution was small as compared to the variation in the measurements of the original dataset. This was empirically defined as an interquartile range in the cut-off distribution lower than 25% of the interquartile range of all data in the original dataset. Figure S2 illustrates this initial step of the methodology.

The remaining cut-off distributions of the exposure/concentration of interest for each neurocognitive test were grouped into 3 categories: low, medium and high cut-offs. The final possibly potentially harmful thresholds were obtained via a second 0.632 bootstrap analysis. All cut-offs in the distributions selected from the previous step for each category are evaluated as potentially harmful thresholds for all neurocognitive tests in the same category via 400 bootstrap samples. The potentially harmful threshold for the category was identified via a minimum P-value approach in a multivariable model [17], and the overall model performance (highest R^2) was used to decide in case of a tie with respect to P-values [12] over all bootstrap samples and all neurocognitive tests in the same threshold category. The potentially harmful threshold for a neurocognitive test is kept for further analysis in the validation cohort only if the median, 25th percentile and 75th percentile p-values of the covariate for this threshold distribution are below 0.05. As in the previous step only the cut-offs that dichotomize the development cohort with at least 10 patients per group were used in the analyses. eFigure 3 illustrates this step.

eMethods 5. Sensitivity analyses for patients with a higher DEHP metabolite concentration on the last day in PICU than upon PICU admission

We assumed that plasma concentrations of DEHP metabolites would be highest upon PICU admission and lowest on the last PICU day. This assumption was based on the fact that many patients were admitted after exposure to extracorporeal circuits for surgery [19] and on the number of indwelling medical devices that typically diminishes throughout PICU stay, taking into account the half-life of the metabolites (between 5-15h) [20]. The available evidence suggests that both the concentration of circulating DEHP metabolites to which the brain is exposed and the duration of this exposure determine any eventual long-term neurocognitive harm [21, 22] within a concept of “threshold” toxicity [23]. Therefore, we decided to consider the product of the last day plasma concentration and the duration of PICU stay as that exposure to circulating phthalates during PICU stay that was minimally present for each patient, further referred to as the phthalate “*exposure*”.

To exclude bias originating from patients in whom plasma concentrations of DEHP metabolites would be higher on the last PICU day than upon PICU admission, we performed two additional sensitivity analyses.

First, we repeated the multivariable analyses for assessment of the associations with DEHP metabolite exposure after exclusion of the patients who had a higher DEHP metabolite concentration on the last day in PICU than at baseline.

Second, we made a new classification of exceeding the potentially harmful threshold for DEHP exposure, where we calculated minimal exposure of patients with a higher DEHP metabolite concentration on the last PICU day as upon PICU admission as concentration of DEHP metabolites upon PICU admission multiplied with length of PICU stay, whereas the previous definition was used for the other patients.

SUPPLEMENTARY ONLINE FIGURES

eFigure 1. Association of alertness with quartiles of exposure to total circulating DEHP metabolites

Patients from the development cohort were divided in four equally sized groups according to the quartiles of the corresponding exposure to circulating DEHP metabolites (total concentration of DEHP metabolites multiplied with ICU stay). Measures of alertness and consistency of alertness are shown for the four groups. Data are presented as box plots, with the central line indicating the medians, the box the interquartile ranges and the whiskers the 10th and 90th percentiles.

eFigure 2. Selection of significant and stable cut-offs

Bootstrap samples are generated from the original dataset of all values in the development cohort for one exposure/concentration (the distribution of these measurements is plotted in black). The 0.632 bootstrap method uses the data from the bootstrap sample and the original dataset to determine the best cut-off for that bootstrap sample. The distribution of best cutoffs for a given neurocognitive test is plotted in green. If a) the median P value of the covariate of this cutoff distribution is <0.05 and b) the cut-off distribution has an IQR $< 25\%$ of the IQR of the original dataset, then this cut-off distribution and neurocognitive test are selected for further analysis.

eFigure 3. Determination of a potentially harmful threshold per grouped responses

The cut-off distributions for the neurocognitive tests remaining from the first analysis are grouped in categories: low (2 example distributions shown in red), medium (2 example distributions shown in green), high (1 example distribution shown in blue). A bootstrap analysis is performed to identify one potentially harmful threshold per grouped responses. If a) for the neurocognitive test in the group, the median, 25th percentile and 75th percentile P values of the covariate of this threshold distribution are < 0.05 and b) the threshold dichotomizes the development cohort with at least 10 patients in each group, this threshold and neurocognitive test are kept for further analysis in the validation cohort.

eFigure 4. Circulating DEHP metabolites and number of indwelling medical devices on the last PICU day

Panel A shows the plasma concentrations of the sum of all DEHP metabolites and the sum of the 3 MEHP metabolites per number of indwelling medical devices that were present during the 24h preceding the blood sampling in patients who were in PICU for more than 24h. The absence of a significant correlation between the number of indwelling medical devices and the plasma DEHP metabolite concentrations was explained by a significant impact of kidney function (multivariable estimate +0.47 (95 CI 0.01-0.92) μmol/l of total DEHP metabolites per mg/dl increase in peak plasma creatinine, $P=0.04$; multivariable estimate +0.42 (95 CI 0.08-0.76) μmol/l of the 3 MEHP metabolites per mg/dl increase in peak plasma creatinine, $P=0.01$). Panel B shows the number of indwelling medical devices present during the 24h preceding the blood sampling of critically ill children with plasma concentrations of the 3 MEHP metabolites exceeding the potentially harmful threshold of 0.245 μmol/l versus those with lower concentrations. Data are presented as box plots, with the central line indicating the medians, the box the interquartile ranges and the whiskers the 10th and 90th percentiles.

SUPPLEMENTARY ONLINE TABLES

eTable 1. Methodological details and quality assessment of phthalate metabolite quantification

A. Mass transitions for quantification of di(2-ethylhexyl)phthalate metabolites in plasma

DEHP Metabolite	Abbreviation	MRM
Mono-(2-ethyl-5-carboxypentyl) phthalate	5cx-MEPP	307-159.1/ 307-113
¹³ C4-Mono-(2-ethyl-5-carboxypentyl) phthalate	¹³ C4-5cx-MEPP	311-159.1/ 311-113
Mono-(2-ethyl-5-hydroxyhexyl) phthalate	5OH-MEHP	293-120.9/ 293-145
¹³ C4-Mono-(2-ethyl-5-hydroxyhexyl) phthalate	¹³ C4-5OH-MEHP	297-123.9
Mono-(2-ethyl-5-oxohexyl) phthalate	5oxo-MEHP	291-121/ 291-143.1
¹³ C4-Mono-(2-ethyl-5-oxohexyl) phthalate	¹³ C4-5oxo-MEHP	295-124
Mono-(2-ethylhexyl) phthalate	MEHP	276.7-134/ 276.7-127.1
¹³ C4-Mono-(2-ethylhexyl) phthalate	¹³ C4-MEHP	280.7-137

Quantified DEHP metabolites and the corresponding internal standards with ions used for the analyte quantification and qualification is given. Bold values for multiple reaction monitoring (MRM) represent the transitions used for the quantification by LC-(ESI)-MS/MS. Individual standards of phthalate metabolites and corresponding ¹³C-labeled standards were obtained from Cambridge Isotope Laboratories, Inc. (Andover, MA).

B. Instrumental conditions employed for the analysis of the DEHP metabolites in plasma

Instrument	Agilent LC 1200, QqQ MS	
Ionization source	ESI, negative	
Column	Kinetex C18 (100 × 4.60 mm) 2.6μ, 100A	
Mobile phase	A: H ₂ O, 0.1% acetic acid B: acetonitrile, 0.1% acetic acid	
Gradient	Time (min)	B (%)
	0	15
	4	15
	4.01	45
	10	45
	10.01	100
	20	100
	20.01	15
	30	15
Flow	0.2 ml/min, constant	

C. Validation of the methodology for determination of DEHP metabolites in plasma

Analyte	LOQ	Spike level	Recovery	Method precision	Linear regression coefficient, <i>r</i>
	(ng/mL)	(ng)	(%)	(%, RSD)	
MEHP	2.0	10	92	6	0.996
5cx-MEPP	2.0	10	85	6	0.996
5OH-MEHP	2.0	10	88	4	0.995
5oxo-MEHP	2.0	10	91	5	0.996

LOQ: limit of quantification; RSD: relative standard deviation.

D. External quality control of DEHP metabolite quantification method

Analyte comparison 2012, round 49	Solution	Result UA	Certified Value	Tolerance range
5cx-MEPP	A	12.7	11.85	8.70 – 15.00
	B	85.7	80.25	67.50 – 93.00
5OH-MEHP	A	10.7	9.77	7.04 – 12.50
	B	87.2	80.27	63.41 – 97.13
5oxo-MEHP	A	6.6	6.15	4.62 – 7.68
	B	48.7	48.11	40.31 – 55.91
Analyte comparison 2013, round 51	Solution	Result UA	Reference Value	Tolerance range
MEHP	A	3.5	3.3	1.7 – 4.8
	B	16.8	14.4	10.5 – 18.3
5cx-MEPP	A	32.1	32.9	24.7 – 41.1
	B	96.4	98.8	85.8 – 111.9
5OH-MEHP	A	22.5	23.1	17.5 – 28.7
	B	74.7	75.8	61.5 – 90.1
5oxo-MEHP	A	16.4	17.6	13.7 – 21.3
	B	56.0	58.9	47.6 – 70.2
Analyte comparison 2014, round 53	Solution	Result UA	Reference Value	Tolerance range
MEHP	A	10.7	9.8	7.0 – 12.7
	B	24.6	22.8	16.7 – 28.9
5cx-MEPP	A	52.6	59.4	46.8 – 72.1
	B	204.2	221.0	186.6 – 255.5
5OH-MEHP	A	43.1	47.0	33.6 – 60.4
	B	168.4	189.3	144.4 – 234.2
5oxo-MEHP	A	28.0	32.5	22.6 – 42.4
	B	118.1	138.0	105.2 – 170.9
Analyte comparison 2014, round 54	Solution	Result UA	Reference Value	Tolerance range
MEHP	A	4.7	4.1	2.8 – 5.4
	B	16.7	14.2	10.2 – 18.1
5cx-MEPP	A	41.8	46.4	33.0 – 59.7
	B	161.6	164.9	141.6 – 188.1
5OH-MEHP	A	30.5	34.0	25.2 – 42.7
	B	114.0	120.0	103.8 – 136.2
5oxo-MEHP	A	22.3	24.5	19.4 – 29.7
	B	97.0	103.8	91.4 – 116.2

Comparison is given between reported data on the analysis of urinary DEHP metabolites (ng/ml) and the consensus range for each individual metabolite included in the inter-laboratory comparison exercise, GERMAN EQUAS 2012 round 49, GERMAN EQUAS 2013 round 51, GERMAN EQUAS 2014 round 53 and round 54. UA-University of Antwerp

eTable 2A. Neurocognitive test results in critically ill and healthy children

Neurocognitive tests	Healthy children ^a	Critically ill children	
		Development cohort	Validation cohort
Attention, motor coordination and executive functions			
Alertness (msec)			
Reaction time dominant hand	558 (521-595)	697 (649-745)	730 (682-778)
Reaction time nondominant hand	562 (524-600)	670 (626-713)	709 (663-754)
Reaction time overall	560 (524-596)	680 (635-724)	718 (672-764)
Inconsistency of alertness (msec)			
SD reaction time dominant hand	259 (229-290)	395 (357-434)	416 (375-457)
SD reaction time nondominant hand	262 (232-292)	347 (313-382)	401 (362-440)
SD reaction time overall	275 (246-304)	385 (351-420)	423 (385-461)
Motor coordination (number of taps in 10s)			
Number of unimanual taps			
Dominant hand	36 (34-38)	32 (30-34)	31 (29-33)
Nondominant hand	32 (30-33)	27 (26-29)	26 (24-28)
Number of valid alternating taps	19 (17-22)	13 (11-15)	13 (11-15)
Number of valid synchronous taps	22 (20-24)	18 (17-20)	17 (16-19)
Inhibition and flexibility			
Δ Reaction time (inhibition), msec	294 (255-333)	323 (278-369)	378 (325-431)
Δ Number of errors (inhibition)	2 (1-2)	2 (1-2)	3 (2-4)
Δ Reaction time (flexibility), msec	584 (537-632)	617 (567-668)	636 (580-692)
Δ Number of errors (flexibility)	2 (2-3)	2 (1-2)	3 (2-3)
Intelligence – full scale IQ (range, 45-155)	102 (100-104)	88 (86-90)	85 (83-88)
Visual-motor integration (range, 0.9-20)	10 (10-10)	9 (8-9)	8 (8-9)
Memory			
Verbal-auditory			
Numbers (range, 1-19)			
Memory span (repeating numbers forward)	9 (9-10)	8 (7-9)	8 (7-8)
Working memory (repeating numbers backward)	11 (10-11)	9 (8-9)	9 (8-9)
Word pairs (proportion of correct responses)			
Learning	0.52 (0.49-0.55)	0.44 (0.41-0.48)	0.41 (0.38-0.45)
Immediate memory	0.50 (0.46-0.53)	0.36 (0.32-0.40)	0.33 (0.29-0.37)
Delayed memory	0.42 (0.38-0.45)	0.31 (0.27-0.34)	0.27 (0.23-0.30)
Recognition	0.96 (0.95-0.98)	0.93 (0.90-0.95)	0.90 (0.87-0.93)
Non-verbal, visual-spatial (proportion of correct responses)			
Pictures: Memory span	0.86 (0.84-0.88)	0.80 (0.78-0.83)	0.75 (0.72-0.78)
Dots: Learning	0.86 (0.84-0.89)	0.78 (0.75-0.81)	0.74 (0.71-0.78)
Dots: Immediate memory	0.87 (0.84-0.90)	0.77 (0.73-0.82)	0.73 (0.68-0.78)
Dots: Delayed memory	0.86 (0.82-0.89)	0.75 (0.70-0.79)	0.73 (0.68-0.78)
Learning index (range, 50-150)	100 (97-102)	92 (89-94)	89 (86-92)
Behavior (by proxy), T score			
CBCL-internalizing problems (range, 29-100)	49 (47-50)	54 (52-55)	52 (51-54)
CBCL-externalizing problems (range, 28-100)	48 (46-49)	50 (49-52)	50 (49-52)
CBCL-total problems (range, 24-100)	48 (46-49)	52 (51-54)	52 (51-54)

IQ, intelligence quotient; CBCL, Child Behavior Checklist. For intelligence, visual-motor integration, motor coordination and memory, higher scores reflect better performance. For reaction times, inconsistency of alertness, inhibition and flexibility, higher scores reflect worse performance. Internalizing problems (e.g. anxious/depressed behavior) and externalizing problems (e.g. aggressive behavior) are calculated as standardized T-scores, which indicate the presence of behavioral problems when higher than 60.^{S10,S11} Memory was only tested from the age of 5 years onwards (N=124 for the healthy control group, N=96 for the development cohort and N=102 for the validation cohort). Ranges indicate the respective range of possible scores. Data are presented as means and 95% confidence intervals.

^a 215 healthy children neurocognitively tested in Mesotten et al [1].

eTable 2B. Neurocognitive test results in critically ill and healthy children

Neurocognitive tests	Healthy children ^a	Critically ill children
Attention, motor coordination and executive functions		
<i>Alertness (msec)</i>		
Reaction time dominant hand	230 – 1557	221 – 2189
Reaction time nondominant hand	223 – 1532	207 – 1883
Reaction time overall	227 – 1428	214 – 1843
<i>Inconsistency of alertness (msec)</i>		
SD reaction time dominant hand	24 – 1004	30 – 1258
SD reaction time nondominant hand	19 – 982	22 – 1168
SD reaction time overall	29 – 861	34 – 1141
<i>Motor coordination (number of taps in 10s)</i>		
Number of unimanual taps		
Dominant hand	10 – 66	1 – 76
Nondominant hand	8 – 79	2 – 89
Number of valid alternating taps	0 – 79	0 – 97
Number of valid synchronous taps	0 – 52	0 – 58
<i>Inhibition and flexibility</i>		
Δ Reaction time (inhibition), msec	-345 – 1363	-557 – 1640
Δ Number of errors (inhibition)	-9 – 26	-11 – 29
Δ Reaction time (flexibility), msec	-361 – 1504	-817 – 1680
Δ Number of errors (flexibility)	-6 – 29	-7 – 16
Intelligence – full scale IQ (range, 45-155)	57 – 142	45 – 139
Visual-motor integration (range, 0.9-20)	4 – 17	0.9 – 19
Memory		
<i>Verbal-auditory</i>		
Numbers (range, 1-19)		
Memory span (repeating numbers forward)	3 – 19	2 – 18
Working memory (repeating numbers backward)	3 – 18	1 – 17
Word pairs (proportion of correct responses)		
Learning	0.17 – 0.93	0.03 – 0.83
Immediate memory	0.00 – 1.00	0.00 – 1.00
Delayed memory	0.00 – 0.93	0.00 – 0.64
Recognition	0.57 – 1.00	0.40 – 1.00
<i>Non-verbal, visual-spatial</i> (proportion of correct responses)		
Pictures: Memory span	0.53 – 1.00	0.27 – 1.00
Dots: Learning	0.50 – 1.00	0.17 – 1.00
Dots: Immediate memory	0.33 – 1.00	0.13 – 1.00
Dots: Delayed memory	0.17 – 1.00	0.13 – 1.00
<i>Learning index</i> (range, 50-150)	67 – 135	50 – 125
Behavior (by proxy), T score		
<i>CBCL-internalizing problems</i> (range, 29-100)	29 – 78	29 – 90
<i>CBCL-externalizing problems</i> (range, 28-100)	28 – 79	28 – 97
<i>CBCL-total problems</i> (range, 24-100)	28 – 76	28 – 86

IQ, intelligence quotient; CBCL, Child Behavior Checklist. For intelligence, visual-motor integration, motor coordination and memory, higher scores reflect better performance. For reaction times, inconsistency of alertness, inhibition and flexibility, higher scores reflect worse performance. Internalizing problems (e.g. anxious/depressed behavior) and externalizing problems (e.g. aggressive behavior) are calculated as standardized T-scores, which indicate the presence of behavioral problems when higher than 60.^{S10,S11} Memory was only tested from the age of 5 years onwards (N=124 for the healthy control group, N=198 for the critically ill group). Ranges indicated with the tests indicate the respective range of possible scores. Data are presented as the ranges of the actual scores of the children that were tested here. ^a 215 healthy children neurocognitively tested in Mesotten et al [1].

eTable 3. Evaluation of DEHP leaching from indwelling medical devices and their accessories

		INDWELLING MEDICAL DEVICES AND ESSENTIAL ACCESSORIES			
ACCESS		Leaching DEHP		Not leaching DEHP	
		Product	Reference	Product	Reference
Intravascular	Intravenous, central: catheters and accessories	Burette from Dialex Biomedica©	1.101.834	2-way infusion system from Dialex Biomedica©	1.101.569
		Monitoring Set from Edwards©	T322242B	Central venous catheters from: Cook© Arrow©	C-SDLM-401J ES-04150
	Intravenous, peripheral: catheters and accessories	Peripheral intravenous catheters from BD©	381323	2-way infusion system from Dialex Biomedica©	1.101.569
	Arterial catheters and accessories	Monitoring Set from Edwards©	T322242B	Baby Flush from ICU Medical©	011-H3543
		Vamp Junior from Edwards©	VMP306	Arterial catheters from BD©	381112 682245
	Blood transfusion systems and accessories	Arterial catheters from BD©	381123	Burette from Hospira©	14202
Extravascular	Parenteral nutrition	Blood infusion system from Baxter©	EMC0349		
		Parenteral nutrition bags from: Fresenius Kabi© Baxter© (Olimel N7E 1500 ml)	B2859061 JDB3WG1F	Parenteral nutrition bags from Baxter©	E13020D E13100D
	Endotracheal tubes	Tracheal tubes from: Portex©	100/105/040 100/111/060		
		Mallinckrodt Pharmaceuticals©	111-50 107-75		
		Hudson RCI©	5-10108		
		Gastric tubes from: Vygon© Covidien©	312.06 8888265215		
	Chest tubes and accessories	Chest tubes from: Biovac© Cook©	MW-3240 C-PPD-850-WCE-IMH	Trocart Catheter from Covidien©	8888561027
	Bladder catheters	Bladder catheters from Coloplast©	AA6106	Bladder catheters from RÜSH©	178000

eTable 4-1. Identification of a potentially harmful threshold for total circulating DEHP metabolite exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
Total DEHP metabolites	228	228	0.779096347	0.342825765	2.65980847	2.316982705

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Memory span, numbers	0.143670286	0.133669352	0.158417234	1.07	0.445208161	0.000511239
Valid alternating taps	0.151467872	0.121789452	0.539447492	18.03	0.392184844	0.025200611
Flexibility, no. of errors	0.191940639	0.051886074	1.670249568	69.85	0.203026651	0.148026269
Delayed memory, word pairs	0.194520746	0.189360531	0.267549318	3.37	0.4366197	0.020672514
Memory, learning dots	0.206213742	0.110435775	0.332131235	9.57	0.383884834	0.005619255
Memory, learning index	0.206213742	0.0742137	0.339191614	11.44	0.50811701	0.014135509
Immediate memory, word pairs	0.267549318	0.194520746	1.099340726	39.05	0.415275622	0.086384103
Memory, learning word pairs	0.515685042	0.320136106	0.750663806	18.58	0.422403776	0.216127217
Valid synchronous taps	0.521530322	0.449562424	0.550840276	4.37	0.665907155	0.000665777
Reaction time dominant hand	0.550840276	0.539447492	0.662911628	5.33	0.58889347	0.000275916
Overall reaction time	0.550840276	0.543450892	0.773896204	9.95	0.610242084	0.000444206
Tapping nondominant hand	0.550840276	0.536405246	0.784296489	10.70	0.771988658	0.017782567
Memory, recognition word pairs	0.614366643	0.091928441	0.627847002	23.13	0.371859993	0.063394432
Delayed memory, dots	0.662911628	0.206213742	5.367595338	222.76	0.376333035	0.135551668
Working memory	0.683336988	0.435053444	0.773896204	14.62	0.368451424	0.036491498
Inhibition, Δ reaction time	0.683336988	0.46387171	3.852489087	146.25	0.287961843	0.06897673
Reaction time nondominant hand	0.753720162	0.550840276	0.883647126	14.36	0.564002771	0.001276149
Tapping dominant hand	0.767363568	0.550840276	7.536841592	301.51	0.768181597	0.031658515
Visual-motor integration	0.784296489	0.398008486	1.354535502	41.28	0.369773452	0.094379326
Externalizing problems	0.886750746	0.261250575	5.012589435	205.07	0.187101664	0.324292474
Total behavioral problems	1.031935378	0.261250575	7.892008515	329.34	0.219259905	0.238124858
Memory span, pictures	1.279688322	0.364714796	5.134469873	205.86	0.483989488	0.185579236
Inhibition, no. of errors	2.662411884	0.424722276	2.866534115	105.39	0.14069656	0.048655446
Verbal IQ	3.38976969	0.136586557	3.579672685	148.60	0.380477581	0.024910988
Full-scale IQ	3.475090696	0.217754045	3.579672685	145.10	0.37081073	0.020084966
Internalizing problems	3.475090696	0.334032527	10.7580311	449.90	0.222447232	0.216614423
Performance IQ	3.579672685	0.804960108	14.92518408	609.42	0.317392131	0.023300757
Immediate memory, dots	7.044402204	1.354535502	10.7580311	405.85	0.401223192	0.001697544
Flexibility, Δ reaction time	8.627097918	2.679551866	16.4259857	593.29	0.317867768	0.029917931

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.133669352	Memory span, numbers	0.456035568	0.000228169	0.000166629	0.00155615
	Memory, learning dots	0.367560744	0.009003253	0.005943164	0.024913385
	Memory, learning index	0.475160863	0.107771088	0.07205136	0.195748668
	Delayed memory, word pairs	0.421010706	0.034506423	0.025037878	0.068810117
	Valid alternating taps	0.371736381	0.59727575	0.520610327	0.718849658
0.550840276	Overall reaction time	0.613460036	0.0000834	0.0000528	0.000596427
	Reaction time dominant hand	0.589378727	0.000125005	0.0000716	0.000500706
	Valid synchronous taps	0.667359331	0.00050767	0.000267123	0.002461922
	Reaction time nondominant hand	0.565142773	0.000529972	0.000366328	0.003027742
	Tapping nondominant hand	0.772780822	0.009737228	0.005759908	0.025941555
	Working memory	0.343977504	0.12523501	0.094619111	0.231083458

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Both thresholds dichotomize the development cohort with at least 10 patients per group and are retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 4-2. Identification of a potentially harmful threshold for total circulating MEHP metabolite exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
Total MEHP metabolites	228	228	0.473072615	0.218775794	1.775369139	1.556593345

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Inhibition, no. of errors	0.021387148	0.021387148	1.191199159	75.15	0.198924332	0.0000113
Memory, recognition word pairs	0.03144131	0.021387148	0.250863337	14.74	0.417899227	0.001761387
Memory, learning index	0.043117112	0.021387148	0.216860657	12.56	0.496707124	0.025819153
Memory, learning dots	0.061242492	0.021387148	0.242893228	14.23	0.362731921	0.087113465
Delayed memory, word pairs	0.061242492	0.043117112	0.236277541	12.41	0.411164461	0.123376802
Valid alternating taps	0.112620719	0.086901369	0.607738767	33.46	0.383348874	0.094179791
Memory span, numbers	0.118667007	0.11672104	0.364705952	15.93	0.400740633	0.028220267
Immediate memory, word pairs	0.213956516	0.045063079	0.445413	25.72	0.4070281	0.187229517
Memory, learning word pairs	0.250863337	0.11022957	0.460060208	22.47	0.425370087	0.098384389
Visual-motor integration	0.264266822	0.045063079	0.64477232	38.53	0.371199871	0.063581423
Memory span, pictures	0.289237642	0.021387148	1.977354132	125.66	0.497322453	0.080253591
Flexibility, no. of errors	0.318487242	0.080396323	2.408666507	149.57	0.196486829	0.154280849
Delayed memory, dots	0.331950185	0.078900475	1.977354132	121.96	0.368035721	0.314942106
Valid synchronous taps	0.352831701	0.35192904	0.389415405	2.41	0.660464737	0.002396296
Overall reaction time	0.364705952	0.362281636	0.391998458	1.91	0.615477434	0.0000971
Reaction time dominant hand	0.364705952	0.364705952	0.432444829	4.35	0.589873273	0.00011341
Reaction time nondominant hand	0.389415405	0.364705952	0.449527327	5.45	0.564489151	0.001005303
Working memory	0.416968924	0.269336151	0.520044835	16.11	0.398837827	0.0075893
Inhibition, Δ reaction time	0.460060208	0.432444829	2.141713834	109.81	0.296746369	0.02675596
Tapping dominant hand	0.586526686	0.128241477	6.12713228	385.39	0.769023437	0.038423401
Tapping nondominant hand	0.606416662	0.268713597	3.917846097	234.43	0.768757733	0.063612044
Performance IQ	0.645051793	0.022360131	6.787361443	434.60	0.327524068	0.004662879
Externalizing problems	0.856153153	0.264266822	4.145566682	249.35	0.187861415	0.248474572
Full-scale IQ	3.109146442	0.022360131	3.885859353	248.20	0.377265652	0.00442295
Verbal IQ	3.109146442	0.095315404	3.117832389	194.18	0.384282106	0.013316581
Total behavioral problems	3.117832389	0.406434099	5.860541167	350.39	0.221104076	0.162878696
Immediate memory, dots	3.238985638	0.235777629	8.245434559	514.56	0.390920609	0.01568226
Internalizing problems	3.238985638	0.712552764	5.124914255	283.46	0.228192537	0.094565592
Flexibility, Δ reaction time	4.53192005	0.119249716	12.30178464	782.64	0.320392501	0.025894113

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.021387148	Memory, recognition word pairs	0.416519471	0.000453118	0.000441799	0.000571175
	Memory, learning index	0.50249533	0.004299438	0.004035218	0.005972278
	Memory span, numbers	0.348377053	0.380427605	0.323205082	0.431830043
0.364705952	Overall reaction time	0.618699698	0.0000368	0.0000204	0.000221145
	Reaction time dominant hand	0.594789034	0.0000491	0.0000286	0.000278926
	Reaction time nondominant hand	0.567307737	0.000335429	0.000203957	0.001901431
	Valid synchronous taps	0.662466894	0.002374469	0.001192846	0.00931671
	Working memory	0.358960568	0.047590038	0.040114119	0.099208925

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Only the green threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 4-3. Identification of a potentially harmful threshold for circulating MEHP exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
MEHP	228	210	0.225982611	0.098800029	0.680283107	0.581483078

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Memory span, numbers	0.01652655	0.01652655	0.030897464	2.47	0.456156939	0.000226
Delayed memory, word pairs	0.046705468	0.041316376	0.05460947	2.29	0.464414384	0.001429523
Valid alternating taps	0.048501832	0.048501832	0.403822663	61.11	0.388447357	0.01932192
Memory, learning dots	0.051016742	0.047424014	0.266580441	37.69	0.374734968	0.011173828
Memory, learning index	0.055328016	0.05460947	0.066106201	1.98	0.524543499	0.004446924
Full-scale IQ	0.055328016	0.040957103	0.517352878	81.93	0.36407142	0.067974087
Verbal IQ	0.055328016	0.030538191	0.477293957	76.83	0.373988538	0.093855571
Memory, learning word pairs	0.08119566	0.055328016	0.118560034	10.87	0.43721618	0.046937764
Immediate memory, word pairs	0.08119566	0.05460947	0.485018323	74.02	0.417195211	0.134193896
Reaction time nondominant hand	0.118560034	0.103470576	0.1573615	9.27	0.559747605	0.002257383
Tapping dominant hand	0.13580513	0.10778185	0.506574693	68.58	0.766258683	0.088347566
Externalizing problems	0.137242222	0.048322196	0.69519293	111.24	0.208736425	0.014992751
Overall reaction time	0.150714953	0.10778185	0.1573615	8.53	0.601436331	0.001913259
Valid synchronous taps	0.155205863	0.109937487	0.1573615	8.16	0.673002843	0.0000923
Reaction time dominant hand	0.155205863	0.10778185	0.1573615	8.53	0.574663982	0.005822439
Tapping nondominant hand	0.1573615	0.115326579	0.364302651	42.82	0.771482955	0.03507091
Total behavioral problems	0.165984048	0.103829849	1.901271826	309.11	0.238312539	0.008833957
Working memory	0.170295322	0.061076381	0.328016095	45.91	0.34648295	0.197715935
Delayed memory, dots	0.198677876	0.055328016	1.921391104	320.91	0.395776692	0.038840386
Visual-motor integration	0.204426241	0.099159302	0.837464971	126.97	0.366179988	0.094847986
Memory, recognition word pairs	0.348135374	0.328016095	0.348135374	3.46	0.416498886	0.001576333
Performance IQ	0.388014658	0.055328016	0.816986419	130.99	0.306226162	0.108983294
Flexibility, no. of errors	0.394481569	0.023712007	1.929295107	327.71	0.199400909	0.110967296
Memory span, pictures	0.395559388	0.027484372	2.512394913	427.34	0.499064093	0.082270048
Inhibition, no. of errors	0.633757275	0.080477114	0.953869368	150.20	0.128412414	0.169810064
Inhibition, Δ reaction time	0.816986419	0.241431343	7.996335417	1333.64	0.283228787	0.235367451
Internalizing problems	1.76223324	0.10778185	1.922828196	312.14	0.244751977	0.008112363
Immediate memory, dots	2.512394913	0.721060573	3.809010563	531.05	0.406544379	0.001508481
Flexibility, Δ reaction time	4.123733563	0.684055472	5.165624775	770.71	0.321264817	0.043496988

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.01652655	Memory span, numbers	0.468627111	0.000115141	0.0000630	0.001830743
	Delayed memory, word pairs	0.399560086	0.122722085	0.093620448	0.19019494
	Memory, learning index	0.45822248	0.387351835	0.304616069	0.500786651
0.1573615	Valid synchronous taps	0.674635535	0.0000572	0.0000207	0.000336337
	Overall reaction time	0.605268151	0.000902865	0.000610691	0.004057737
	Reaction time nondominant hand	0.562165676	0.001344824	0.000892403	0.004666121
	Reaction time dominant hand	0.577159492	0.002661985	0.001815565	0.008299062
0.348135374	Memory, recognition word pairs	0.427473318	0.000679273	0.000492455	0.008760581

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Only the green and blue thresholds dichotomize the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 4-4. Identification of a potentially harmful threshold for circulating 5cx-MEPP exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5cx-MEPP	228	214	0.386436611	0.165407194	1.230824117	1.065416923

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Inhibition, no. of errors	0.008432524	0.008432524	0.526059741	48.58	0.204914231	0.00000751
Memory, learning index	0.018486686	0.008432524	0.201083255	18.08	0.497880348	0.021096827
Memory, recognition word pairs	0.018486686	0.008432524	0.18681283	16.74	0.402612983	0.021986774
Memory, learning dots	0.040540979	0.008432524	0.231894399	20.97	0.361895257	0.087121698
Flexibility, no. of errors	0.056433043	0.032108455	0.991794506	90.08	0.203939268	0.057235519
Delayed memory, word pairs	0.082379269	0.032108455	0.18681283	14.52	0.417082958	0.071529196
Immediate memory, word pairs	0.09275776	0.050270814	0.244218856	18.20	0.409251866	0.181386072
Memory span, numbers	0.11805533	0.02237862	0.306814128	26.70	0.395681763	0.037212558
Valid alternating taps	0.145298868	0.057406026	5.69584536	529.22	0.380053094	0.178293631
Memory, learning word pairs	0.177082995	0.069406156	0.304219505	22.04	0.424458983	0.13162662
Memory span, pictures	0.252002725	0.008432524	1.452988681	135.59	0.499004961	0.098760616
Valid synchronous taps	0.305516816	0.213083385	0.687575001	44.54	0.651481804	0.069236927
Delayed memory, dots	0.305516816	0.040540979	1.628774365	149.07	0.369450978	0.190295554
Working memory	0.378814906	0.262056887	0.38270684	11.32	0.405943121	0.003988965
Overall reaction time	0.387571758	0.244218856	0.670709954	40.03	0.597955832	0.005962203
Inhibition, Δ reaction time	0.387571758	0.344436156	2.084130639	163.29	0.29968163	0.009767576
Reaction time dominant hand	0.395193462	0.244218856	0.670709954	40.03	0.578355551	0.004191985
Reaction time nondominant hand	0.402815166	0.241948562	0.687575001	41.83	0.551504913	0.024145523
Visual-motor integration	0.433626309	0.060324976	3.038465281	279.53	0.373362084	0.053500674
Tapping dominant hand	0.526059741	0.165407194	4.352155158	392.97	0.767152192	0.031265811
Performance IQ	0.53514092	0.009405507	4.352155158	407.61	0.328978642	0.005337256
Flexibility, Δ reaction time	0.636817696	0.05546006	8.268089385	770.84	0.320594629	0.033636118
Tapping nondominant hand	0.711250933	0.09567671	2.830733305	256.71	0.76848645	0.075051208
Immediate memory, dots	1.663801771	0.056433043	4.91259365	455.80	0.397862514	0.010912635
Full-scale IQ	2.530405734	0.018162359	4.36383096	407.88	0.378248984	0.00308717
Internalizing problems	2.530405734	2.516783965	3.942529108	133.82	0.245045925	0.003891829
Verbal IQ	2.530405734	0.091136121	3.988907988	365.84	0.386256884	0.013705281
Externalizing problems	3.455388707	0.199461616	10.07362242	926.79	0.193329051	0.196570563
Total behavioral problems	3.942529108	2.452891383	10.07362242	715.28	0.228085349	0.044486037

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.008432524	Memory, learning index	0.500464381	0.004395556	0.004031862	0.006697831
	Memory, recognition word pairs	0.416093382	0.000457298	0.000441704	0.000643282
0.378814906	Working memory	0.418206604	0.000917655	0.00082055	0.002173791

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Only the green threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 4-5. Identification of a potentially harmful threshold for circulating 5OH-MEHP exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5OH-MEHP	228	161	0.055378135	0.023102534	0.262281715	0.239179181

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Inhibition, no. of errors	0.008432524	0.008432524	0.526059741	216.42	0.204914231	0.00000751
Memory, learning index	0.018486686	0.008432524	0.201083255	80.55	0.497880348	0.021096827
Memory, recognition word pairs	0.018486686	0.008432524	0.18681283	74.58	0.402612983	0.021986774
Memory, learning dots	0.040540979	0.008432524	0.231894399	93.43	0.361895257	0.087121698
Flexibility, no. of errors	0.056433043	0.032108455	0.991794506	401.24	0.203939268	0.057235519
Delayed memory, word pairs	0.082379269	0.032108455	0.18681283	64.68	0.417082958	0.071529196
Immediate memory, word pairs	0.09275776	0.050270814	0.244218856	81.09	0.409251866	0.181386072
Memory span, numbers	0.11805533	0.02237862	0.306814128	118.92	0.395681763	0.037212558
Valid alternating taps	0.145298868	0.057406026	5.69584536	2357.41	0.380053094	0.178293631
Memory, learning word pairs	0.177082995	0.069406156	0.304219505	98.17	0.424458983	0.13162662
Memory span, pictures	0.252002725	0.008432524	1.452988681	603.96	0.499004961	0.098760616
Valid synchronous taps	0.305516816	0.213083385	0.687575001	198.38	0.651481804	0.069236927
Delayed memory, dots	0.305516816	0.040540979	1.628774365	664.03	0.369450978	0.190295554
Working memory	0.378814906	0.262056887	0.38270684	50.44	0.405943121	0.003988965
Overall reaction time	0.387571758	0.244218856	0.670709954	178.31	0.597955832	0.005962203
Inhibition, Δ reaction time	0.387571758	0.344436156	2.084130639	727.36	0.29968163	0.009767576
Reaction time dominant hand	0.395193462	0.244218856	0.670709954	178.31	0.578355551	0.004191985
Reaction time nondominant hand	0.402815166	0.241948562	0.687575001	186.31	0.551504913	0.024145523
Visual-motor integration	0.433626309	0.060324976	3.038465281	1245.15	0.373362084	0.053500674
Tapping dominant hand	0.526059741	0.165407194	4.352155158	1750.47	0.767152192	0.031265811
Performance IQ	0.53514092	0.009405507	4.352155158	1815.69	0.328978642	0.005337256
Flexibility, Δ reaction time	0.636817696	0.05546006	8.268089385	3433.67	0.320594629	0.033636118
Tapping nondominant hand	0.711250933	0.09567671	2.830733305	1143.52	0.76848645	0.075051208
Immediate memory, dots	1.663801771	0.056433043	4.91259365	2030.34	0.397862514	0.010912635
Full-scale IQ	2.530405734	0.018162359	4.36383096	1816.91	0.378248984	0.00308717
Internalizing problems	2.530405734	2.516783965	3.942529108	596.10	0.245045925	0.003891829
Verbal IQ	2.530405734	0.091136121	3.988907988	1629.65	0.386256884	0.013705281
Externalizing problems	3.455388707	0.199461616	10.07362242	4128.35	0.193329051	0.196570563
Total behavioral problems	3.942529108	2.452891383	10.07362242	3186.20	0.228085349	0.044486037

For none of the neurocognitive tests, criteria for selection are met (median, 25th and 75th percentile lower than or equal to 0.05. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

eTable 4-6. Identification of a potentially harmful threshold for circulating 5oxo-MEHP exposure

A. Descriptive statistics

Exposure to	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5oxo-MEHP	228	127	0.029247768	0.013683166	0.118701468	0.105018302

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Valid alternating taps	0.01231485	0.008551979	0.038312866	28.34	0.386470139	0.0358
Memory, recognition word pairs	0.01231485	0.006499504	0.024629699	17.26	0.359232535	0.091314531
Memory, learning index	0.019840591	0.019840591	0.051996032	30.62	0.48758716	0.028042766
Delayed memory, word pairs	0.019840591	0.014367325	0.045496528	29.64	0.41074448	0.154760835
Verbal IQ	0.020524749	0.019840591	0.081414839	58.63	0.376472053	0.054768623
Valid synchronous taps	0.023603462	0.017788117	0.028734649	10.42	0.652936677	0.02174489
Delayed memory, dots	0.024629699	0.015051483	0.170013341	147.56	0.371486219	0.120945667
Memory, learning dots	0.024629699	0.019840591	0.170013341	143.00	0.337850591	0.190970481
Immediate memory, word pairs	0.025998016	0.012999008	0.045496528	30.94	0.415157103	0.099743387
Memory, learning word pairs	0.026682174	0.013683166	0.051996032	36.48	0.428197592	0.123253886
Tapping nondominant hand	0.028734649	0.004789108	0.035918312	29.64	0.775871956	0.00182606
Memory span, numbers	0.028734649	0.023603462	0.06499504	39.41	0.366148304	0.27531837
Overall reaction time	0.029760887	0.028734649	0.03249752	3.58	0.622493453	0.0000128
Reaction time dominant hand	0.029760887	0.027366333	0.033523757	5.86	0.58950272	0.000166767
Memory span, pictures	0.029760887	0.026682174	0.038997024	11.73	0.506648251	0.013025399
Reaction time nondominant hand	0.030787124	0.029760887	0.033523757	3.58	0.583298906	0.00000719
Tapping dominant hand	0.030787124	0.028734649	0.042759895	13.36	0.770433799	0.003932781
Visual-motor integration	0.041733657	0.025998016	0.06499504	37.13	0.365084558	0.09127876
Working memory	0.041733657	0.019498512	0.045496528	24.76	0.358098753	0.118349624
Full-scale IQ	0.049943557	0.020524749	0.281360107	248.37	0.362530866	0.100886835
Performance IQ	0.049943557	0.042417815	0.431019738	370.03	0.304956134	0.114359709
Flexibility, no. of errors	0.058495536	0.029760887	0.307871241	264.82	0.205594865	0.053638862
Inhibition, Δ reaction time	0.070981425	0.036260391	0.243218281	197.07	0.294004649	0.034270297
Flexibility, Δ reaction time	0.156501214	0.044128211	0.636951391	564.50	0.312811148	0.068752976
Inhibition, no. of errors	0.160093046	0.055074745	0.189853932	128.34	0.139740833	0.04261267
Externalizing problems	0.170013341	0.060205932	0.172407895	106.84	0.205615656	0.023100389
Total behavioral problems	0.172407895	0.037970786	0.189853932	144.63	0.229445291	0.033112994
Internalizing problems	0.181644032	0.035576232	0.445387063	390.23	0.231914244	0.047053046
Immediate memory, dots	0.517223686	0.038997024	0.889747888	810.10	0.384466955	0.038611691

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.023603462	Valid synchronous taps	0.657438104	0.011034807	0.007472748	0.029778369
0.030787124	Reaction time nondominant hand	0.584787654	0.00000443	0.00000352	0.0000194
	Overall reaction time	0.620162398	0.0000167	0.0000128	0.0000977
	Reaction time dominant hand	0.585388226	0.000414661	0.000286864	0.001806588
	Tapping dominant hand	0.770650078	0.00239275	0.001495413	0.007403731
	Memory span, pictures	0.502271868	0.019683833	0.011171404	0.051572301

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Both thresholds dichotomize the development cohort with at least 10 patients per group and are retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 5-1. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-9.84 [-44.56;24.88]	0.57	-3.88 [-40.54;32.79]	0.83
Age at sampling (per year added)	-435.61 [-505.28;-365.94]	<0.001	-430.78 [-521.67;-339.89]	<0.001
Caucasian vs. other race	28.94 [-97.07;154.96]	0.65	83.54 [-38.65;205.72]	0.17
Exclusively European vs. other origin	-13.16 [-117.90;91.58]	0.80	-127.62 [-253.73;-1.51]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	54.88 [-0.09;109.85]	0.05	51.21 [-14.97;117.38]	0.12
Socioeconomic status (per category of 1 to 66)	-101.22 [-183.18;-19.25]	0.01	-60.87 [-149.46;27.73]	0.17
Pre-existing syndrome vs. no pre-existing syndrome	24.35 [-20.16;68.87]	0.28	50.94 [2.81;99.07]	0.03
History vs. no history of malignancy	-41.03 [-167.36;85.30]	0.52	7.64 [-105.23;120.50]	0.89
History vs. no history of diabetes	-38.42 [-214.86;138.01]	0.66		
Randomization to strict glycemic control vs. conventional therapy	5.27 [-28.77;39.32]	0.76	-4.25 [-40.87;32.37]	0.81
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	59.00 [-54.74;172.73]	0.30	199.94 [84.47;315.42]	<0.001
randomized for glycemic control postoperatively	-74.71 [-157.86;8.43]	0.07	78.11 [-15.99;172.21]	0.10
Complicated/high risk surgery or trauma	-56.29 [-180.33;67.74]	0.37	-74.16 [-218.37;70.05]	0.31
Neurological medical disorders	209.21 [-20.64;439.06]	0.07	2.28 [-258.28;262.85]	0.98
Infectious medical diseases	-173.01 [-330.31;-15.71]	0.03	-78.90 [-312.46;154.67]	0.50
Other medical disorders	-63.71 [-227.83;100.41]	0.44	-44.00 [-224.46;136.46]	0.63
Solid organ transplants	99.51 [-153.78;352.80]	0.43	-83.29 [-322.10;155.53]	0.49
PeLOD score first 24 hrs (per point added)	-56.42 [-147.55;34.70]	0.22	33.20 [-62.02;128.41]	0.49
PICU stay (per day added)	17.67 [-88.95;124.28]	0.74	161.03 [-16.63;338.69]	0.07
Exceeding potentially harmful threshold for phthalate exposure	78.26 [37.75;118.76]	0.0002	58.30 [17.88;98.72]	0.004

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-1. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-13.19 [-50.25;23.88]	0.48	-14.61 [-51.37;22.15]	0.43
Age at sampling (per year added)	-434.23 [-521.75;-346.71]	<0.001	-384.52 [-485.88;-283.17]	<0.001
Caucasian vs. other race	7.20 [-125.35;139.76]	0.91	78.55 [-43.18;200.28]	0.20
Exclusively European vs. other origin	-3.01 [-112.88;106.87]	0.95	-125.19 [-250.42;0.04]	0.05
Exclusively Dutch language vs. non-exclusively Dutch language	49.93 [-9.50;109.37]	0.09	62.93 [-2.90;128.75]	0.06
Socioeconomic status (per category of 1 to 66)	-112.52 [-199.78;-25.26]	0.01	-77.58 [-166.60;11.44]	0.08
Pre-existing syndrome vs. no pre-existing syndrome	28.66 [-20.11;77.42]	0.24	57.94 [9.92;105.96]	0.01
History vs. no history of malignancy	-47.43 [-181.89;87.02]	0.48	-8.54 [-119.94;102.87]	0.88
History vs. no history of diabetes	-51.38 [-233.82;131.05]	0.57		
Randomization to strict glycemic control vs. conventional therapy	4.04 [-32.48;40.56]	0.82	6.16 [-31.71;44.02]	0.74
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	247.90 [20.61;475.19]	0.03	131.23 [-40.49;302.95]	0.13
randomized for glycemic control postoperatively	115.29 [-95.03;325.60]	0.28	45.47 [-97.56;188.49]	0.53
Complicated/high risk surgery or trauma	61.29 [-162.22;284.80]	0.58	-42.07 [-204.23;120.09]	0.60
Neurological medical disorders	52.17 [-311.14;415.49]	0.77	-93.68 [-386.10;198.75]	0.52
Infectious medical diseases	-378.65 [-657.44;-99.85]	0.008	18.16 [-237.26;273.59]	0.88
Other medical disorders	-189.13 [-411.63;33.37]	0.09	-8.07 [-261.05;244.91]	0.94
Solid organ transplants	91.13 [-291.72;473.97]	0.63	-51.04 [-327.27;225.18]	0.71
PeLOD score first 24 hrs (per point added)	-48.02 [-156.17;60.13]	0.38	5.91 [-94.06;105.88]	0.90
PICU stay (per day added)	-292.13 [-782.08;197.82]	0.24	-274.46 [-1160.07;611.16]	0.54
Extracorporeal circulation versus no extracorporeal circulation ^a	-40.23 [-122.26;41.79]	0.33	-31.67 [-98.97;35.63]	0.35
Aortic clamp time (per min added)	19.21 [-89.02;127.45]	0.72	146.35 [-4.01;296.71]	0.05
Duration of mechanical ventilation (per day added)	316.60 [-79.68;712.88]	0.11	1804.99 [-12.66;1622.65]	0.05
Peak creatinine (per mg/dl added)	-17.09 [-252.04;217.86]	0.88	-121.82 [-360.72;117.09]	0.31
Peak bilirubine (per mg/dl added)	-75.73 [-250.56;99.10]	0.39	348.95 [7.32;690.57]	0.04
Infection vs. no infection	6.32 [-57.12;69.75]	0.84	38.86 [-16.77;94.48]	0.16
Antibiotics (per day added)	11.77 [-239.13;262.66]	0.92	-595.12 [-1237.02;46.78]	0.06
Duration of hemodynamic support (per day added)	31.25 [-186.85;249.35]	0.77	191.65 [-461.00;844.31]	0.56
Duration of corticosteroid treatment (per day added)	243.95 [-139.05;626.94]	0.21	145.62 [-303.70;594.34]	0.52
Cumulative dose of opioids (per mg morphine-equivalent added)	11.57 [-263.33;286.47]	0.93	-203.07 [-465.07;58.93]	0.12
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	9.30 [-269.57;288.17]	0.94	-89.94 [-280.73;100.84]	0.35
Received hypnotics versus no hypnotics	-155.36 [-349.14;38.41]	0.11	14.62 [-136.98;166.22]	0.84
Exceeding potentially harmful threshold for phthalate exposure	79.37 [34.84; 123.90]	0.0006	61.47 [19.87;103.07]	0.004

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-2. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-19.44 [-51.56;12.68]	0.23	9.26 [-24.61;43.13]	0.59
Age at sampling (per year added)	-392.03 [-456.39;-327.66]	<0.001	-408.37 [-492.34;-324.40]	<0.001
Caucasian vs. other race	-17.03 [-134.36;100.30]	0.77	27.17 [-85.71;140.05]	0.63
Exclusively European vs. other origin	-19.36 [-116.81;78.09]	0.69	-104.86 [-221.36;11.65]	0.07
Exclusively Dutch language vs. non-exclusively Dutch language	52.19 [1.14;103.23]	0.04	64.73 [3.59;125.86]	0.03
Socioeconomic status (per category of 1 to 66)	-52.70 [-128.48;23.09]	0.16	-100.37 [-182.22;-18.52]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	10.05 [-30.91;51.00]	0.62	46.33 [1.86;90.80]	0.04
History vs. no history of malignancy	-28.02 [-145.65;89.61]	0.63	24.86 [-79.41;129.13]	0.63
History vs. no history of diabetes	-6.05 [-170.29;158.18]	0.94		
Randomization to strict glycemic control vs. conventional therapy	5.19 [-26.22;36.60]	0.74	0.90 [-32.93;34.73]	0.95
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	66.70 [-72.16;139.55]	0.53	184.34 [77.65;291.03]	<0.001
randomized for glycemic control postoperatively	-34.00 [-111.02;43.03]	0.38	65.22 [-21.72;152.16]	0.14
Complicated/high risk surgery or trauma	-16.50 [-132.01;99.00]	0.77	-178.35 [-311.58;-45.12]	0.009
Neurological medical disorders	85.91 [-127.79;299.61]	0.42	94.57 [-146.16;335.30]	0.43
Infectious medical diseases	-103.18 [-249.63;43.26]	0.16	-68.99 [-284.78;146.79]	0.52
Other medical disorders	-88.95 [-241.70;63.79]	0.25	-43.84 [-210.57;122.88]	0.60
Solid organ transplants	123.03 [-112.77;358.84]	0.30	-52.94 [-273.58;167.69]	0.63
PeLOD score first 24 hrs (per point added)	-15.20 [-99.69;69.30]	0.72	7.23 [-80.74;95.19]	0.87
PICU stay (per day added)	-14.97 [-112.64;82.69]	0.76	191.94 [27.80;356.07]	0.02
Exceeding potentially harmful threshold for phthalate exposure	64.94 [27.61;102.27]	0.0007	47.92 [10.58;85.27]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-2. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-19.80 [-53.08;13.48]	0.24	3.08 [-31.34;37.50]	0.85
Age at sampling (per year added)	-401.54 [-479.99;-323.09]	<0.001	-376.13 [-471.03;-281.22]	<0.001
Caucasian vs. other race	-41.56 [-161.26;78.14]	0.49	30.11 [-83.88;144.09]	0.60
Exclusively European vs. other origin	-10.14 [-109.27;88.98]	0.84	-104.85 [-222.11;12.42]	0.07
Exclusively Dutch language vs. non-exclusively Dutch language	52.31 [-1.19;105.80]	0.05	74.89 [13.25;136.52]	0.01
Socioeconomic status (per category of 1 to 66)	-61.72 [-139.92;16.48]	0.12	-118.72 [-202.08;-35.36]	0.005
Pre-existing syndrome vs. no pre-existing syndrome	12.51 [-30.87;55.90]	0.57	48.85 [3.89;93.82]	0.03
History vs. no history of malignancy	-28.12 [-149.48;93.24]	0.64	9.27 [-95.05;113.58]	0.86
History vs. no history of diabetes	-25.20 [-189.87;139.47]	0.76		
Randomization to strict glycemic control vs. conventional therapy	6.73 [-25.86;39.33]	0.68	13.09 [-22.37;48.55]	0.46
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	222.03 [18.17;425.89]	0.03	132.77 [-28.03;293.57]	0.10
randomized for glycemic control postoperatively	143.83 [-44.91;332.58]	0.13	35.83 [-98.10;169.76]	0.59
Complicated/high risk surgery or trauma	51.31 [-149.80;252.42]	0.61	-181.13 [-332.97;-29.28]	0.01
Neurological medical disorders	-25.15 [-352.74;302.44]	0.87	82.40 [-191.43;356.23]	0.55
Infectious medical diseases	-277.14 [-528.62;-25.66]	0.03	-25.82 [-265.00;213.36]	0.83
Other medical disorders	-257.33 [-457.91;-56.74]	0.01	44.53 [-192.35;281.42]	0.71
Solid organ transplants	142.45 [-203.28;488.17]	0.41	-88.59 [-347.25;170.07]	0.49
PeLOD score first 24 hrs (per point added)	-7.04 [-104.16;90.07]	0.88	-4.80 [-98.41;88.81]	0.91
PICU stay (per day added)	-167.36 [-601.49;266.78]	0.44	-505.23 [-1334.51;324.06]	0.23
Extracorporeal circulation versus no extracorporeal circulation ^a	-49.11 [-120.84;22.62]	0.17	-55.88 [-118.90;7.14]	0.08
Aortic clamp time (per min added)	-21.89 [-118.94;75.16]	0.65	115.46 [-25.33;256.26]	0.10
Duration of mechanical ventilation (per day added)	192.84 [-158.64;544.32]	0.28	514.37 [-251.27;1280.02]	0.18
Peak creatinine (per mg/dl added)	26.95 [-184.67;238.57]	0.80	-72.47 [-296.18;151.24]	0.52
Peak bilirubine (per mg/dl added)	-184.60 [-342.06;-27.14]	0.02	255.12 [-64.78;575.02]	0.11
Infection vs. no infection	3.70 [-53.36;60.76]	0.89	29.57 [-22.52;81.66]	0.26
Antibiotics (per day added)	-58.12 [-284.48;168.25]	0.61	-153.94 [-755.01;447.13]	0.61
Duration of hemodynamic support (per day added)	57.55 [-139.11;254.21]	0.56	337.02 [-274.12;948.16]	0.27
Duration of corticosteroid treatment (per day added)	189.21 [-155.17;533.59]	0.27	210.17 [-210.57;630.90]	0.32
Cumulative dose of opioids (per mg morphine-equivalent added)	128.19 [-120.15;376.53]	0.30	-169.02 [-414.36;76.32]	0.17
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	117.21 [-134.36;368.78]	0.35	-77.29 [-255.94;101.36]	0.39
Received hypnotics versus no hypnotics	-128.61 [-303.59;46.37]	0.14	69.49 [-72.47;211.45]	0.33
Exceeding potentially harmful threshold for phthalate exposure	70.51 [30.66;110.36]	0.0006	50.89 [11.94;89.85]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-3. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-16.08 [-46.99;14.82]	0.30	3.89 [-29.66;37.45]	0.81
Age at sampling (per year added)	-409.36 [-471.36;-347.35]	<0.001	-419.27 [-502.46;-336.09]	<0.001
Caucasian vs. other race	6.06 [-106.09;118.22]	0.91	55.25 [-56.58;167.07]	0.33
Exclusively European vs. other origin	-15.92 [-109.14;77.30]	0.73	-115.74 [-231.15;-0.32]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	51.47 [2.54;100.39]	0.03	57.25 [-3.31;117.82]	0.06
Socioeconomic status (per category of 1 to 66)	-72.94 [-145.89;0.01]	0.05	-82.78 [-163.86;-1.70]	0.04
Pre-existing syndrome vs. no pre-existing syndrome	14.70 [-24.92;54.32]	0.46	45.98 [1.93;90.03]	0.04
History vs. no history of malignancy	-34.69 [-147.12;77.75]	0.54	16.76 [-86.54;120.05]	0.74
History vs. no history of diabetes	-19.62 [-176.65;137.40]	0.80		
Randomization to strict glycemic control vs. conventional therapy	4.59 [-25.72;34.89]	0.76	-2.38 [-35.90;31.13]	0.88
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	45.33 [-55.89;146.56]	0.37	189.34 [83.65;295.03]	<0.001
randomized for glycemic control postoperatively	-58.25 [-132.25;15.75]	0.12	68.18 [-17.95;154.31]	0.12
Complicated/high risk surgery or trauma	-36.33 [-146.72;74.07]	0.51	-125.59 [-257.57;6.40]	0.06
Neurological medical disorders	151.90 [-52.68;356.47]	0.14	52.36 [-186.12;290.84]	0.66
Infectious medical diseases	-137.53 [-277.53;2.47]	0.05	-75.29 [-289.05;138.48]	0.48
Other medical disorders	-78.85 [-224.91;67.22]	0.28	-42.09 [-207.25;123.07]	0.61
Solid organ transplants	113.72 [-111.71;339.15]	0.32	-66.91 [-285.48;151.66]	0.54
PeLOD score first 24 hrs (per point added)	-33.91 [-115.01;47.20]	0.41	18.12 [-69.02;105.26]	0.68
PICU stay (per day added)	4.14 [-90.74;99.03]	0.93	177.83 [15.23;340.43]	0.03
Exceeding potentially harmful threshold for phthalate exposure	71.44 [35.39;107.49]	0.0001	54.43 [17.44;91.43]	0.004

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-3. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-17.94 [-50.38;14.50]	0.27	-4.31 [-38.07;29.45]	0.80
Age at sampling (per year added)	-412.91 [-489.51;-336.31]	<0.001	-378.36 [-471.45;-285.28]	<0.001
Caucasian vs. other race	-17.14 [-133.16;98.87]	0.77	54.18 [-57.62;165.97]	0.34
Exclusively European vs. other origin	-6.01 [-102.18;90.16]	0.90	-114.97 [-229.98;0.04]	0.05
Exclusively Dutch language vs. non-exclusively Dutch language	49.08 [-2.94;101.10]	0.06	68.29 [7.84;128.75]	0.02
Socioeconomic status (per category of 1 to 66)	-83.53 [-159.91;-7.16]	0.03	-100.21 [-181.97;-18.46]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	18.18 [-24.50;60.87]	0.40	50.27 [6.17;94.38]	0.02
History vs. no history of malignancy	-37.78 [-155.46;79.90]	0.52	1.10 [-101.21;103.42]	0.98
History vs. no history of diabetes	-36.93 [-196.61;122.74]	0.64		
Randomization to strict glycemic control vs. conventional therapy	5.14 [-26.83;37.10]	0.75	8.68 [-26.10;43.46]	0.62
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	239.60 [40.66;438.53]	0.01	130.46 [-27.25;288.17]	0.10
randomized for glycemic control postoperatively	131.45 [-52.62;315.53]	0.16	38.17 [-93.18;169.53]	0.56
Complicated/high risk surgery or trauma	55.35 [-140.28;250.97]	0.57	-111.72 [-260.64;37.21]	0.14
Neurological medical disorders	12.76 [-305.23;330.75]	0.93	-2.85 [-271.42;265.71]	0.98
Infectious medical diseases	-331.22 [-575.23;-87.20]	0.008	-6.49 [-241.07;228.10]	0.95
Other medical disorders	-227.89 [-422.63;-33.15]	0.02	18.87 [-213.47;251.20]	0.87
Solid organ transplants	119.95 [-215.13;455.03]	0.48	-66.45 [-320.13;187.24]	0.60
PeLOD score first 24 hrs (per point added)	-26.31 [-120.96;68.35]	0.58	-2.12 [-93.93;89.69]	0.96
PICU stay (per day added)	-231.16 [-659.98;197.66]	0.28	-384.91 [-1198.26;428.44]	0.35
Extracorporeal circulation versus no extracorporeal circulation ^a	-44.26 [-120.05;23.53]	0.18	-44.29 [-106.10;17.52]	0.15
Aortic clamp time (per min added)	-0.05 [-94.78;94.68]	0.99	130.46 [-7.63;268.55]	0.06
Duration of mechanical ventilation (per day added)	257.58 [-89.36;604.32]	0.14	673.66 [-77.28;1424.59]	0.07
Peak creatinine (per mg/dl added)	6.92 [-198.72;212.56]	0.94	-96.51 [-315.93;122.90]	0.38
Peak bilirubine (per mg/dl added)	-126.67 [-279.69;26.35]	0.10	289.75 [-24.00;603.50]	0.07
Infection vs. no infection	5.81 [-49.71;61.33]	0.83	35.35 [-15.73;86.44]	0.17
Antibiotics (per day added)	-20.26 [-239.86;199.33]	0.85	-380.14 [-969.66;209.39]	0.20
Duration of hemodynamic support (per day added)	45.13 [-145.76;236.02]	0.64	260.13 [-339.27;859.53]	0.39
Duration of corticosteroid treatment (per day added)	213.32 [-121.89;548.53]	0.21	169.05 [-243.61;581.70]	0.41
Cumulative dose of opioids (per mg morphine-equivalent added)	68.47 [-172.14;309.08]	0.57	-187.64 [-428.27;52.98]	0.12
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	61.67 [-182.41;305.75]	0.61	-82.49 [-257.70;92.73]	0.35
Received hypnotics versus no hypnotics	-143.41 [-313.01;26.18]	0.09	42.20 [-97.03;181.43]	0.55
Exceeding potentially harmful threshold for phthalate exposure	74.37 [35.40;113.35]	0.0002	57.59 [19.39;95.80]	0.003

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-4. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	17.39 [-12.31;47.08]	0.24	-0.79 [-34.95;33.38]	0.96
Age at sampling (per year added)	-325.58 [-385.17;-266.00]	<0.001	-337.00 [-421.70;-252.30]	<0.001
Caucasian vs. other race	40.37 [-67.41;148.15]	0.46	69.89 [-43.97;183.75]	0.22
Exclusively European vs. other origin	-36.82 [-126.40;52.76]	0.41	-95.38 [-212.89;22.14]	0.11
Exclusively Dutch language vs. non-exclusively Dutch language	24.77 [-22.25;71.78]	0.30	28.49 [-33.18;90.15]	0.36
Socioeconomic status (per category of 1 to 66)	-80.80 [-150.90;-10.70]	0.02	-109.15 [-191.71;-26.60]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	22.86 [-15.21;60.94]	0.23	63.59 [18.74;108.44]	0.005
History vs. no history of malignancy	-25.34 [-133.38;82.71]	0.64	45.89 [-59.29;151.06]	0.39
History vs. no history of diabetes	-15.98 [-166.88;143.91]	0.83		
Randomization to strict glycemic control vs. conventional therapy	-8.73 [-37.85;20.39]	0.55	7.10 [-27.02;41.23]	0.67
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	72.48 [-24.80;169.75]	0.14	140.59 [32.97;248.20]	0.01
randomized for glycemic control postoperatively	-27.65 [-98.76;43.46]	0.44	58.82 [-28.87;146.51]	0.18
Complicated/high risk surgery or trauma	-22.28 [-128.36;83.80]	0.67	-76.10 [-210.48;58.28]	0.26
Neurological medical disorders	130.64 [-65.94;327.22]	0.19	-0.69 [-243.51;242.13]	0.99
Infectious medical diseases	-126.84 [-261.37;7.69]	0.06	-46.02 [-263.67;171.64]	0.67
Other medical disorders	-12.55 [-152.92;127.81]	0.86	-80.61 [-248.77;87.56]	0.34
Solid organ transplants	-13.80 [-230.42;202.83]	0.90	4.01 [-218.53;226.56]	0.96
PeLOD score first 24 hrs (per point added)	-22.65 [-100.59;55.28]	0.56	29.11 [-59.62;117.84]	0.51
PICU stay (per day added)	9.14 [-82.04;100.32]	0.84	77.28 [-88.28;242.84]	0.36
Exceeding potentially harmful threshold for phthalate exposure	55.81 [21.17;90.46]	0.001	55.76 [18.10;93.43]	0.003

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-4. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	12.14 [-19.90;44.18]	0.45	-12.73 [-46.73;21.28]	0.46
Age at sampling (per year added)	-330.86 [-406.52;-255.21]	<0.001	-292.50 [-386.27;-198.74]	<0.001
Caucasian vs. other race	33.97 [-80.62;148.55]	0.55	80.69 [-31.92;193.31]	0.15
Exclusively European vs. other origin	-37.86 [-132.84;57.12]	0.43	-112.50 [-228.35;3.35]	0.05
Exclusively Dutch language vs. non-exclusively Dutch language	23.56 [-27.82;74.94]	0.36	35.11 [-25.78;96.00]	0.25
Socioeconomic status (per category of 1 to 66)	-81.16 [-156.60;-5.73]	0.03	-122.33 [-204.68;-39.98]	0.003
Pre-existing syndrome vs. no pre-existing syndrome	29.95 [-12.20;72.11]	0.16	69.05 [24.62;113.47]	0.002
History vs. no history of malignancy	-26.34 [-142.57;89.88]	0.65	37.13 [-65.93;140.19]	0.47
History vs. no history of diabetes	-25.59 [-183.29;132.11]	0.74		
Randomization to strict glycemic control vs. conventional therapy	-6.91 [-38.48;24.66]	0.66	15.03 [-20.00;50.06]	0.39
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	198.96 [2.49;395.44]	0.04	48.58 [-110.28;207.44]	0.54
randomized for glycemic control postoperatively	99.33 [-82.47;281.13]	0.28	0.78 [-131.54;133.09]	0.99
Complicated/high risk surgery or trauma	42.46 [-150.74;235.67]	0.66	-97.37 [-247.38;52.65]	0.20
Neurological medical disorders	-6.14 [-320.20;307.92]	0.96	-27.27 [-297.80;243.26]	0.84
Infectious medical diseases	-223.48 [-464.48;17.52]	0.06	37.62 [-198.67;273.92]	0.75
Other medical disorders	-78.98 [-271.32;113.35]	0.41	-32.65 [-266.68;201.39]	0.78
Solid organ transplants	-32.16 [-363.10;298.79]	0.84	70.31 [-185.24;325.85]	0.58
PeLOD score first 24 hrs (per point added)	-32.55 [-126.04;60.93]	0.49	-20.27 [-112.75;72.21]	0.66
PICU stay (per day added)	-168.06 [-591.58;255.46]	0.43	682.78 [-136.52;1502.07]	0.10
Extracorporeal circulation versus no extracorporeal circulation ^a	-19.67 [-90.58;51.23]	0.58	-2.77 [-65.03;59.49]	0.93
Aortic clamp time (per min added)	-4.44 [-98.00;89.11]	0.92	174.48 [35.38;313.58]	0.01
Duration of mechanical ventilation (per day added)	144.69 [-197.86;487.24]	0.40	427.98 [-328.44;1184.40]	0.26
Peak creatinine (per mg/dl added)	26.57 [-176.53;229.67]	0.79	-1.66 [-222.68;219.36]	0.98
Peak bilirubine (per mg/dl added)	-4.13 [-155.26;147.00]	0.95	279.52 [-36.53;595.56]	0.08
Infection vs. no infection	23.01 [-31.83;77.84]	0.40	53.17 [1.71;104.63]	0.04
Antibiotics (per day added)	11.73 [-205.14;228.61]	0.91	-947.58 [-1541.41;-353.75]	0.001
Duration of hemodynamic support (per day added)	11.62 [-176.91;200.15]	0.90	-257.20 [-860.97;346.58]	0.40
Duration of corticosteroid treatment (per day added)	141.94 [-189.13;473.01]	0.39	23.37 [-392.29;439.04]	0.91
Cumulative dose of opioids (per mg morphine-equivalent added)	40.02 [-197.62;277.65]	0.74	-278.65 [-521.03;-36.27]	0.02
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	30.47 [-210.59;271.54]	0.80	-39.56 [-216.05;136.94]	0.65
Received hypnotics versus no hypnotics	-80.90 [-248.41;86.60]	0.34	61.84 [-78.41;202.09]	0.38
Exceeding potentially harmful threshold for phthalate exposure	51.48 [12.98;89.97]	0.009	55.10 [16.62;93.58]	0.005

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-5. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-1.15 [-29.81;27.51]	0.93	4.25 [-28.66;37.17]	0.79
Age at sampling (per year added)	-270.91 [-328.35;-213.48]	<0.001	-310.99 [-392.59;-229.39]	<0.001
Caucasian vs. other race	13.00 [-91.70;117.70]	0.80	21.21 [-88.48;130.91]	0.70
Exclusively European vs. other origin	-48.31 [-135.27;38.65]	0.27	-86.58 [-199.80;26.63]	0.13
Exclusively Dutch language vs. non-exclusively Dutch language	44.86 [-0.69;90.41]	0.05	49.86 [-9.55;109.26]	0.09
Socioeconomic status (per category of 1 to 66)	-33.47 [-101.10;34.16]	0.33	-87.72 [-167.26;-8.19]	0.03
Pre-existing syndrome vs. no pre-existing syndrome	15.58 [-20.97;52.12]	0.40	43.96 [0.75;87.17]	0.04
History vs. no history of malignancy	-57.33 [-162.29;47.64]	0.28	14.67 [-86.66;116.00]	0.77
History vs. no history of diabetes	2.05 [-144.51;148.60]	0.97		
Randomization to strict glycemic control vs. conventional therapy	-7.27 [-35.30;20.76]	0.61	7.44 [-25.44;40.32]	0.65
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	28.50 [-65.95;122.96]	0.55	159.21 [55.54;262.89]	0.002
randomized for glycemic control postoperatively	16.94 [-51.80;85.67]	0.62	46.63 [-37.86;131.11]	0.28
Complicated/high risk surgery or trauma	47.77 [-55.31;150.84]	0.36	-207.07 [-336.54;-77.60]	0.002
Neurological medical disorders	29.35 [-161.34;220.05]	0.76	152.36 [-81.57;386.29]	0.20
Infectious medical diseases	-123.44 [-254.12;7.24]	0.06	-118.29 [-327.98;91.40]	0.27
Other medical disorders	-61.02 [-197.32;75.28]	0.37	-50.80 [-212.81;111.22]	0.53
Solid organ transplants	61.89 [-148.53;272.32]	0.56	17.95 [-196.45;232.35]	0.86
PeLOD score first 24 hrs (per point added)	-5.34 [-80.73;70.06]	0.88	32.25 [-53.23;117.73]	0.45
PICU stay (per day added)	7.91 [-79.24;95.07]	0.85	88.04 [-71.46;247.54]	0.27
Exceeding potentially harmful threshold for phthalate exposure	43.16 [9.84;76.47]	0.01	30.15 [-6.15;66.44]	0.10

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-5. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	2.63 [-27.31;32.57]	0.86	0.21 [-33.98;34.41]	0.99
Age at sampling (per year added)	-295.79 [-366.37;-225.21]	<0.001	-299.07 [-393.37;-204.78]	<0.001
Caucasian vs. other race	-4.84 [-112.53;102.86]	0.92	22.64 [-90.61;135.89]	0.69
Exclusively European vs. other origin	-45.76 [-134.94;43.43]	0.31	-84.94 [-201.44;31.56]	0.15
Exclusively Dutch language vs. non-exclusively Dutch language	49.63 [1.50;97.76]	0.04	58.14 [-3.10;119.38]	0.06
Socioeconomic status (per category of 1 to 66)	-43.48 [-113.83;26.88]	0.22	-110.02 [-192.84;-27.20]	0.009
Pre-existing syndrome vs. no pre-existing syndrome	18.90 [-20.13;57.93]	0.34	45.19 [0.51;89.86]	0.04
History vs. no history of malignancy	-75.93 [-185.11;33.26]	0.17	3.06 [-100.58;106.70]	0.95
History vs. no history of diabetes	-6.07 [-154.22;142.08]	0.93		
Randomization to strict glycemic control vs. conventional therapy	-9.30 [-38.63;20.02]	0.53	16.71 [-18.52;51.94]	0.35
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	127.66 [-55.75;311.08]	0.17	184.21 [24.45;343.97]	0.02
randomized for glycemic control postoperatively	113.20 [-56.61;283.01]	0.19	78.60 [-54.46;211.66]	0.24
Complicated/high risk surgery or trauma	110.52 [-70.41;291.46]	0.22	-221.02 [-371.89;-70.16]	0.004
Neurological medical disorders	-7.04 [-301.76;287.69]	0.96	152.41 [-119.64;424.46]	0.27
Infectious medical diseases	-186.53 [-412.78;39.73]	0.10	-105.75 [-343.38;131.88]	0.38
Other medical disorders	-147.21 [-327.67;33.26]	0.10	-2.03 [-237.39;233.32]	0.98
Solid organ transplants	-10.61 [-321.65;300.44]	0.94	-86.41 [-343.40;170.57]	0.50
PeLOD score first 24 hrs (per point added)	-5.96 [-93.33;81.42]	0.89	17.01 [-75.99;110.01]	0.71
PICU stay (per day added)	-177.19 [-567.78;213.40]	0.37	-437.67 [-1261.58;386.25]	0.29
Extracorporeal circulation versus no extracorporeal circulation ^a	-24.12 [-88.66;40.41]	0.46	-63.43 [-126.04;-0.81]	0.04
Aortic clamp time (per min added)	-3.31 [-90.63;84.01]	0.94	127.45 [-12.43;267.34]	0.07
Duration of mechanical ventilation (per day added)	210.43 [-105.79;526.66]	0.19	422.23 [-338.45;1182.92]	0.27
Peak creatinine (per mg/dl added)	97.85 [-92.54;288.25]	0.31	18.98 [-203.29;241.24]	0.86
Peak bilirubine (per mg/dl added)	-176.52 [-318.19;-34.85]	0.01	122.78 [-195.04;440.61]	0.44
Infection vs. no infection	-17.17 [-68.50;34.17]	0.51	29.54 [-22.21;81.29]	0.26
Antibiotics (per day added)	-57.36 [-261.01;146.30]	0.57	-174.71 [-771.89;422.47]	0.56
Duration of hemodynamic support (per day added)	73.11 [-103.83;250.04]	0.41	110.37 [-496.81;717.55]	0.72
Duration of corticosteroid treatment (per day added)	295.25 [-14.59;605.09]	0.06	350.06 [-67.95;768.07]	0.10
Cumulative dose of opioids (per mg morphine-equivalent added)	129.64 [-93.79;353.07]	0.25	-64.81 [-308.56;178.93]	0.60
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	106.94 [-119.40;333.27]	0.35	-41.26 [-218.75;136.23]	0.64
Received hypnotics versus no hypnotics	-64.26 [-221.69;93.17]	0.42	52.07 [-88.97;193.11]	0.46
Exceeding potentially harmful threshold for phthalate exposure	47.68 [11.83;83.53]	0.009	30.20 [-8.50;68.90]	0.12

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-6. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	7.64 [-17.97;33.25]	0.55	-0.45 [-30.25;29.34]	0.97
Age at sampling (per year added)	-305.31 [-356.70;-253.92]	<0.001	-330.18 [-403.78;-256.58]	<0.001
Caucasian vs. other race	29.14 [-63.81;122.09]	0.53	44.97 [-53.97;143.91]	0.37
Exclusively European vs. other origin	-42.62 [-119.88;34.64]	0.27	-91.44 [-193.56;10.69]	0.07
Exclusively Dutch language vs. non-exclusively Dutch language	37.11 [-3.44;77.66]	0.07	42.63 [-10.96;96.23]	0.11
Socioeconomic status (per category of 1 to 66)	-50.68 [-111.14;9.78]	0.09	-98.65 [-170.51;-26.79]	0.007
Pre-existing syndrome vs. no pre-existing syndrome	18.49 [-14.35;51.33]	0.26	53.02 [13.69;92.35]	0.008
History vs. no history of malignancy	-43.47 [-136.65;49.71]	0.35	31.14 [-60.27;122.54]	0.50
History vs. no history of diabetes	-14.51 [-144.65;115.63]	0.82		
Randomization to strict glycemic control vs. conventional therapy	-7.07 [-32.18;18.04]	0.57	4.87 [-24.84;34.58]	0.74
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	50.97 [-32.92;134.87]	0.23	144.80 [51.08;238.51]	0.002
randomized for glycemic control postoperatively	-12.67 [-73.99;48.66]	0.68	54.28 [-22.23;130.79]	0.16
Complicated/high risk surgery or trauma	11.30 [-80.19;102.79]	0.80	-128.45 [-245.24;-11.67]	0.03
Neurological medical disorders	93.02 [-76.52;262.57]	0.28	75.45 [-135.67;286.57]	0.48
Infectious medical diseases	-117.66 [-233.69;-1.63]	0.04	-87.25 [-276.41;101.90]	0.36
Other medical disorders	-31.17 [-152.23;89.89]	0.61	-66.38 [-212.57;79.80]	0.37
Solid organ transplants	6.20 [-180.63;193.03]	0.94	7.56 [-185.86;200.98]	0.93
PeLOD score first 24 hrs (per point added)	-9.85 [-77.06;57.37]	0.77	31.36 [-45.81;108.54]	0.42
PICU stay (per day added)	9.05 [-69.59;87.69]	0.82	83.35 [-60.52;227.23]	0.25
Exceeding potentially harmful threshold for phthalate exposure	53.91 [24.03;83.79]	0.0005	44.36 [11.54;77.17]	0.008

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-6. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and inconsistency of reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	6.49 [-20.81;33.79]	0.63	-8.36 [-38.80;22.09]	0.58
Age at sampling (per year added)	-325.69 [-390.14;-261.23]	<0.001	-301.39 [-385.02;-217.76]	<0.001
Caucasian vs. other race	15.81 [-81.81;113.44]	0.74	50.32 [-50.09;150.72]	0.32
Exclusively European vs. other origin	-42.46 [-123.38;38.47]	0.30	-98.79 [-202.08;4.49]	0.06
Exclusively Dutch language vs. non-exclusively Dutch language	38.57 [-5.20;82.34]	0.08	50.41 [-3.88;104.71]	0.06
Socioeconomic status (per category of 1 to 66)	-54.87 [-119.14;9.40]	0.09	-117.57 [-191.11;-44.02]	0.001
Pre-existing syndrome vs. no pre-existing syndrome	23.91 [-12.01;59.82]	0.19	56.33 [16.27;96.39]	0.006
History vs. no history of malignancy	-54.58 [-153.60;44.44]	0.27	20.96 [-70.95;112.86]	0.65
History vs. no history of diabetes	-24.01 [-158.37;110.35]	0.72		
Randomization to strict glycemic control vs. conventional therapy	-7.12 [-34.02;19.77]	0.60	13.54 [-17.77;44.85]	0.39
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	168.24 [0.84;335.63]	0.04	117.30 [-24.35;258.95]	0.10
randomized for glycemic control postoperatively	104.13 [-50.76;259.02]	0.18	46.81 [-71.20;164.82]	0.43
Complicated/high risk surgery or trauma	81.58 [-83.03;246.19]	0.32	-143.60 [-277.36;-9.85]	0.03
Neurological medical disorders	-18.70 [-286.28;248.87]	0.89	53.40 [-187.84;294.65]	0.66
Infectious medical diseases	-207.57 [-412.90;-2.24]	0.04	-44.65 [-255.43;166.13]	0.67
Other medical disorders	-107.94 [-271.81;55.93]	0.19	-28.14 [-236.80;180.52]	0.79
Solid organ transplants	-19.74 [-301.70;262.22]	0.89	-1.12 [-229.05;226.82]	0.99
PeLOD score first 24 hrs (per point added)	-21.84 [-101.49;57.81]	0.58	-1.89 [-84.48;80.69]	0.96
PICU stay (per day added)	-188.51 [-549.34;172.33]	0.30	131.71 [-598.81;862.22]	0.72
Extracorporeal circulation versus no extracorporeal circulation ^a	-17.90 [-78.31;42.51]	0.55	-33.12 [-88.65;22.42]	0.24
Aortic clamp time (per min added)	-7.55 [-87.27;72.16]	0.85	150.69 [26.67;274.70]	0.01
Duration of mechanical ventilation (per day added)	191.81 [-100.04;483.67]	0.19	405.99 [-268.91;1080.88]	0.23
Peak creatinine (per mg/dl added)	91.48 [-81.56;264.51]	0.29	-0.78 [-197.86;196.29]	0.99
Peak bilirubine (per mg/dl added)	-85.87 [-214.62;42.89]	0.18	223.92 [-58.18;506.03]	0.11
Infection vs. no infection	3.52 [-43.20;50.24]	0.88	43.34 [-2.59;89.27]	0.06
Antibiotics (per day added)	-13.71 [-198.49;171.07]	0.88	-542.53 [-1072.04;-13.02]	0.04
Duration of hemodynamic support (per day added)	32.22 [-128.41;192.85]	0.69	-81.43 [-620.07;457.20]	0.76
Duration of corticosteroid treatment (per day added)	209.02 [-73.05;491.09]	0.14	171.12 [-199.68;541.92]	0.36
Cumulative dose of opioids (per mg morphine-equivalent added)	76.28 [-126.18;278.74]	0.45	-166.31 [-382.43;49.80]	0.13
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	62.36 [-143.02;267.75]	0.54	-54.05 [-211.42;103.31]	0.49
Received hypnotics versus no hypnotics	-81.73 [-224.44;60.98]	0.25	46.62 [-78.42;171.66]	0.46
Exceeding potentially harmful threshold for phthalate exposure	53.42 [20.62;86.21]	0.001	43.98 [9.58;78.38]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-7. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and tapping dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.26 [-0.68;1.20]	0.58	0.02 [-1.17;1.22]	0.96
Age at sampling (per year added)	19.50 [17.63;21.37]	<0.001	19.90 [16.93;22.86]	<0.001
Caucasian vs. other race	2.14 [-1.27;5.56]	0.21	-1.63 [-5.60;2.35]	0.42
Exclusively European vs. other origin	-2.09 [-4.93;0.76]	0.14	2.88 [-1.29;7.04]	0.17
Exclusively Dutch language vs. non-exclusively Dutch language	-0.73 [-2.22;0.75]	0.33	-0.81 [-3.11;1.49]	0.48
Socioeconomic status (per category of 1 to 66)	1.41 [-0.82;3.64]	0.21	-1.91 [-4.77;0.95]	0.18
Pre-existing syndrome vs. no pre-existing syndrome	0.74 [-0.46;1.93]	0.22	-1.08 [-2.67;0.50]	0.17
History vs. no history of malignancy	0.04 [-3.37;3.44]	0.98	0.38 [-3.27;4.03]	0.83
History vs. no history of diabetes	1.94 [-2.84;6.73]	0.42		
Randomization to strict glycemic control vs. conventional therapy	0.17 [-0.75;1.10]	0.71	0.37 [-0.82;1.56]	0.53
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	1.28 [-1.81;4.37]	0.41	-2.07 [-5.81;1.67]	0.27
randomized for glycemic control postoperatively	3.10 [0.85;5.36]	0.007	-0.78 [-3.85;2.30]	0.61
Complicated/high risk surgery or trauma	-0.53 [-3.82;2.76]	0.75	1.93 [-6.48;2.62]	0.40
Neurological medical disorders	-3.03 [-9.26;3.19]	0.33	-0.34 [-8.82;8.13]	0.93
Infectious medical diseases	-2.38 [-6.64;1.89]	0.27	-0.22 [-7.81;7.37]	0.95
Other medical disorders	1.66 [-2.79;6.11]	0.46	2.52 [-3.34;8.39]	0.40
Solid organ transplants	-0.10 [-6.98;6.77]	0.98	2.81 [-4.93;10.55]	0.47
PeLOD score first 24 hrs (per point added)	0.45 [-2.02;2.92]	0.71	0.34 [-2.73;3.41]	0.83
PICU stay (per day added)	-0.43 [-3.33;2.47]	0.76	-1.45 [-7.16;4.25]	0.61
Exceeding potentially harmful threshold for phthalate exposure	-1.10 [-2.20;-0.01]	0.04	-0.83 [-2.14;0.49]	0.21

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-7. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and tapping dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.37 [-0.61;1.36]	0.45	0.03 [-1.20;1.27]	0.95
Age at sampling (per year added)	18.11 [15.78;20.44]	<0.001	18.37 [14.97;21.77]	<0.001
Caucasian vs. other race	2.19 [-1.34;5.73]	0.22	-1.90 [-6.00;2.20]	0.36
Exclusively European vs. other origin	-2.24 [-5.17;0.69]	0.13	3.47 [-0.81;7.74]	0.11
Exclusively Dutch language vs. non-exclusively Dutch language	-0.80 [-2.38;0.78]	0.31	-0.84 [-3.23;1.55]	0.48
Socioeconomic status (per category of 1 to 66)	1.52 [-0.80;3.84]	0.19	-1.72 [-4.69;1.25]	0.25
Pre-existing syndrome vs. no pre-existing syndrome	0.89 [-0.40;2.18]	0.17	-1.04 [-2.68;0.60]	0.21
History vs. no history of malignancy	-0.50 [-4.05;3.06]	0.78	0.71 [-3.04;4.46]	0.70
History vs. no history of diabetes	2.50 [-2.36;7.36]	0.31		
Randomization to strict glycemic control vs. conventional therapy	0.01 [-0.96;0.99]	0.98	0.19 [-1.06;1.43]	0.76
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	-3.09 [-9.12;2.93]	0.31	-0.69 [-6.45;5.07]	0.81
randomized for glycemic control postoperatively	-0.69 [-6.26;4.88]	0.80	0.17 [-4.60;4.95]	0.94
Complicated/high risk surgery or trauma	-0.06 [-5.95;5.84]	0.98	-0.23 [-5.65;5.20]	0.93
Neurological medical disorders	-2.64 [-12.33;7.04]	0.59	0.31 [-9.54;10.16]	0.95
Infectious medical diseases	-0.39 [-7.82;7.04]	0.91	-0.02 [-8.36;8.32]	0.99
Other medical disorders	4.12 [-1.81;10.05]	0.17	0.98 [-7.51;9.47]	0.81
Solid organ transplants	2.75 [-7.44;12.94]	0.59	-0.52 [-9.73;8.69]	0.91
PeLOD score first 24 hrs (per point added)	-0.42 [-3.29;2.45]	0.77	0.70 [-2.68;4.07]	0.68
PICU stay (per day added)	-5.02 [-18.05;8.02]	0.44	-19.07 [-45.72;7.58]	0.15
Extracorporeal circulation versus no extracorporeal circulation ^a	2.51 [0.37;4.65]	0.02	0.70 [-1.55;2.94]	0.54
Aortic clamp time (per min added)	0.61 [-2.29;3.52]	0.68	-2.45 [-7.56;2.65]	0.34
Duration of mechanical ventilation (per day added)	7.04 [-3.52;17.60]	0.19	2.73 [-23.61;29.08]	0.83
Peak creatinine (per mg/dl added)	4.39 [-1.87;10.64]	0.16	4.73 [-3.24;12.71]	0.24
Peak bilirubine (per mg/dl added)	1.26 [-3.39;5.92]	0.59	0.22 [-11.86;12.29]	0.97
Infection vs. no infection	0.15 [-1.54;1.84]	0.86	-0.91 [-2.73;0.92]	0.32
Antibiotics (per day added)	-1.72 [-8.41;4.97]	0.61	7.44 [-13.53;28.40]	0.48
Duration of hemodynamic support (per day added)	-4.36 [-10.15;1.43]	0.13	0.05 [-19.20;19.31]	0.99
Duration of corticosteroid treatment (per day added)	-0.89 [-11.10;9.32]	0.86	11.26 [-2.88;25.40]	0.11
Cumulative dose of opioids (per mg morphine-equivalent added)	-2.39 [-9.72;4.94]	0.52	3.89 [-4.71;12.49]	0.37
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	2.35 [-5.07;9.78]	0.53	3.72 [-2.66;10.11]	0.25
Received hypnotics versus no hypnotics	1.01 [-4.16;6.18]	0.69	-1.34 [-6.45;3.77]	0.60
Exceeding potentially harmful threshold for phthalate exposure	-1.34 [-2.52;-0.16]	0.02	-0.78 [-2.18;0.61]	0.26

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-8. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and tapping nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.74 [-0.14;1.61]	0.09	0.33 [-0.83;1.49]	0.57
Age at sampling (per year added)	18.12 [16.38;19.87]	<0.001	18.84 [15.97;21.70]	<0.001
Caucasian vs. other race	1.30 [-1.88;4.48]	0.42	-3.69 [-7.53;0.15]	0.05
Exclusively European vs. other origin	-2.32 [-4.96;0.32]	0.08	3.27 [-0.76;7.29]	0.11
Exclusively Dutch language vs. non-exclusively Dutch language	-0.35 [-1.73;1.03]	0.61	-0.84 [-3.06;1.38]	0.45
Socioeconomic status (per category of 1 to 66)	1.73 [-0.34;3.79]	0.10	0.17 [-2.60;2.95]	0.90
Pre-existing syndrome vs. no pre-existing syndrome	0.59 [-0.53;1.70]	0.29	0.26 [-1.27;1.80]	0.73
History vs. no history of malignancy	1.37 [-1.79;4.54]	0.39	-0.48 [-4.01;3.04]	0.78
History vs. no history of diabetes	-0.10 [-4.55;4.35]	0.96		
Randomization to strict glycemic control vs. conventional therapy	0.59 [-0.26;1.45]	0.17	0.46 [-0.70;1.61]	0.43
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	1.67 [-1.20;4.54]	0.25	1.44 [-2.19;5.07]	0.43
randomized for glycemic control postoperatively	2.84 [0.75;4.94]	0.008	0.22 [-2.75;3.20]	0.88
Complicated/high risk surgery or trauma	0.59 [-2.47;3.65]	0.70	3.69 [-0.70;8.09]	0.09
Neurological medical disorders	-3.91 [-9.70;1.88]	0.18	-5.36 [-13.55;2.82]	0.19
Infectious medical diseases	-1.10 [-5.07;2.86]	0.58	4.31 [-3.03;11.65]	0.24
Other medical disorders	-1.98 [-6.12;2.16]	0.35	-0.57 [-6.24;5.09]	0.84
Solid organ transplants	1.89 [-4.50;8.28]	0.56	-3.73 [-11.21;3.75]	0.32
PeLOD score first 24 hrs (per point added)	0.43 [-1.86;2.73]	0.71	1.08 [-1.91;4.06]	0.47
PICU stay (per day added)	-0.45 [-3.14;2.24]	0.74	-2.00 [-7.53;3.52]	0.47
Exceeding potentially harmful threshold for phthalate exposure	-1.31 [-2.32;-0.29]	0.01	-1.57 [-2.84;-0.30]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-8. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and tapping nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.93 [0.04;1.83]	0.04	0.15 [-1.03;1.34]	0.79
Age at sampling (per year added)	17.92 [15.81;20.04]	<0.001	17.27 [14.00;20.54]	<0.001
Caucasian vs. other race	1.90 [-1.32;5.11]	0.24	-4.61 [-8.54;-0.68]	0.02
Exclusively European vs. other origin	-2.69 [-5.36;-0.02]	0.04	4.11 [0.01;8.20]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	-0.52 [-1.96;0.91]	0.47	-0.62 [-2.90;1.66]	0.59
Socioeconomic status (per category of 1 to 66)	1.92 [-0.19;4.02]	0.07	0.19 [-2.67;3.04]	0.89
Pre-existing syndrome vs. no pre-existing syndrome	0.40 [-0.77;1.58]	0.49	0.46 [-1.11;2.03]	0.56
History vs. no history of malignancy	0.84 [-2.40;4.07]	0.61	-0.48 [-4.06;3.11]	0.79
History vs. no history of diabetes	0.30 [-4.12;4.72]	0.89		
Randomization to strict glycemic control vs. conventional therapy	0.42 [-0.46;1.31]	0.34	0.25 [-0.96;1.45]	0.68
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	-1.05 [-6.53;4.44]	0.70	1.67 [-3.87;7.21]	0.55
randomized for glycemic control postoperatively	0.86 [-4.21;5.93]	0.73	0.83 [-3.78;5.43]	0.72
Complicated/high risk surgery or trauma	1.64 [-3.73;7.00]	0.54	6.38 [1.15;11.61]	0.01
Neurological medical disorders	-5.40 [-14.21;3.41]	0.22	-5.88 [-15.32;3.56]	0.22
Infectious medical diseases	-0.36 [-7.12;6.40]	0.91	4.97 [-3.01;12.95]	0.22
Other medical disorders	2.37 [-3.02;7.77]	0.38	-2.90 [-11.05;5.24]	0.48
Solid organ transplants	1.94 [-7.33;11.21]	0.68	-5.07 [-13.89;3.76]	0.25
PeLOD score first 24 hrs (per point added)	-0.15 [-2.76;2.46]	0.90	1.70 [-1.54;4.94]	0.30
PICU stay (per day added)	0.12 [-11.72;11.96]	0.98	-17.24 [-46.77;12.29]	0.25
Extracorporeal circulation versus no extracorporeal circulation ^a	1.93 [-0.00;3.87]	0.05	1.49 [-0.68;3.67]	0.17
Aortic clamp time (per min added)	1.13 [-1.49;3.76]	0.39	0.39 [-4.50;5.28]	0.87
Duration of mechanical ventilation (per day added)	7.51 [-2.09;17.10]	0.12	3.75 [-22.67;30.17]	0.77
Peak creatinine (per mg/dl added)	0.97 [-4.72;6.65]	0.73	3.22 [-4.46;10.89]	0.40
Peak bilirubine (per mg/dl added)	-0.87 [-5.11;3.36]	0.68	1.79 [-9.81;13.39]	0.76
Infection vs. no infection	0.40 [-1.14;1.94]	0.60	-1.81 [-3.57;-0.05]	0.04
Antibiotics (per day added)	-5.89 [-11.97;0.19]	0.05	12.48 [-8.65;33.61]	0.24
Duration of hemodynamic support (per day added)	-4.74 [-10.01;0.53]	0.07	-5.56 [-24.15;13.04]	0.55
Duration of corticosteroid treatment (per day added)	4.18 [-5.12;13.47]	0.37	10.19 [-3.69;24.07]	0.14
Cumulative dose of opioids (per mg morphine-equivalent added)	-3.91 [-10.58;2.76]	0.24	2.08 [-6.18;10.34]	0.62
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-5.78 [-12.54;0.98]	0.09	1.41 [-4.72;7.54]	0.65
Received hypnotics versus no hypnotics	0.67 [-4.03;5.37]	0.77	-3.12 [-8.01;1.77]	0.20
Exceeding potentially harmful threshold for phthalate exposure	-1.24 [-2.31;-0.16]	0.02	-1.63 [-2.96;-0.29]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-9. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and no. of valid synchronous taps

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.46 [-0.58;1.51]	0.38	-0.08 [-1.25;1.08]	0.88
Age at sampling (per year added)	16.05 [13.97;18.12]	<0.001	16.78 [13.91;19.65]	<0.001
Caucasian vs. other race	-0.11 [-4.00;3.77]	0.95	-1.4 [-5.25;2.40]	0.46
Exclusively European vs. other origin	-1.57 [-4.72;1.58]	0.32	1.74 [-2.27;5.76]	0.39
Exclusively Dutch language vs. non-exclusively Dutch language	0.58 [-1.09;2.25]	0.49	-0.07 [-2.29;2.14]	0.94
Socioeconomic status (per category of 1 to 66)	1.34 [-1.12;3.80]	0.28	0.67 [-2.11;3.46]	0.63
Pre-existing syndrome vs. no pre-existing syndrome	-0.13 [-1.48;1.21]	0.84	-2.14 [-3.69;-0.60]	0.006
History vs. no history of malignancy	-0.88 [-4.64;2.88]	0.64	1.88 [-1.63;5.39]	0.29
History vs. no history of diabetes	3.39 [-1.89;8.66]	0.20		
Randomization to strict glycemic control vs. conventional therapy	0.23 [-0.79;1.26]	0.65	0.51 [-0.66;1.69]	0.38
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	5.05 [1.63;8.47]	0.004	1.77 [-1.88;5.42]	0.33
randomized for glycemic control postoperatively	1.88 [-0.62;4.37]	0.14	2.27 [-0.71;5.25]	0.13
Complicated/high risk surgery or trauma	2.23 [-1.40;5.85]	0.22	3.48 [-0.90;7.86]	0.11
Neurological medical disorders	-3.27 [-10.13;3.60]	0.34	-5.55 [-13.71;2.61]	0.18
Infectious medical diseases	-0.33 [-5.03;4.37]	0.89	-0.05 [-7.36;7.27]	0.98
Other medical disorders	-0.34 [-5.25;4.57]	0.89	6.16 [0.52;11.81]	0.03
Solid organ transplants	-5.22 [-12.79;2.36]	0.17	-8.08 [-15.54;-0.63]	0.03
PeLOD score first 24 hrs (per point added)	1.75 [-0.99;4.49]	0.20	1.71 [-1.28;4.71]	0.25
PICU stay (per day added)	-1.07 [-4.28;2.15]	0.51	-1.80 [-7.32;3.72]	0.52
Exceeding potentially harmful threshold for phthalate exposure	-2.19 [-3.40;-0.97]	0.0005	-1.09 [-2.37;0.19]	0.09

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-9. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP exposure and no. of valid synchronous taps (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.54 [-0.56;1.65]	0.33	-0.18 [-1.35;1.00]	0.76
Age at sampling (per year added)	16.07 [13.48;18.67]	<0.001	15.24 [12.00;18.47]	<0.001
Caucasian vs. other race	0.42 [-3.66;4.50]	0.83	-1.85 [-5.72;2.01]	0.34
Exclusively European vs. other origin	-1.17 [-4.44;2.10]	0.48	2.80 [-1.23;6.84]	0.17
Exclusively Dutch language vs. non-exclusively Dutch language	-0.14 [-1.93;1.65]	0.87	-0.55 [-2.80;1.69]	0.62
Socioeconomic status (per category of 1 to 66)	1.60 [-0.98;4.18]	0.22	0.86 [-1.97;3.70]	0.54
Pre-existing syndrome vs. no pre-existing syndrome	-0.49 [-1.94;0.96]	0.50	-2.07 [-3.64;-0.50]	0.01
History vs. no history of malignancy	-0.77 [-4.72;3.18]	0.69	2.58 [-0.95;6.11]	0.15
History vs. no history of diabetes	3.35 [-2.05;8.74]	0.22		
Randomization to strict glycemic control vs. conventional therapy	0.46 [-0.63;1.54]	0.40	-0.03 [-1.23;1.17]	0.96
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	3.45 [-3.32;10.23]	0.31	1.58 [-3.92;7.09]	0.57
randomized for glycemic control postoperatively	0.65 [-5.59;6.89]	0.83	2.21 [-2.34;6.75]	0.33
Complicated/high risk surgery or trauma	1.42 [-5.13;7.97]	0.66	4.96 [-0.19;10.11]	0.05
Neurological medical disorders	-3.14 [-13.91;7.63]	0.56	-6.41 [-15.71;2.89]	0.17
Infectious medical diseases	-1.40 [-9.66;6.86]	0.73	1.41 [-6.45;9.26]	0.72
Other medical disorders	1.81 [-4.78;8.39]	0.58	3.34 [-4.67;11.35]	0.41
Solid organ transplants	-2.79 [-14.13;8.54]	0.62	-7.09 [-15.77;1.60]	0.10
PeLOD score first 24 hrs (per point added)	1.34 [-1.90;4.59]	0.41	1.08 [-2.15;4.30]	0.51
PICU stay (per day added)	2.42 [-12.18;17.01]	0.74	-15.84 [-45.05;13.37]	0.28
Extracorporeal circulation versus no extracorporeal circulation ^a	1.14 [-1.30;3.58]	0.35	2.64 [0.46;4.83]	0.01
Aortic clamp time (per min added)	0.05 [-3.17;3.28]	0.97	-4.23 [-9.04;0.59]	0.08
Duration of mechanical ventilation (per day added)	3.15 [-8.63;14.94]	0.59	23.23 [-3.04;49.50]	0.08
Peak creatinine (per mg/dl added)	-0.72 [-7.75;6.32]	0.84	8.82 [1.25;16.40]	0.02
Peak bilirubine (per mg/dl added)	-0.70 [-5.95;4.55]	0.79	-5.81 [-17.28;5.67]	0.31
Infection vs. no infection	1.10 [-0.80;3.00]	0.25	-0.77 [-2.54;1.00]	0.39
Antibiotics (per day added)	-4.25 [-11.70;3.20]	0.26	-1.59 [-22.92;19.74]	0.88
Duration of hemodynamic support (per day added)	-5.82 [-12.25;0.61]	0.07	-5.89 [-24.19;12.42]	0.52
Duration of corticosteroid treatment (per day added)	-2.51 [-13.84;8.82]	0.66	-0.27 [-14.01;13.48]	0.96
Cumulative dose of opioids (per mg morphine-equivalent added)	-5.74 [-13.87;2.39]	0.16	6.22 [-1.90;14.33]	0.13
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-1.65 [-9.92;6.62]	0.69	-0.41 [-6.49;5.67]	0.89
Received hypnotics versus no hypnotics	0.54 [-5.21;6.29]	0.85	-1.79 [-6.61;3.02]	0.46
Exceeding potentially harmful threshold for phthalate exposure	-2.35 [-3.68;-1.03]	0.0006	-1.46 [-2.80;-0.13]	0.03

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-10. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-8.66 [-43.35;26.02]	0.62	-3.95 [-41.02;33.12]	0.83
Age at sampling (per year added)	-411.10 [-484.31;-337.89]	<0.001	-437.05 [-529.09;-345.01]	<0.001
Caucasian vs. other race	24.73 [-100.99;150.45]	0.69	72.63 [-50.06;195.33]	0.24
Exclusively European vs. other origin	-21.04 [-125.73;83.65]	0.69	-107.82 [-233.84;18.20]	0.09
Exclusively Dutch language vs. non-exclusively Dutch language	63.73 [9.07;118.38]	0.02	50.43 [-16.31;117.16]	0.13
Socioeconomic status (per category of 1 to 66)	-96.53 [-178.55;-14.50]	0.02	-62.03 [-151.47;27.41]	0.17
Pre-existing syndrome vs. no pre-existing syndrome	19.77 [-24.80;64.34]	0.38	51.83 [3.27;100.38]	0.03
History vs. no history of malignancy	-64.41 [-191.32;62.49]	0.32	13.07 [-100.97;127.10]	0.82
History vs. no history of diabetes	-36.65 [-212.77;139.48]	0.68		
Randomization to strict glycemic control vs. conventional therapy	3.02 [-31.06;37.09]	0.86	-4.63 [-41.56;32.31]	0.80
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	50.57 [-63.42;164.57]	0.38	205.13 [88.81;321.45]	<0.001
randomized for glycemic control postoperatively	-72.66 [-155.57;10.26]	0.08	72.36 [-22.67;167.39]	0.13
Complicated/high risk surgery or trauma	-48.71 [-172.58;75.15]	0.43	-82.16 [-227.45;63.14]	0.26
Neurological medical disorders	215.73 [-13.81;445.28]	0.06	-8.31 [-270.82;254.20]	0.95
Infectious medical diseases	-168.80 [-325.94;-11.65]	0.03	-74.74 [-310.24;160.76]	0.53
Other medical disorders	-71.06 [-234.89;92.77]	0.39	-28.07 [-209.80;153.66]	0.76
Solid organ transplants	94.92 [-157.92;347.76]	0.45	-84.21 [-325.10;156.68]	0.49
PeLOD score first 24 hrs (per point added)	-56.51 [-147.41;34.40]	0.22	43.51 [-52.08;139.11]	0.37
PICU stay (per day added)	20.71 [-84.97;126.39]	0.69	172.68 [-6.42;351.77]	0.05
Exceeding potentially harmful threshold for phthalate exposure	84.05 [41.57;126.52]	0.0001	45.05 [4.77;85.33]	0.03

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-10. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-13.03 [-49.95;23.89]	0.48	-14.30 [-51.53;22.94]	0.44
Age at sampling (per year added)	-392.79 [-486.82;-298.75]	<0.001	-395.42 [-498.87;-291.97]	<0.001
Caucasian vs. other race	8.73 [-123.33;140.79]	0.89	69.04 [-53.73;191.80]	0.26
Exclusively European vs. other origin	-10.68 [-120.24;98.88]	0.84	-105.12 [-230.52;20.28]	0.09
Exclusively Dutch language vs. non-exclusively Dutch language	55.77 [-3.25;114.80]	0.06	60.87 [-5.69;127.42]	0.07
Socioeconomic status (per category of 1 to 66)	-106.81 [-193.92;-19.70]	0.01	-78.01 [-168.06;12.03]	0.08
Pre-existing syndrome vs. no pre-existing syndrome	24.25 [-24.60;73.09]	0.32	59.50 [10.87;108.13]	0.01
History vs. no history of malignancy	-70.99 [-205.42;63.43]	0.29	-2.52 [-115.44;110.40]	0.96
History vs. no history of diabetes	-52.61 [-234.34;129.11]	0.56		
Randomization to strict glycemic control vs. conventional therapy	3.08 [-33.33;39.50]	0.86	5.98 [-32.33;40.30]	0.75
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	252.80 [26.46;479.14]	0.02	127.65 [-46.01;301.31]	0.14
randomized for glycemic control postoperatively	133.01 [-76.49;342.51]	0.21	31.01 [-113.28;175.29]	0.67
Complicated/high risk surgery or trauma	56.40 [-166.17;278.98]	0.61	-56.87 [-220.76;107.03]	0.49
Neurological medical disorders	58.79 [-303.02;420.60]	0.74	-96.40 [-392.17;199.38]	0.52
Infectious medical diseases	-370.72 [-648.35;-93.09]	0.009	27.82 [-230.39;286.03]	0.83
Other medical disorders	-199.56 [-421.31;22.18]	0.07	21.26 [-233.93;276.46]	0.87
Solid organ transplants	69.28 [-311.47;450.03]	0.71	-54.48 [-333.88;224.93]	0.70
PeLOD score first 24 hrs (per point added)	-47.92 [-155.59;59.76]	0.38	16.54 [-84.64;117.72]	0.74
PICU stay (per day added)	-223.65 [-714.92;267.63]	0.37	-251.14 [-1147.03;644.75]	0.58
Extracorporeal circulation versus no extracorporeal circulation ^a	-61.24 [-143.38;20.90]	0.14	-30.19 [-98.48;38.10]	0.38
Aortic clamp time (per min added)	39.68 [-68.55;147.91]	0.47	142.01 [-10.28;294.30]	0.06
Duration of mechanical ventilation (per day added)	238.09 [-161.44;637.61]	0.24	798.18 [-29.03;1625.40]	0.05
Peak creatinine (per mg/dl added)	-52.00 [-288.01;184.01]	0.66	-113.50 [-355.84;128.83]	0.35
Peak bilirubine (per mg/dl added)	-56.04 [-228.93;116.85]	0.52	332.38 [-13.89;678.65]	0.05
Infection vs. no infection	14.55 [-47.59;76.68]	0.64	37.58 [-18.76;93.92]	0.18
Antibiotics (per day added)	-0.80 [-250.93;249.32]	0.99	-607.54 [-1256.71;41.63]	0.06
Duration of hemodynamic support (per day added)	43.28 [-173.92;260.48]	0.69	223.77 [-435.66;883.20]	0.50
Duration of corticosteroid treatment (per day added)	221.27 [-160.77;603.32]	0.25	121.44 [-333.28;576.17]	0.59
Cumulative dose of opioids (per mg morphine-equivalent added)	13.20 [-260.60;287.01]	0.92	-183.41 [-448.25;81.44]	0.17
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	1.79 [-276.23;279.80]	0.98	-103.10 [-297.01;90.81]	0.29
Received hypnotics versus no hypnotics	-149.33 [-342.07;43.41]	0.12	26.92 [-126.23;180.08]	0.72
Exceeding potentially harmful threshold for phthalate exposure	88.58 [41.61;135.56]	0.0003	44.64 [2.71;86.57]	0.03

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-11. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-18.47 [-50.62;13.68]	0.25	8.44 [-25.59;42.48]	0.62
Age at sampling (per year added)	-372.99 [-440.76;-305.22]	<0.001	-408.81 [-493.32;-324.31]	<0.001
Caucasian vs. other race	-20.67 [-137.96;96.63]	0.72	19.64 [-93.01;132.29]	0.73
Exclusively European vs. other origin	-25.71 [-123.29;71.86]	0.60	-89.50 [-205.20;26.21]	0.12
Exclusively Dutch language vs. non-exclusively Dutch language	59.59 [8.73;110.45]	0.02	64.59 [3.32;125.86]	0.02
Socioeconomic status (per category of 1 to 66)	-49.26 [-125.22;26.71]	0.20	-102.31 [-184.43;-20.19]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	6.51 [-34.59;47.62]	0.75	46.37 [1.79;90.95]	0.04
History vs. no history of malignancy	-46.84 [-165.21;71.53]	0.43	25.29 [-79.41;129.99]	0.63
History vs. no history of diabetes	-4.65 [-168.93;159.62]	0.95		
Randomization to strict glycemic control vs. conventional therapy	3.47 [-28.03;34.97]	0.82	0.44 [-33.47;34.36]	0.97
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	27.38 [-78.92;133.69]	0.61	186.85 [80.05;293.65]	<0.001
randomized for glycemic control postoperatively	-31.95 [-108.90;45.00]	0.41	59.59 [-27.66;146.85]	0.17
Complicated/high risk surgery or trauma	-10.34 [-125.90;105.23]	0.86	-184.77 [-318.18;-51.37]	0.006
Neurological medical disorders	90.77 [-123.07;304.62]	0.40	87.98 [-153.05;329.00]	0.47
Infectious medical diseases	-100.09 [-246.67;46.49]	0.17	-67.25 [-283.48;148.98]	0.54
Other medical disorders	-94.89 [-247.67;57.89]	0.22	-30.44 [-197.30;136.42]	0.71
Solid organ transplants	119.11 [-116.73;354.96]	0.32	-51.96 [-273.13;169.21]	0.63
PeLOD score first 24 hrs (per point added)	-14.61 [-99.08;69.85]	0.73	15.20 [-72.57;102.97]	0.73
PICU stay (per day added)	-11.24 [-108.27;85.79]	0.82	195.11 [30.67;359.54]	0.02
Exceeding potentially harmful threshold for phthalate exposure	67.94 [28.72;107.17]	0.0008	44.23 [7.25;81.21]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-11. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-19.77 [-53.06;13.52]	0.24	2.58 [-32.00;37.16]	0.88
Age at sampling (per year added)	-369.19 [-453.84;-284.54]	<0.001	-376.69 [-472.76;-280.62]	<0.001
Caucasian vs. other race	-40.64 [-160.40;79.12]	0.50	24.08 [-89.92;138.09]	0.67
Exclusively European vs. other origin	-16.67 [-115.92;82.57]	0.74	-90.04 [-206.49;26.41]	0.12
Exclusively Dutch language vs. non-exclusively Dutch language	57.70 [4.35;111.05]	0.03	74.04 [12.24;135.85]	0.01
Socioeconomic status (per category of 1 to 66)	-57.43 [-135.81;20.95]	0.14	-119.39 [-203.02;-35.77]	0.005
Pre-existing syndrome vs. no pre-existing syndrome	9.69 [-33.94;53.32]	0.66	48.82 [3.66;93.98]	0.03
History vs. no history of malignancy	-48.27 [-170.12;73.58]	0.43	9.64 [-95.22;114.51]	0.85
History vs. no history of diabetes	-25.92 [-190.65;138.81]	0.75		
Randomization to strict glycemic control vs. conventional therapy	5.98 [-26.67;38.63]	0.71	12.60 [-22.98;48.19]	0.48
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	225.05 [21.15;428.95]	0.03	130.29 [-30.97;291.56]	0.11
randomized for glycemic control postoperatively	157.72 [-31.08;346.53]	0.10	24.07 [-109.92;158.05]	0.72
Complicated/high risk surgery or trauma	47.86 [-153.28;249.00]	0.63	-194.24 [-346.44;-42.03]	0.01
Neurological medical disorders	-18.80 [-346.44;308.85]	0.91	81.59 [-193.08;356.26]	0.55
Infectious medical diseases	-268.79 [-520.28;-17.30]	0.03	-21.68 [-261.47;218.11]	0.85
Other medical disorders	-264.91 [-465.66;-64.16]	0.01	69.24 [-167.75;306.23]	0.56
Solid organ transplants	121.86 [-223.46;467.19]	0.48	-89.27 [-348.74;170.19]	0.49
PeLOD score first 24 hrs (per point added)	-6.10 [-103.21;91.01]	0.90	5.15 [-88.81;99.11]	0.91
PICU stay (per day added)	-117.29 [-554.08;319.50]	0.59	-428.39 [-1314.35;349.57]	0.25
Extracorporeal circulation versus no extracorporeal circulation ^a	-65.51 [-137.62;6.61]	0.07	-56.87 [-120.28;6.55]	0.07
Aortic clamp time (per min added)	-4.55 [-101.90;92.80]	0.93	109.92 [-31.51;251.34]	0.12
Duration of mechanical ventilation (per day added)	133.00 [-222.57;488.58]	0.46	504.08 [-264.10;1272.27]	0.19
Peak creatinine (per mg/dl added)	-0.47 [-214.02;213.08]	0.99	-74.22 [-299.26;150.82]	0.51
Peak bilirubine (per mg/dl added)	-165.64 [-322.07;-9.21]	0.03	236.17 [-85.39;557.73]	0.14
Infection vs. no infection	11.90 [-44.22;68.03]	0.67	27.76 [-24.56;80.08]	0.29
Antibiotics (per day added)	-68.26 [-294.85;158.34]	0.55	-163.12 [-765.96;439.72]	0.59
Duration of hemodynamic support (per day added)	67.73 [-128.98;264.44]	0.49	359.10 [-253.27;971.47]	0.24
Duration of corticosteroid treatment (per day added)	173.76 [-171.15;518.67]	0.32	186.52 [-235.75;608.79]	0.38
Cumulative dose of opioids (per mg morphine-equivalent added)	130.34 [-118.06;378.74]	0.30	-163.23 [-409.17;82.72]	0.19
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	113.42 [-138.41;365.25]	0.37	-77.35 [-257.42;102.72]	0.39
Received hypnotics versus no hypnotics	-122.21 [-297.00;52.59]	0.16	79.93 [-62.29;222.16]	0.26
Exceeding potentially harmful threshold for phthalate exposure	74.16 [32.00;116.33]	0.0006	46.46 [7.52;85.40]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-12. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-15.03 [-45.91;15.86]	0.33	3.41 [-30.44;37.26]	0.84
Age at sampling (per year added)	-387.41 [-452.61;-322.22]	<0.001	-422.56 [-506.60;-338.52]	<0.001
Caucasian vs. other race	2.17 [-109.80;114.13]	0.96	45.85 [-66.18;157.88]	0.42
Exclusively European vs. other origin	-23.03 [-116.27;70.20]	0.62	-97.75 [-212.82;17.32]	0.09
Exclusively Dutch language vs. non-exclusively Dutch language	59.54 [10.87;108.22]	0.01	56.80 [-4.14;117.73]	0.06
Socioeconomic status (per category of 1 to 66)	-68.79 [-141.83;4.26]	0.06	-84.40 [-166.07;-2.74]	0.04
Pre-existing syndrome vs. no pre-existing syndrome	10.57 [-29.13;50.26]	0.60	46.43 [2.10;90.77]	0.04
History vs. no history of malignancy	-55.81 [-168.83;57.20]	0.33	19.63 [-84.50;123.75]	0.71
History vs. no history of diabetes	-17.99 [-174.84;138.86]	0.82		
Randomization to strict glycemic control vs. conventional therapy	2.58 [-27.77;32.92]	0.86	-2.82 [-36.54;30.91]	0.86
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	37.87 [-63.65;139.39]	0.46	193.22 [87.01;299.44]	<0.001
randomized for glycemic control postoperatively	-56.29 [-130.13;17.56]	0.12	62.32 [-24.45;149.09]	0.15
Complicated/high risk surgery or trauma	-29.46 [-139.76;80.85]	0.59	-132.97 [-265.64;-0.30]	0.04
Neurological medical disorders	157.73 [-46.70;362.16]	0.13	43.62 [-196.08;283.32]	0.72
Infectious medical diseases	-133.84 [-273.78;6.11]	0.06	-72.32 [-287.36;142.72]	0.50
Other medical disorders	-85.54 [-231.44;60.36]	0.24	-27.05 [-192.99;138.89]	0.74
Solid organ transplants	109.52 [-115.65;334.68]	0.33	-66.83 [-286.78;153.13]	0.54
PeLOD score first 24 hrs (per point added)	-33.72 [-114.68;47.23]	0.41	27.47 [-59.81;114.76]	0.53
PICU stay (per day added)	7.43 [-86.68;101.55]	0.87	185.22 [21.69;348.75]	0.02
Exceeding potentially harmful threshold for phthalate exposure	76.07 [38.25;113.89]	0.0001	45.99 [9.21;82.76]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-12. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-17.85 [-50.20;14.50]	0.27	-4.44 [-38.53;29.66]	0.79
Age at sampling (per year added)	-375.33 [-457.71;-292.94]	<0.001	-383.91 [-478.63;-289.20]	<0.001
Caucasian vs. other race	-15.83 [-131.52;99.87]	0.78	46.29 [-66.11;158.69]	0.41
Exclusively European vs. other origin	-13.04 [-109.03;82.94]	0.78	-97.16 [-211.97;17.65]	0.09
Exclusively Dutch language vs. non-exclusively Dutch language	54.60 [2.89;106.31]	0.03	66.84 [5.90;127.77]	0.03
Socioeconomic status (per category of 1 to 66)	-78.41 [-154.72;-2.09]	0.04	-100.79 [-183.23;-18.34]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	14.28 [-28.51;57.08]	0.51	51.01 [6.48;95.53]	0.02
History vs. no history of malignancy	-59.50 [-177.27;58.28]	0.32	4.20 [-99.19;107.59]	0.93
History vs. no history of diabetes	-38.06 [-197.28;121.16]	0.63		
Randomization to strict glycemic control vs. conventional therapy	4.35 [-27.55;36.25]	0.78	8.33 [-26.75;43.42]	0.63
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	244.30 [46.00;442.60]	0.01	127.37 [-31.63;286.37]	0.11
randomized for glycemic control postoperatively	147.91 [-35.64;331.46]	0.11	24.74 [-107.36;156.84]	0.71
Complicated/high risk surgery or trauma	50.66 [-144.34;245.66]	0.60	-126.05 [-276.11;24.01]	0.09
Neurological medical disorders	19.15 [-297.84;336.14]	0.90	-4.61 [-275.41;266.20]	0.97
Infectious medical diseases	-323.71 [-566.94;-80.47]	0.009	0.44 [-235.98;236.85]	0.99
Other medical disorders	-237.44 [-431.72;-43.16]	0.01	46.58 [-187.07;280.24]	0.69
Solid organ transplants	99.12 [-234.46;432.71]	0.55	-68.47 [-324.28;187.34]	0.59
PeLOD score first 24 hrs (per point added)	-25.90 [-120.23;68.44]	0.58	8.47 [-84.17;101.11]	0.85
PICU stay (per day added)	-168.95 [-599.36;261.47]	0.43	-361.12 [-1181.38;459.14]	0.38
Extracorporeal circulation versus no extracorporeal circulation ^a	-67.67 [-139.64;4.29]	0.06	-44.13 [-106.65;18.40]	0.16
Aortic clamp time (per min added)	18.82 [-76.00;113.65]	0.69	125.32 [-14.11;264.75]	0.07
Duration of mechanical ventilation (per day added)	186.00 [-164.03;536.03]	0.29	664.71 [-92.67;1422.09]	0.08
Peak creatinine (per mg/dl added)	-24.70 [-231.47;182.07]	0.81	-93.48 [-315.35;128.40]	0.40
Peak bilirubine (per mg/dl added)	-107.82 [-259.29;43.65]	0.16	271.35 [-45.69;588.39]	0.09
Infection vs. no infection	13.84 [-40.59;68.28]	0.61	33.75 [-17.84;85.33]	0.19
Antibiotics (per day added)	-31.69 [-250.83;187.45]	0.77	-391.16 [-985.53;203.20]	0.19
Duration of hemodynamic support (per day added)	56.36 [-133.93;246.65]	0.55	287.74 [-316.02;891.49]	0.34
Duration of corticosteroid treatment (per day added)	192.81 [-141.90;527.53]	0.25	144.39 [-271.94;560.73]	0.49
Cumulative dose of opioids (per mg morphine-equivalent added)	70.19 [169.70;310.08]	0.56	-175.00 [-417.49;67.49]	0.15
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	55.34 [-188.24;298.91]	0.65	-88.85 [-266.38;88.69]	0.32
Received hypnotics versus no hypnotics	-137.40 [-306.27;31.46]	0.11	53.87 [-86.35;194.10]	0.44
Exceeding potentially harmful threshold for phthalate exposure	81.54 [40.38;122.70]	0.0001	47.06 [8.67;85.45]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-13. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	18.28 [-11.34;47.90]	0.22	-1.11 [-35.62;33.40]	0.94
Age at sampling (per year added)	-306.85 [-369.38;-244.32]	<0.001	-341.45 [-427.12;-255.77]	<0.001
Caucasian vs. other race	37.52 [-69.87;144.91]	0.49	59.93 [-54.28;174.14]	0.30
Exclusively European vs. other origin	-42.69 [-132.11;46.74]	0.34	-76.74 [-194.04;40.56]	0.19
Exclusively Dutch language vs. non-exclusively Dutch language	31.06 [-15.63;77.75]	0.19	27.91 [-34.21;90.03]	0.37
Socioeconomic status (per category of 1 to 66)	-77.07 [-147.13;-7.00]	0.03	-110.59 [-193.85;-27.34]	0.009
Pre-existing syndrome vs. no pre-existing syndrome	19.43 [-18.65;57.50]	0.31	64.21 [19.01;109.41]	0.005
History vs. no history of malignancy	-42.67 [-151.07;65.73]	0.43	49.75 [-56.40;155.90]	0.35
History vs. no history of diabetes	-14.73 [-165.17;135.72]	0.84		
Randomization to strict glycemic control vs. conventional therapy	-10.48 [-39.59;18.62]	0.47	6.69 [-27.69;41.07]	0.70
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	65.80 [-31.57;163.17]	0.18	144.97 [36.69;253.25]	0.009
randomized for glycemic control postoperatively	-26.43 [-97.25;44.40]	0.46	53.02 [-35.44;141.48]	0.23
Complicated/high risk surgery or trauma	-16.73 [-122.53;89.07]	0.75	-83.70 [-218.95;51.55]	0.22
Neurological medical disorders	135.65 [-60.42;331.72]	0.17	-10.13 [-254.49;234.23]	0.93
Infectious medical diseases	-123.39 [-257.62;10.84]	0.07	-42.60 [-261.81;176.62]	0.70
Other medical disorders	-17.86 [-157.80;122.07]	0.80	-65.27 [-234.44;103.89]	0.44
Solid organ transplants	-17.04 [-233.01;198.93]	0.87	3.71 [-220.53;227.94]	0.97
PeLOD score first 24 hrs (per point added)	-23.48 [-101.13;54.17]	0.55	38.81 [-50.17;127.79]	0.39
PICU stay (per day added)	9.80 [-80.47;100.07]	0.83	86.31 [-80.40;253.02]	0.30
Exceeding potentially harmful threshold for phthalate exposure	61.87 [25.59;98.14]	0.0009	45.46 [7.97;82.95]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-13. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	12.40 [-19.46;44.26]	0.44	-12.64 [-47.01;21.73]	0.46
Age at sampling (per year added)	-300.33 [-381.48;-219.19]	<0.001	-300.13 [-395.63;-204.64]	<0.001
Caucasian vs. other race	35.29 [-78.67;149.25]	0.54	72.63 [-40.69;185.96]	0.20
Exclusively European vs. other origin	-43.29 [-137.83;51.25]	0.36	-94.97 [-210.73;20.78]	0.10
Exclusively Dutch language vs. non-exclusively Dutch language	27.21 [-23.72;78.14]	0.29	33.48 [-27.96;94.92]	0.28
Socioeconomic status (per category of 1 to 66)	-76.81 [-151.98;-1.64]	0.04	-122.80 [-205.92;-39.68]	0.004
Pre-existing syndrome vs. no pre-existing syndrome	26.42 [-15.73;68.58]	0.21	70.12 [25.22;115.01]	0.002
History vs. no history of malignancy	-42.68 [-158.68;73.32]	0.46	41.35 [-62.89;145.59]	0.43
History vs. no history of diabetes	-26.48 [-183.30;130.34]	0.73		
Randomization to strict glycemic control vs. conventional therapy	-7.84 [-39.27;23.58]	0.62	14.79 [-20.58;50.16]	0.41
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	201.79 [6.47;397.10]	0.04	45.49 [-114.81;205.79]	0.57
randomized for glycemic control postoperatively	111.28 [-69.51;292.07]	0.22	-12.13 [-145.32;121.06]	0.85
Complicated/high risk surgery or trauma	39.62 [-152.44;231.69]	0.68	-110.85 [-262.14;40.45]	0.15
Neurological medical disorders	-2.42 [-314.64;309.80]	0.98	-29.34 [-302.38;243.69]	0.83
Infectious medical diseases	-218.60 [-458.18;20.98]	0.07	45.30 [-193.06;283.66]	0.70
Other medical disorders	-86.41 [-277.76;104.95]	0.37	-6.24 [-241.82;229.33]	0.95
Solid organ transplants	-45.26 [-373.83;283.30]	0.78	67.78 [-190.14;325.69]	0.60
PeLOD score first 24 hrs (per point added)	-33.40 [-126.32;59.51]	0.47	-10.45 [-103.85;82.95]	0.82
PICU stay (per day added)	-117.92 [-541.86;306.02]	0.58	704.57 [-122.43;1531.57]	0.09
Extracorporeal circulation versus no extracorporeal circulation ^a	-34.10 [-104.98;36.79]	0.34	-2.01 [-65.04;61.03]	0.95
Aortic clamp time (per min added)	9.70 [-83.69;103.10]	0.83	170.09 [29.51;310.67]	0.01
Duration of mechanical ventilation (per day added)	87.63 [-257.13;432.40]	0.61	420.69 [-342.91;1184.30]	0.27
Peak creatinine (per mg/dl added)	0.72 [-202.94;204.39]	0.99	3.61 [-220.09;227.30]	0.97
Peak bilirubine (per mg/dl added)	7.46 [-141.73;156.65]	0.92	263.35 [-56.30;582.99]	0.10
Infection vs. no infection	27.41 [-26.21;81.02]	0.31	51.84 [-0.17;103.85]	0.05
Antibiotics (per day added)	2.55 [-213.29;218.39]	0.98	-958.44 [-1557.68;-359.19]	0.001
Duration of hemodynamic support (per day added)	19.56 [-167.87;206.99]	0.83	-229.55 [-838.27;379.17]	0.45
Duration of corticosteroid treatment (per day added)	125.07 [-204.61;454.76]	0.45	0.78 [-418.97;420.53]	0.99
Cumulative dose of opioids (per mg morphine-equivalent added)	40.52 [-195.75;276.80]	0.73	-263.68 [-508.16;-19.20]	0.03
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	23.54 [-216.37;263.45]	0.84	-48.61 [-227.61;130.38]	0.59
Received hypnotics versus no hypnotics	-78.03 [-244.36;88.29]	0.35	72.94 [-68.44;214.31]	0.31
Exceeding potentially harmful threshold for phthalate exposure	61.74 [21.19;102.28]	0.003	42.42 [3.71;81.13]	0.03

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-14. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-0.30 [-28.86;28.26]	0.98	3.79 [-29.25;36.83]	0.82
Age at sampling (per year added)	-254.60 [-314.81;-194.39]	<0.001	-311.59 [-393.62;-229.56]	<0.001
Caucasian vs. other race	10.99 [-93.22;115.19]	0.83	16.38 [-92.97;125.73]	0.76
Exclusively European vs. other origin	-53.18 [-139.87;33.50]	0.22	-76.86 [-189.18;35.46]	0.17
Exclusively Dutch language vs. non-exclusively Dutch language	49.74 [4.56;94.92]	0.03	49.74 [-9.74;109.21]	0.10
Socioeconomic status (per category of 1 to 66)	-30.16 [-97.65;37.33]	0.37	-88.88 [-168.59;-9.16]	0.02
Pre-existing syndrome vs. no pre-existing syndrome	12.67 [-23.85;49.19]	0.49	44.03 [0.76;87.31]	0.04
History vs. no history of malignancy	-71.71 [-176.87;33.45]	0.18	15.22 [-86.42;116.85]	0.76
History vs. no history of diabetes	2.98 [-142.96;148.92]	0.96		
Randomization to strict glycemic control vs. conventional therapy	-8.86 [-36.85;19.12]	0.53	7.16 [-25.76;40.08]	0.66
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	22.30 [-72.14;116.74]	0.64	160.91 [57.24;264.59]	0.002
randomized for glycemic control postoperatively	17.54 [-50.82;85.91]	0.61	43.15 [-41.55;127.85]	0.31
Complicated/high risk surgery or trauma	52.26 [-50.41;154.93]	0.31	-211.12 [-340.62;-81.62]	0.001
Neurological medical disorders	33.77 [-156.21;223.75]	0.72	148.07 [-85.90;382.04]	0.21
Infectious medical diseases	-120.07 [-250.30;10.15]	0.07	-117.08 [-326.97;92.82]	0.27
Other medical disorders	-65.19 [-200.92;70.54]	0.34	-42.39 [-204.36;119.58]	0.60
Solid organ transplants	59.39 [-150.14;268.92]	0.57	18.45 [-196.25;233.15]	0.86
PeLOD score first 24 hrs (per point added)	-7.08 [-82.12;67.96]	0.85	37.29 [-47.91;122.49]	0.38
PICU stay (per day added)	6.05 [-80.15;92.26]	0.89	90.47 [-69.15;250.09]	0.26
Exceeding potentially harmful threshold for phthalate exposure	50.73 [15.88;85.57]	0.004	27.33 [-8.57;63.23]	0.13

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-14. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	2.75 [-27.15;32.64]	0.85	0.05 [-34.26;34.36]	0.99
Age at sampling (per year added)	-271.88 [-347.89;-195.87]	<0.001	-300.90 [-396.22;-205.58]	<0.001
Caucasian vs. other race	-4.05 [-111.59;103.48]	0.94	18.74 [-94.38;131.86]	0.74
Exclusively European vs. other origin	-50.40 [-139.52;38.71]	0.26	-75.84 [-191.38;0.39.71]	0.19
Exclusively Dutch language vs. non-exclusively Dutch language	53.20 [5.30;101.10]	0.02	57.49 [-3.84;118.81]	0.06
Socioeconomic status (per category of 1 to 66)	-40.25 [-110.62;30.13]	0.26	-110.37 [-193.34;-27.39]	0.009
Pre-existing syndrome vs. no pre-existing syndrome	16.60 [-22.57;55.78]	0.40	45.40 [0.59;90.21]	0.04
History vs. no history of malignancy	-90.14 [-199.55;19.28]	0.10	-4.10 [-108.15;99.95]	0.93
History vs. no history of diabetes	-6.59 [-154.50;141.33]	0.93		
Randomization to strict glycemic control vs. conventional therapy	-10 [-39.32;19.32]	0.50	16.48 [-18.82;51.79]	0.35
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	129.49 [-53.59;312.58]	0.16	182.65 [22.64;342.67]	0.02
randomized for glycemic control postoperatively	122.80 [-46.73;292.34]	0.15	71.58 [-61.37;204.52]	0.28
Complicated/high risk surgery or trauma	108.40 [-72.20;289.01]	0.23	-228.65 [-379.67;-77.63]	0.003
Neurological medical disorders	-3.01 [-297.21;291.18]	0.98	151.68 [-120.86;424.21]	0.27
Infectious medical diseases	-181.01 [-406.82;44.81]	0.11	-102.61 [-340.53;135.31]	0.39
Other medical disorders	-152.71 [-332.97;27.55]	0.09	12.55 [-222.59;247.70]	0.91
Solid organ transplants	-23.97 [-334.04;286.10]	0.87	-87.20 [-344.64;170.25]	0.50
PeLOD score first 24 hrs (per point added)	-5.77 [-92.97;81.43]	0.89	22.71 [-70.51;115.94]	0.63
PICU stay (per day added)	-140.41 [-532.61;251.79]	0.48	-424.74 [-1250.23;400.76]	0.31
Extracorporeal circulation versus no extracorporeal circulation ^a	-35.62 [-100.37;29.13]	0.27	-63.62 [-126.55;-0.70]	0.04
Aortic clamp time (per min added)	8.84 [-78.58;96.25]	0.84	124.50 [-15.82;264.83]	0.08
Duration of mechanical ventilation (per day added)	166.73 [-152.55;486.00]	0.30	416.95 [-345.27;1179.16]	0.28
Peak creatinine (per mg/dl added)	77.48 [-114.27;269.23]	0.42	19.46 [-203.83;242.75]	0.86
Peak bilirubine (per mg/dl added)	-164.29 [-304.76;-23.83]	0.02	112.46 [-206.60;431.52]	0.48
Infection vs. no infection	-12.15 [-62.54;38.24]	0.63	28.60 [-23.31;80.51]	0.28
Antibiotics (per day added)	-64.70 [-268.17;138.76]	0.53	-108.35 [-778.51;417.80]	0.55
Duration of hemodynamic support (per day added)	80.11 [-96.52;256.74]	0.37	124.27 [-483.34;731.88]	0.68
Duration of corticosteroid treatment (per day added)	283.68 [-26.02;593.38]	0.07	336.67 [-82.33;755.66]	0.11
Cumulative dose of opioids (per mg morphine-equivalent added)	130.77 [-92.27;353.81]	0.24	-59.53 [-303.57;184.51]	0.63
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	103.24 [-122.89;329.36]	0.36	-43.20 [-221.88;135.47]	0.63
Received hypnotics versus no hypnotics	-60.51 [-217.46;96.44]	0.44	58.22 [-82.90;199.34]	0.41
Exceeding potentially harmful threshold for phthalate exposure	52.50 [14.65;90.36]	0.006	25.90 [-12.74;64.53]	0.18

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-15. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	8.56 [-16.90;34.03]	0.50	-0.95 [-30.95;29.06]	0.95
Age at sampling (per year added)	-285.89 [-339.64;-232.14]	<0.001	-332.39 [-406.64;-258.14]	<0.001
Caucasian vs. other race	26.54 [-65.77;118.85]	0.57	37.46 [-61.52;136.45]	0.45
Exclusively European vs. other origin	-48.55 [-125.41;28.32]	0.21	-76.89 [-178.57;24.79]	0.13
Exclusively Dutch language vs. non-exclusively Dutch language	43.17 [3.04;83.31]	0.03	42.32 [-11.52;96.17]	0.12
Socioeconomic status (per category of 1 to 66)	-46.67 [-106.90;13.55]	0.12	-100.03 [-172.31;-27.75]	0.006
Pre-existing syndrome vs. no pre-existing syndrome	14.99 [-17.74;47.72]	0.36	53.38 [13.85;92.91]	0.008
History vs. no history of malignancy	-60.90 [-154.08;32.28]	0.19	33.06 [-58.95;125.07]	0.47
History vs. no history of diabetes	-13.31 [-142.63;116.01]	0.83		
Randomization to strict glycemic control vs. conventional therapy	-8.92 [-33.94;16.10]	0.48	4.52 [-25.34;34.37]	0.76
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	43.81 [-39.89;127.51]	0.30	147.85 [53.82;241.89]	0.002
randomized for glycemic control postoperatively	-11.74 [-72.62;49.14]	0.70	49.49 [-27.51;126.50]	0.20
Complicated/high risk surgery or trauma	16.82 [-74.13;107.77]	0.71	-134.47 [-251.69;-17.24]	0.02
Neurological medical disorders	98.24 [-70.31;266.78]	0.25	68.47 [-143.42;280.35]	0.52
Infectious medical diseases	-113.86 [-229.24;1.52]	0.05	-84.97 [-274.98;105.03]	0.37
Other medical disorders	-36.36 [-156.66;83.93]	0.55	-54.14 [-200.82;92.54]	0.46
Solid organ transplants	3.10 [-182.55;188.74]	0.97	7.77 [-186.59;202.14]	0.94
PeLOD score first 24 hrs (per point added)	-11.44 [-78.19;55.30]	0.73	38.97 [-38.21;116.15]	0.32
PICU stay (per day added)	8.10 [-69.50;85.70]	0.83	88.72 [-55.77;233.21]	0.22
Exceeding potentially harmful threshold for phthalate exposure	61.78 [30.60;92.97]	0.0001	38.16 [5.58;70.74]	0.02

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-15. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and inconsistency of reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	6.67 [-20.47;33.82]	0.62	-8.48 [-39.15;22.20]	0.58
Age at sampling (per year added)	-295.99 [-365.13;-226.86]	<0.001	-305.81 [-390.73;-220.89]	<0.001
Caucasian vs. other race	17.00 [-80.09;114.09]	0.73	44.26 [-56.47;144.99]	0.38
Exclusively European vs. other origin	-47.85 [-128.39;32.70]	0.24	-85.18 [-188.07;17.72]	0.10
Exclusively Dutch language vs. non-exclusively Dutch language	42.44 [-0.96;85.83]	0.05	49.29 [-5.32;103.91]	0.07
Socioeconomic status (per category of 1 to 66)	-50.71 [-114.75;13.34]	0.12	-117.94 [-191.95;-43.94]	0.002
Pre-existing syndrome vs. no pre-existing syndrome	20.61 [-15.31;56.52]	0.25	57.00 [16.63;97.37]	0.005
History vs. no history of malignancy	-70.96 [-169.79;27.87]	0.16	23.38 [-69.29;116.05]	0.61
History vs. no history of diabetes	-24.88 [-158.49;108.73]	0.71		
Randomization to strict glycemic control vs. conventional therapy	-7.92 [-34.69;18.85]	0.56	13.31 [-12.21;44.83]	0.40
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	171.36 [4.96;337.77]	0.04	114.95 [-27.54;257.45]	0.11
randomized for glycemic control postoperatively	116.28 [-37.74;270.31]	0.13	36.60 [-81.85;155.04]	0.54
Complicated/high risk surgery or trauma	78.46 [-85.18;242.10]	0.34	-154.51 [-289.00;-20.03]	0.02
Neurological medical disorders	-14.53 [-280.54;251.48]	0.91	51.97 [-190.76;294.71]	0.67
Infectious medical diseases	-202.37 [-406.48;1.75]	0.05	-39.21 [-251.18;172.76]	0.71
Other medical disorders	-115.29 [-278.32;47.74]	0.16	-7.01 [-216.41;202.39]	0.94
Solid organ transplants	-33.92 [-313.85;246.01]	0.81	-2.79 [-232.15;226.56]	0.98
PeLOD score first 24 hrs (per point added)	-22.22 [-101.39;56.94]	0.58	6.23 [-76.89;89.35]	0.88
PICU stay (per day added)	-139.59 [-500.78;221.60]	0.44	149.68 [-585.48;884.83]	0.69
Extracorporeal circulation versus no extracorporeal circulation ^a	-32.43 [-92.82;27.96]	0.29	-32.93 [-88.99;23.13]	0.24
Aortic clamp time (per min added)	6.65 [-72.92;86.22]	0.86	146.80 [21.84;271.75]	0.02
Duration of mechanical ventilation (per day added)	135.94 [-157.79;429.68]	0.36	398.91 [-280.30;1078.12]	0.24
Peak creatinine (per mg/dl added)	66.40 [-107.12;239.92]	0.45	1.65 [-197.20;200.51]	0.98
Peak bilirubine (per mg/dl added)	-73.20 [-200.30;53.91]	0.25	210.17 [-74.34;494.67]	0.14
Infection vs. no infection	8.60 [-37.08;54.28]	0.71	42.10 [-4.17;88.37]	0.07
Antibiotics (per day added)	-22.68 [-206.57;161.22]	0.80	-550.85 [-1083.58;-18.13]	0.04
Duration of hemodynamic support (per day added)	40.39 [-119.30;200.08]	0.61	-60.03 [-601.39;481.33]	0.82
Duration of corticosteroid treatment (per day added)	192.69 [-88.19;473.58]	0.17	152.66 [-220.81;525.90]	0.42
Cumulative dose of opioids (per mg morphine-equivalent added)	77.10 [-124.20;278.41]	0.45	-156.43 [-373.76;60.89]	0.15
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	55.29 [-148.11;260.69]	0.58	-59.13 [-218.25;99.98]	0.46
Received hypnotics versus no hypnotics	-78.19 [-219.89;63.52]	0.27	55.51 [-70.15;181.18]	0.38
Exceeding potentially harmful threshold for phthalate exposure	61.73 [27.19;96.27]	0.0005	35.73 [1.22;70.23]	0.04

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-16. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and no. of valid synchronous taps

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.42 [-0.64;1.47]	0.43	-0.10 [-1.28;1.07]	0.86
Age at sampling (per year added)	15.48 [13.27;17.68]	<0.001	17.02 [14.13;19.92]	<0.001
Caucasian vs. other race	0.04 [-3.87;3.95]	0.98	-1.18 [-5.01;2.66]	0.54
Exclusively European vs. other origin	-1.40 [-4.58;1.77]	0.38	1.35 [-2.65;5.36]	0.50
Exclusively Dutch language vs. non-exclusively Dutch language	0.35 [-1.33;2.03]	0.68	-0.05 [-2.28;2.17]	0.96
Socioeconomic status (per category of 1 to 66)	1.21 [-1.28;3.69]	0.33	0.67 [-2.13;3.48]	0.63
Pre-existing syndrome vs. no pre-existing syndrome	0.01 [-1.34;1.37]	0.98	-2.17 [-3.73;-0.62]	0.006
History vs. no history of malignancy	-0.44 [-4.24;3.36]	0.81	1.67 [-1.87;5.20]	0.35
History vs. no history of diabetes	3.29 [-2.02;8.60]	0.22		
Randomization to strict glycemic control vs. conventional therapy	0.30 [-0.73;1.34]	0.56	0.52 [-0.66;1.69]	0.38
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	5.19 [1.73;8.65]	0.003	1.61 [-2.05;5.28]	0.39
randomized for glycemic control postoperatively	1.78 [-0.73;4.29]	0.16	2.37 [-0.63;5.36]	0.12
Complicated/high risk surgery or trauma	2.23 [-1.42;5.88]	0.22	3.63 [-0.77;8.03]	0.10
Neurological medical disorders	-3.51 [-10.43;3.41]	0.31	-5.30 [-13.49;2.89]	0.20
Infectious medical diseases	-0.44 [-5.18;4.30]	0.85	-0.18 [-7.53;7.17]	0.96
Other medical disorders	-0.13 [-5.07;4.81]	0.95	5.88 [0.21;11.55]	0.03
Solid organ transplants	-5.12 [-12.75;2.51]	0.18	-8.01 [-15.51;-0.52]	0.04
PeLOD score first 24 hrs (per point added)	1.57 [-1.18;4.32]	0.26	1.52 [-1.48;4.52]	0.31
PICU stay (per day added)	-1.43 [-4.63;1.78]	0.38	-2.20 [-7.75;3.34]	0.43
Exceeding potentially harmful threshold for phthalate exposure	-2.05 [-3.33;-0.77]	0.001	-0.63 [-1.90;0.63]	0.32

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-16. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP metabolite exposure and no. of valid synchronous taps (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.53 [-0.58;1.64]	0.34	-0.19 [-1.37;1.00]	0.75
Age at sampling (per year added)	15.14 [12.30;17.98]	<0.001	15.54 [12.26;18.83]	<0.001
Caucasian vs. other race	0.39 [-3.72;4.51]	0.85	-1.61 [-5.49;2.28]	0.41
Exclusively European vs. other origin	-0.99 [-4.29;2.31]	0.55	2.32 [-1.71;6.34]	0.25
Exclusively Dutch language vs. non-exclusively Dutch language	-0.30 [-2.10;0.74]	0.74	-0.50 [-2.77;1.76]	0.66
Socioeconomic status (per category of 1 to 66)	1.40 [-1.20;4.01]	0.28	0.87 [-1.98;3.73]	0.54
Pre-existing syndrome vs. no pre-existing syndrome	-0.39 [-1.86;1.09]	0.60	-2.11 [-3.69;-0.53]	0.009
History vs. no history of malignancy	-0.34 [-4.38;3.66]	0.86	2.41 [-1.16;5.97]	0.18
History vs. no history of diabetes	3.33 [-2.11;8.78]	0.22		
Randomization to strict glycemic control vs. conventional therapy	0.47 [-0.63;1.57]	0.39	-0.02 [-1.23;1.19]	0.97
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	3.23 [-3.60;10.07]	0.35	1.66 [-3.89;7.20]	0.55
randomized for glycemic control postoperatively	0.13 [-6.17;6.43]	0.96	2.56 [-2.01;7.12]	0.27
Complicated/high risk surgery or trauma	1.86 [-4.75;8.46]	0.57	5.29 [0.10;10.48]	0.04
Neurological medical disorders	-3.49 [-14.36;7.37]	0.52	-6.37 [-15.74;3.00]	0.18
Infectious medical diseases	-1.70 [-10.03;6.63]	0.68	1.22 [-6.68;9.13]	0.76
Other medical disorders	2.06 [-4.58;8.71]	0.54	2.66 [-5.39;10.71]	0.51
Solid organ transplants	-2.09 [-13.51;9.33]	0.71	-7.01 [-15.76;1.73]	0.11
PeLOD score first 24 hrs (per point added)	1.17 [-2.09;4.44]	0.47	0.85 [-2.40;4.11]	0.60
PICU stay (per day added)	0.88 [-13.95;15.71]	0.80	-16.25 [-45.68;13.17]	0.27
Extracorporeal circulation versus no extracorporeal circulation ^a	1.68 [-0.81;4.17]	0.18	2.58 [0.37;4.79]	0.02
Aortic clamp time (per min added)	-0.47 [-3.74;2.80]	0.77	-4.12 [-8.98;0.73]	0.09
Duration of mechanical ventilation (per day added)	4.81 [-7.24;16.85]	0.43	23.43 [-3.04;49.89]	0.08
Peak creatinine (per mg/dl added)	-0.02 [-7.17;7.13]	0.99	8.52 [0.87;16.18]	0.02
Peak bilirubine (per mg/dl added)	-1.36 [-6.62;3.90]	0.61	-5.42 [-17.06;6.18]	0.35
Infection vs. no infection	0.72 [-1.16;2.59]	0.45	-0.75 [-2.54;1.03]	0.40
Antibiotics (per day added)	-3.95 [-11.48;3.57]	0.30	-1.72 [-23.22;19.77]	0.87
Duration of hemodynamic support (per day added)	-6.01 [-12.49;0.48]	0.06	-6.50 [-24.94;11.93]	0.48
Duration of corticosteroid treatment (per day added)	-2.00 [-13.45;9.46]	0.73	0.34 [-13.51;14.20]	0.96
Cumulative dose of opioids (per mg morphine-equivalent added)	-5.85 [-14.06;2.35]	0.16	5.73 [-2.44;13.90]	0.16
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-1.74 [-10.09;6.61]	0.68	-0.03 [-6.18;6.12]	0.99
Received hypnotics versus no hypnotics	0.24 [5.55;6.03]	0.93	-2.07 [-6.92;2.77]	0.39
Exceeding potentially harmful threshold for phthalate exposure	-2.16 [-3.57;-0.75]	0.003	-1.00 [-2.34;0.34]	0.14

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-17. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-10.68 [-45.94;24.58]	0.55	-5.93 [-43.19;31.34]	0.75
Age at sampling (per year added)	-443.35 [-514.02;-372.67]	<0.001	-452.09 [-541.11;-363.06]	<0.001
Caucasian vs. other race	25.23 [-102.72;153.18]	0.69	77.86 [-45.12;200.83]	0.21
Exclusively European vs. other origin	-13.08 [-119.46;93.30]	0.80	-119.16 [-245.87;7.55]	0.06
Exclusively Dutch language vs. non-exclusively Dutch language	59.40 [3.69;115.11]	0.03	47.73 [-18.90;114.37]	0.15
Socioeconomic status (per category of 1 to 66)	-106.36 [-189.50;-23.22]	0.01	-58.56 [-147.81;30.69]	0.19
Pre-existing syndrome vs. no pre-existing syndrome	31.17 [-14.10;76.44]	0.17	54.54 [6.15;102.93]	0.02
History vs. no history of malignancy	-36.06 [-164.33;92.21]	0.57	20.68 [-92.08;133.44]	0.71
History vs. no history of diabetes	-38.78 [-217.97;140.40]	0.66		
Randomization to strict glycemic control vs. conventional therapy	5.48 [-29.13;40.10]	0.75	-2.89 [-39.80;34.02]	0.87
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	86.13 [-28.94;201.19]	0.14	200.58 [83.96;317.20]	<0.001
randomized for glycemic control postoperatively	-58.44 [-142.65;25.77]	0.17	82.50 [-12.42;177.42]	0.08
Complicated/high risk surgery or trauma	-50.59 [-176.60;75.41]	0.42	-76.31 [-221.63;69.01]	0.30
Neurological medical disorders	219.24 [-14.51;453.00]	0.06	-0.67 [-263.37;262.04]	>0.99
Infectious medical diseases	-163.48 [-323.95;-3.02]	0.04	-73.47 [-308.78;161.83]	0.53
Other medical disorders	-94.05 [-261.65;73.56]	0.26	-28.69 [-210.30;152.92]	0.75
Solid organ transplants	61.19 [-196.99;319.37]	0.64	-103.95 [-344.61;136.71]	0.39
PeLOD score first 24 hrs (per point added)	-36.36 [-127.69;54.98]	0.43	36.47 [-59.44;132.37]	0.45
PICU stay (per day added)	36.28 [-71.47;144.04]	0.50	170.10 [-9.16;349.36]	0.06
Exceeding potentially harmful threshold for phthalate exposure	58.79 [18.29;99.28]	0.004	45.57 [5.83;85.31]	0.02

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-17. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-14.94 [-52.54;22.66]	0.43	-17.02 [-54.73;20.70]	0.37
Age at sampling (per year added)	-442.56 [-531.42;-353.69]	<0.001	-419.77 [-517.72;-321.82]	<0.001
Caucasian vs. other race	5.54 [-129.02;140.10]	0.93	72.48 [-50.88;195.85]	0.24
Exclusively European vs. other origin	-1.29 [-112.83;110.25]	0.98	-110.20 [-236.37;15.97]	0.08
Exclusively Dutch language vs. non-exclusively Dutch language	53.55 [-6.71;113.80]	0.08	57.21 [-9.37;123.79]	0.09
Socioeconomic status (per category of 1 to 66)	-117.30 [-205.81;-28.80]	0.009	-77.84 [-168.07;12.38]	0.09
Pre-existing syndrome vs. no pre-existing syndrome	37.59 [-11.65;86.78]	0.13	62.83 [14.37;111.30]	0.01
History vs. no history of malignancy	-45.03 [-181.56;91.49]	0.51	7.25 [-107.71;119.22]	0.89
History vs. no history of diabetes	-53.51 [-238.72;131.70]	0.56		
Randomization to strict glycemic control vs. conventional therapy	4.85 [-32.26;41.97]	0.79	6.87 [-31.50;45.25]	0.72
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	274.17 [43.29;505.05]	0.02	130.71 [-43.37;304.79]	0.14
randomized for glycemic control postoperatively	128.63 [-84.85;342.11]	0.23	47.34 [-98.31;193.00]	0.52
Complicated/high risk surgery or trauma	57.83 [-169.05;284.71]	0.61	-46.96 [-211.25;117.33]	0.57
Neurological medical disorders	88.35 [-280.56;457.27]	0.63	-89.44 [-386.08;207.19]	0.55
Infectious medical diseases	-346.62 [-629.91;-63.34]	0.01	31.78 [-226.79;290.35]	0.80
Other medical disorders	-205.57 [-431.93;20.78]	0.07	4.46 [-251.69;260.62]	0.97
Solid organ transplants	3.21 [-389.08;392.50]	0.99	-77.89 [-358.02;202.24]	0.58
PeLOD score first 24 hrs (per point added)	-27.00 [-136.26;82.27]	0.62	4.45 [-97.03;105.94]	0.93
PICU stay (per day added)	-345.63 [-842.19;150.94]	0.17	-313.24 [-1212.00;585.52]	0.49
Extracorporeal circulation versus no extracorporeal circulation ^a	-39.96 [-123.26;43.35]	0.34	-26.38 [-94.43;41.68]	0.44
Aortic clamp time (per min added)	2.47 [-108.34;113.28]	0.96	135.96 [-17.18;289.11]	0.08
Duration of mechanical ventilation (per day added)	347.31 [-54.25;748.87]	0.08	845.07 [16.06;1674.09]	0.04
Peak creatinine (per mg/dl added)	-16.56 [-255.54;222.42]	0.89	-52.46 [-293.18;188.26]	0.66
Peak bilirubine (per mg/dl added)	-51.49 [-227.83;124.85]	0.56	325.93 [-21.72;673.58]	0.06
Infection vs. no infection	18.56 [-44.97;82.08]	0.56	34.35 [-22.43;91.13]	0.23
Antibiotics (per day added)	27.41 [-227.28;282.12]	0.83	-580.12 [-1231.43;71.19]	0.08
Duration of hemodynamic support (per day added)	34.40 [-186.99;255.79]	0.75	208.56 [-451.89;871.00]	0.53
Duration of corticosteroid treatment (per day added)	281.30 [-107.47;670.07]	0.15	155.88 [-299.82;611.58]	0.50
Cumulative dose of opioids (per mg morphine-equivalent added)	-11.96 [-292.30;268.39]	0.93	-169.14 [-432.89;94.61]	0.20
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	46.39 [-239.01;328.79]	0.74	-121.20 [-312.48;70.07]	0.21
Received hypnotics versus no hypnotics	-133.49 [-329.62;62.64]	0.18	20.13 [-133.44;173.69]	0.79
Exceeding potentially harmful threshold for phthalate exposure	57.95 [14.07;101.82]	0.009	40.09 [-1.01;81.20]	0.05

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-18. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-20.16 [-52.48;12.17]	0.22	7.85 [-26.56;42.26]	0.65
Age at sampling (per year added)	-395.60 [-460.32;-330.88]	<0.001	-426.46 [-508.66;-344.26]	<0.001
Caucasian vs. other race	-19.15 [-137.24;98.95]	0.74	21.93 [-91.62;135.48]	0.70
Exclusively European vs. other origin	-19.74 [-117.85;78.37]	0.69	-97.22 [-214.22;19.78]	0.10
Exclusively Dutch language vs. non-exclusively Dutch language	55.29 [4.01;106.57]	0.03	61.85 [0.33;123.38]	0.04
Socioeconomic status (per category of 1 to 66)	-55.93 [-132.14;20.28]	0.14	-98.37 [-180.78;-15.96]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	16.31 [-24.91;57.54]	0.43	49.35 [4.67;94.03]	0.03
History vs. no history of malignancy	-23.94 [-142.34;94.45]	0.69	36.29 [-67.83;140.41]	0.49
History vs. no history of diabetes	-6.74 [-172.09;158.60]	0.93		
Randomization to strict glycemic control vs. conventional therapy	4.90 [-26.76;36.56]	0.76	1.99 [-32.09;36.07]	0.90
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	57.09 [-49.00;163.19]	0.28	185.49 [77.81;293.17]	<0.001
randomized for glycemic control postoperatively	-20.00 [-97.29;57.29]	0.61	68.65 [-19.00;156.29]	0.12
Complicated/high risk surgery or trauma	-11.17 [-127.48;105.14]	0.85	-180.39 [-314.57;-46.21]	0.008
Neurological medical disorders	96.43 [-119.04;311.91]	0.38	91.30 [-151.27;333.88]	0.45
Infectious medical diseases	-92.14 [-240.21;55.94]	0.22	-64.17 [-281.44;153.10]	0.56
Other medical disorders	-117.35 [-272.00;37.31]	0.13	-31.31 [-199.00;136.38]	0.71
Solid organ transplants	87.13 [-151.10;325.36]	0.47	-69.57 [-291.79;152.65]	0.53
PeLOD score first 24 hrs (per point added)	-0.33 [-84.35;83.68]	0.99	10.33 [-78.23;98.88]	0.81
PICU stay (per day added)	-5.94 [-103.78;91.91]	0.90	201.11 [35.58;366.63]	0.01
Exceeding potentially harmful threshold for phthalate exposure	56.24 [19.25;93.24]	0.003	35.62 [-1.07;72.32]	0.05

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-18. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-21.27 [-54.77;12.24]	0.21	1.31 [-34.09;36.35]	0.94
Age at sampling (per year added)	-405.23 [-484.30;-326.15]	<0.001	-405.42 [-496.89;-313.94]	<0.001
Caucasian vs. other race	-42.35 [-162.97;78.27]	0.49	25.00 [-90.20;140.20]	0.66
Exclusively European vs. other origin	-8.75 [-108.64;91.13]	0.86	-92.34 [-210.16;25.47]	0.12
Exclusively Dutch language vs. non-exclusively Dutch language	54.78 [0.95;106.62]	0.04	70.15 [7.98;132.33]	0.02
Socioeconomic status (per category of 1 to 66)	-65.36 [-144.10;13.38]	0.10	-118.93 [-203.18;-34.67]	0.005
Pre-existing syndrome vs. no pre-existing syndrome	20.43 [-22.96;63.83]	0.35	52.92 [7.67;98.18]	0.02
History vs. no history of malignancy	-25.33 [-147.65;96.99]	0.68	22.42 [-82.13;126.97]	0.67
History vs. no history of diabetes	-27.54 [-193.49;138.40]	0.74		
Randomization to strict glycemic control vs. conventional therapy	6.79 [-26.10;37.67]	0.68	13.68 [-22.15;49.52]	0.45
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	247.37 [41.76;452.97]	0.01	132.30 [-30.25;294.86]	0.11
randomized for glycemic control postoperatively	156.38 [-33.79;346.56]	0.10	37.27 [-98.75;173.28]	0.58
Complicated/high risk surgery or trauma	49.31 [-153.33;251.94]	0.63	-185.21 [-338.63;-31.80]	0.01
Neurological medical disorders	9.64 [-320.61;339.89]	0.95	85.81 [-191.19;362.81]	0.54
Infectious medical diseases	-245.78 [-499.40;7.83]	0.05	-14.45 [-255.92;227.01]	0.90
Other medical disorders	-274.75 [-477.35;-72.16]	0.008	55.01 [-184.19;294.21]	0.65
Solid organ transplants	57.84 [-291.16;406.84]	0.74	-110.73 [-372.32;150.86]	0.40
PeLOD score first 24 hrs (per point added)	11.63 [-85.88;109.15]	0.81	-5.96 [-100.73;88.81]	0.90
PICU stay (per day added)	-213.65 [-650.47;223.18]	0.33	-537.03 [-1376.31;302.25]	0.20
Extracorporeal circulation versus no extracorporeal circulation ^a	-48.18 [120.49;24.13]	0.19	-51.45 [-115.01;12.10]	0.11
Aortic clamp time (per min added)	-39.26 [-138.02;59.50]	0.43	106.97 [-36.04;249.98]	0.14
Duration of mechanical ventilation (per day added)	216.32 [-137.25;569.89]	0.22	547.39 [-226.76;1321.54]	0.16
Peak creatinine (per mg/dl added)	23.20 [-190.49;236.89]	0.83	-15.18 [-239.97;209.61]	0.89
Peak bilirubine (per mg/dl added)	-166.41 [-324.13;-8.69]	0.03	236.28 [-88.37;560.92]	0.15
Infection vs. no infection	12.27 [-44.49;68.98]	0.67	25.89 [-27.14;78.91]	0.34
Antibiotics (per day added)	-43.76 [-271.91;184.40]	0.70	-141.75 [-749.95;466.46]	0.64
Duration of hemodynamic support (per day added)	59.19 [-138.97;257.34]	0.55	352.09 [-265.58;969.75]	0.26
Duration of corticosteroid treatment (per day added)	224.34 [-122.65;571.32]	0.20	218.55 [-206.99;644.09]	0.31
Cumulative dose of opioids (per mg morphine-equivalent added)	101.94 [-149.47;353.35]	0.42	-140.69 [-386.98;105.60]	0.26
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	150.43 [-102.41;403.27]	0.24	-103.40 [-282.02;75.22]	0.25
Received hypnotics versus no hypnotics	-109.94 [-285.75;65.86]	0.21	74.09 [-69.31;217.49]	0.30
Exceeding potentially harmful threshold for phthalate exposure	60.27 [21.21;99.33]	0.002	32.92 [-5.46;71.31]	0.09

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-19. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-16.82 [-48.14;14.49]	0.29	2.16 [-31.98;36.31]	0.90
Age at sampling (per year added)	-415.06 [-477.82;-352.31]	<0.001	-439.56 [-521.13;-357.99]	<0.001
Caucasian vs. other race	3.10 [-110.52;116.73]	0.95	49.55 [-63.13;162.24]	0.38
Exclusively European vs. other origin	-16.02 [-110.48;78.45]	0.73	-107.37 [-223.47;8.73]	0.06
Exclusively Dutch language vs. non-exclusively Dutch language	55.30 [5.83;104.77]	0.02	54.00 [-7.06;115.05]	0.08
Socioeconomic status (per category of 1 to 66)	-77.22 [-151.05;-3.39]	0.04	-80.56 [-162.33;1.22]	0.05
Pre-existing syndrome vs. no pre-existing syndrome	21.16 [-19.04;61.36]	0.30	49.38 [5.04;93.72]	0.02
History vs. no history of malignancy	-30.16 [-144.07;83.75]	0.60	29.42 [-73.90;132.74]	0.57
History vs. no history of diabetes	-20.11 [-179.23;139.01]	0.80		
Randomization to strict glycemic control vs. conventional therapy	4.54 [-26.20;35.28]	0.77	-1.14 [-34.96;32.68]	0.94
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	70.47 [-31.71;172.65]	0.17	190.36 [83.50;297.21]	<0.001
randomized for glycemic control postoperatively	-43.18 [-117.96;31.60]	0.25	72.16 [-14.82;159.13]	0.10
Complicated/high risk surgery or trauma	-30.86 [-142.75;81.04]	0.58	-127.78 [-260.93;5.38]	0.05
Neurological medical disorders	162.20 [-45.38;369.78]	0.12	49.03 [-191.68;289.74]	0.68
Infectious medical diseases	-127.34 [-269.84;15.15]	0.07	-69.97 [-285.58;145.63]	0.52
Other medical disorders	-108.09 [-256.93;40.74]	0.15	-27.83 [-194.24;138.57]	0.74
Solid organ transplants	76.80 [-152.47;306.06]	0.50	-85.96 [-306.47;134.55]	0.44
PeLOD score first 24 hrs (per point added)	-16.38 [-97.49;64.73]	0.69	21.45 [-66.42;109.33]	0.63
PICU stay (per day added)	18.12 [-77.56;113.81]	0.70	187.47 [23.22;351.73]	0.02
Exceeding potentially harmful threshold for phthalate exposure	57.19 [21.24;93.15]	0.002	41.30 [4.88;77.71]	0.02

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-19. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-19.49 [-52.36;13.38]	0.24	-6.52 [-41.18;28.14]	0.71
Age at sampling (per year added)	-418.92 [-496.61;-341.24]	<0.001	-411.49 [-501.52;-321.47]	<0.001
Caucasian vs. other race	-18.44 [-136.07;99.18]	0.75	48.41 [-64.97;161.79]	0.40
Exclusively European vs. other origin	-4.40 [-101.90;93.10]	0.92	-100.83 [-216.78;15.12]	0.08
Exclusively Dutch language vs. non-exclusively Dutch language	52.11 [-0.56;104.78]	0.05	62.94 [1.75;124.13]	0.04
Socioeconomic status (per category of 1 to 66)	-87.81 [-165.18;-10.44]	0.02	-100.45 [-183.37;-17.52]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	26.50 [-16.53;69.52]	0.22	54.88 [10.34;99.42]	0.01
History vs. no history of malignancy	-35.24 [-154.58;84.10]	0.56	15.98 [-86.92;118.88]	0.75
History vs. no history of diabetes	-39.11 [-201.02;122.79]	0.63		
Randomization to strict glycemic control vs. conventional therapy	5.57 [-26.87;38.02]	0.73	9.36 [-25.91;44.62]	0.60
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	265.20 [63.37;467.02]	0.01	129.94 [-30.05;289.92]	0.11
randomized for glycemic control postoperatively	144.30 [-42.31;330.91]	0.12	39.81 [-94.05;173.68]	0.55
Complicated/high risk surgery or trauma	52.68 [-145.65;251.01]	0.60	-116.34 [-267.33;34.66]	0.13
Neurological medical disorders	47.90 [-274.59;370.39]	0.76	1.02 [-271.60;273.64]	0.99
Infectious medical diseases	-299.90 [-547.53;-52.27]	0.01	6.36 [-231.28;244.01]	0.95
Other medical disorders	-244.66 [-442.53;-46.79]	0.01	30.71 [-204.70;266.13]	0.79
Solid organ transplants	34.49 [-305.81;374.79]	0.84	-91.51 [-348.96;165.94]	0.48
PeLOD score first 24 hrs (per point added)	-6.47 [-101.98;89.05]	0.89	-3.44 [-96.71;89.83]	0.94
PICU stay (per day added)	-281.54 [-715.61;152.54]	0.20	-420.94 [-1246.95;405.06]	0.31
Extracorporeal circulation versus no extracorporeal circulation ^a	-47.67 [-120.50;25.15]	0.19	-39.29 [-101.84;23.26]	0.21
Aortic clamp time (per min added)	-17.07 [-113.93;79.79]	0.72	120.83 [-19.91;261.58]	0.09
Duration of mechanical ventilation (per day added)	285.02 [-66.00;636.05]	0.11	711.04 [-50.86;1472.94]	0.06
Peak creatinine (per mg/dl added)	5.27 [-203.64;214.18]	0.96	-31.66 [-252.89;189.57]	0.77
Peak bilirubine (per mg/dl added)	-105.33 [-259.47;48.82]	0.17	268.40 [-51.11;587.90]	0.09
Infection vs. no infection	16.20 [-39.32;71.73]	0.56	31.18 [-21.00;83.36]	0.23
Antibiotics (per day added)	-5.12 [-227.77;217.53]	0.96	-366.30 [-964.88;232.28]	0.22
Duration of hemodynamic support (per day added)	47.66 [-145.87;241.19]	0.62	277.14 [-330.75;885.04]	0.36
Duration of corticosteroid treatment (per day added)	249.39 [-90.45;589.23]	0.14	178.55 [-240.26;597.35]	0.40
Cumulative dose of opioids (per mg morphine-equivalent added)	43.87 [-201.19;288.94]	0.72	-155.62 [-398.02;86.77]	0.20
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	96.57 [-150.29;343.43]	0.44	-112.00 [-287.79;63.79]	0.21
Received hypnotics versus no hypnotics	-123.32 [-294.76;48.13]	0.15	47.40 [-93.73;188.54]	0.50
Exceeding potentially harmful threshold for phthalate exposure	58.33 [19.98;96.69]	0.003	37.30 [-0.48;75.07]	0.05

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-20. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and no. of valid synchronous taps

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.48 [-0.55;1.51]	0.36	0.08 [-1.08;1.24]	0.89
Age at sampling (per year added)	15.85 [13.79;17.91]	<0.001	16.84 [14.08;19.60]	<0.001
Caucasian vs. other race	-0.13 [-3.97;3.71]	0.94	-1.59 [-5.36;2.18]	0.40
Exclusively European vs. other origin	-1.52 [-4.64;1.59]	0.33	1.89 [-2.06;5.84]	0.34
Exclusively Dutch language vs. non-exclusively Dutch language	0.59 [-1.06;2.24]	0.48	0.05 [-2.14;2.23]	0.96
Socioeconomic status (per category of 1 to 66)	1.21 [-1.22;3.64]	0.32	0.65 [-2.09;3.40]	0.63
Pre-existing syndrome vs. no pre-existing syndrome	-0.32 [-1.65;1.00]	0.63	-2.16 [-3.68;-0.64]	0.005
History vs. no history of malignancy	-1.01 [-4.72;2.70]	0.59	1.99 [-1.44;5.42]	0.25
History vs. no history of diabetes	3.42 [-1.80;8.63]	0.19		
Randomization to strict glycemic control vs. conventional therapy	0.33 [-0.69;1.34]	0.52	0.48 [-0.67;1.64]	0.41
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	4.17 [0.79;7.54]	0.01	2.08 [-1.53;5.69]	0.25
randomized for glycemic control postoperatively	1.43 [-1.03;3.90]	0.25	2.12 [-0.82;5.06]	0.15
Complicated/high risk surgery or trauma	1.96 [-1.63;5.55]	0.28	3.37 [-0.95;7.69]	0.12
Neurological medical disorders	-3.85 [-10.65;2.94]	0.26	-5.96 [-14.02;2.09]	0.14
Infectious medical diseases	-0.94 [-5.61;3.72]	0.69	0.02 [-7.19;7.23]	>0.99
Other medical disorders	0.97 [-3.91;5.86]	0.69	5.89 [0.33;11.45]	0.03
Solid organ transplants	-3.74 [-11.25;3.78]	0.32	-7.52 [-14.87;-0.17]	0.04
PeLOD score first 24 hrs (per point added)	1.54 [-1.15;4.22]	0.26	1.86 [-1.09;4.81]	0.21
PICU stay (per day added)	-0.98 [-4.12;2.15]	0.53	-1.15 [-6.60;4.30]	0.67
Exceeding potentially harmful threshold for phthalate exposure	-2.53 [-3.72;-1.34]	0.00004	-1.77 [-3.00;-0.53]	0.005

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-20. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating MEHP exposure and no. of valid synchronous taps (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.59 [-0.50;1.67]	0.28	-0.02 [-1.21;1.17]	0.97
Age at sampling (per year added)	15.86 [13.30;18.43]	<0.001	15.80 [12.73;18.88]	<0.001
Caucasian vs. other race	0.41 [-3.61;4.43]	0.84	-1.87 [-5.72;1.98]	0.33
Exclusively European vs. other origin	-1.22 [-4.44;2.00]	0.45	2.61 [-1.38;6.60]	0.19
Exclusively Dutch language vs. non-exclusively Dutch language	-0.09 [-1.85;1.67]	0.91	-0.38 [-2.61;1.86]	0.74
Socioeconomic status (per category of 1 to 66)	1.48 [-1.07;4.02]	0.25	0.88 [-1.94;3.70]	0.53
Pre-existing syndrome vs. no pre-existing syndrome	-0.68 [-2.10;0.75]	0.35	-2.12 [-3.68;-0.56]	0.007
History vs. no history of malignancy	-0.90 [-4.79;3.00]	0.65	2.39 [-1.10;5.88]	0.17
History vs. no history of diabetes	3.29 [-2.03;8.61]	0.22		
Randomization to strict glycemic control vs. conventional therapy	0.56 [-0.52;1.64]	0.30	-0.03 [-1.22;1.17]	0.96
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	2.85 [-3.83;9.53]	0.40	1.60 [-3.88;7.09]	0.56
randomized for glycemic control postoperatively	0.60 [-5.55;6.75]	0.84	1.98 [-2.56;6.53]	0.38
Complicated/high risk surgery or trauma	1.01 [-5.45;7.47]	0.75	4.91 [-0.23;10.04]	0.06
Neurological medical disorders	-4.49 [-15.11;6.12]	0.40	-6.86 [-16.14;2.41]	0.14
Infectious medical diseases	-2.65 [-10.80;5.49]	0.52	1.32 [-6.50;9.13]	0.74
Other medical disorders	2.61 [-3.89;9.12]	0.42	3.27 [-4.70;11.25]	0.41
Solid organ transplants	0.08 [-11.11;11.26]	0.98	-6.22 [-14.88;2.45]	0.15
PeLOD score first 24 hrs (per point added)	0.97 [-2.21;4.15]	0.54	1.24 [-1.97;4.46]	0.44
PICU stay (per day added)	4.27 [-10.10;18.63]	0.55	-13.08 [-42.27;16.11]	0.37
Extracorporeal circulation versus no extracorporeal circulation ^a	0.63 [-1.79;3.05]	0.60	2.56 [0.39;4.73]	0.02
Aortic clamp time (per min added)	0.95 [-2.27;4.16]	0.56	-3.68 [-8.51;1.14]	0.13
Duration of mechanical ventilation (per day added)	2.06 [-9.53;13.64]	0.72	22.11 [-4.07;48.30]	0.09
Peak creatinine (per mg/dl added)	-0.20 [-7.14;6.75]	0.95	6.81 [-0.66;14.28]	0.07
Peak bilirubine (per mg/dl added)	-1.17 [-6.31;3.97]	0.65	-4.77 [-16.25;6.71]	0.41
Infection vs. no infection	0.97 [-0.87;2.81]	0.30	-0.60 [-2.37;1.18]	0.50
Antibiotics (per day added)	-4.72 [-12.06;2.63]	0.20	-3.37 [-24.63;17.89]	0.75
Duration of hemodynamic support (per day added)	-5.77 [-12.11;0.56]	0.07	-6.35 [-24.58;11.88]	0.49
Duration of corticosteroid treatment (per day added)	-3.98 [-15.15;7.19]	0.48	-1.00 [-14.72;12.72]	0.88
Cumulative dose of opioids (per mg morphine-equivalent added)	-4.38 [-12.43;3.68]	0.28	5.94 [-2.10;13.97]	0.14
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-2.40 [-10.53;5.74]	0.56	-0.05 [-6.02;5.92]	0.98
Received hypnotics versus no hypnotics	0.13 [-5.52;5.78]	0.96	-1.81 [-6.60;2.98]	0.46
Exceeding potentially harmful threshold for phthalate exposure	-2.73 [-4.00;-1.45]	0.00004	-1.60 [-2.90;-0.31]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-21. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5cx-MEPP exposure and working memory (repeating numbers, backward)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-0.49 [-1.05;0.07]	0.08	-0.03 [-0.72;0.66]	0.93
Age at sampling (per year added)	-0.98 [-2.12;0.17]	0.09	-1.52 [-2.96;-0.08]	0.03
Caucasian vs. other race	-0.02 [-2.29;2.26]	0.98	-1.35 [-3.53;0.82]	0.21
Exclusively European vs. other origin	-0.69 [-2.35;0.97]	0.41	-0.02 [-2.06;2.03]	0.98
Exclusively Dutch language vs. non-exclusively Dutch language	0.03 [-0.86;0.91]	0.94	1.25 [-0.02;2.51]	0.05
Socioeconomic status (per category of 1 to 66)	1.28 [-0.04;2.59]	0.05	0.72 [-0.67;2.12]	0.30
Pre-existing syndrome vs. no pre-existing syndrome	-0.75 [-1.41;-0.09]	0.02	-1.05 [-1.86;-0.24]	0.01
History vs. no history of malignancy	0.33 [-1.25;1.91]	0.67	0.24 [-1.60;2.09]	0.79
History vs. no history of diabetes	-1.50 [-4.44;1.44]	0.31		
Randomization to strict glycemic control vs. conventional therapy	0.28 [-0.28;0.85]	0.32	-0.51 [-1.25;0.24]	0.18
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	3.48 [1.21;5.76]	0.003	0.65 [-1.90;3.19]	0.61
randomized for glycemic control postoperatively	0.52 [-0.73;1.77]	0.41	0.77 [-0.90;2.44]	0.36
Complicated/high risk surgery or trauma	0.66 [-1.08;2.40]	0.45	0.61 [-1.61;2.83]	0.58
Neurological medical disorders	-0.74 [-4.27;2.79]	0.67	0.79 [-3.41;4.99]	0.70
Infectious medical diseases	-1.46 [-3.87;0.95]	0.23	-0.48 [-3.61;2.65]	0.76
Other medical disorders	-2.46 [-4.90;-0.02]	0.04	0.50 [-2.27;3.27]	0.71
Solid organ transplants			-2.84 [-7.53;1.85]	0.23
PeLOD score first 24 hrs (per point added)	-0.54 [-2.16;1.08]	0.50	0.74 [-1.18;2.66]	0.44
PICU stay (per day added)	0.46 [-1.33;2.25]	0.60	0.02 [-3.51;3.55]	0.99
Exceeding potentially harmful threshold for phthalate exposure	-0.95 [-1.67;-0.22]	0.01	0.26 [-0.50;1.03]	0.49

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-21. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5cx-MEPP exposure and working memory (repeating numbers, backward) (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-0.40 [-1.03;0.23]	0.20	0.05 [-0.67;0.78]	0.88
Age at sampling (per year added)	-1.01 [-2.47;0.46]	0.17	-0.99 [-2.64;0.65]	0.23
Caucasian vs. other race	-0.01 [-2.89;2.87]	0.99	-0.29 [-2.51;1.94]	0.79
Exclusively European vs. other origin	-0.74 [-2.74;1.27]	0.46	0.38 [-1.69;2.45]	0.71
Exclusively Dutch language vs. non-exclusively Dutch language	-0.38 [-1.42;0.67]	0.47	0.39 [-1.02;1.81]	0.58
Socioeconomic status (per category of 1 to 66)	1.11 [-0.37;2.59]	0.13	0.97 [-0.43;2.36]	0.17
Pre-existing syndrome vs. no pre-existing syndrome	-0.56 [-1.34;0.22]	0.15	-0.86 [-1.73; 0.00]	0.05
History vs. no history of malignancy	-0.16 [-1.95;1.64]	0.85	-0.43 [-2.45;1.59]	0.67
History vs. no history of diabetes	-1.21 [-4.30;1.87]	0.43		
Randomization to strict glycemic control vs. conventional therapy	0.22 [-0.44;0.87]	0.51	-0.53 [-1.36;0.31]	0.21
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	2.85 [-4.71;10.40]	0.45	-1.63 [-5.38;2.11]	0.38
randomized for glycemic control postoperatively	0.60 [-6.58;7.78]	0.86	1.93 [-4.81;0.96]	0.18
Complicated/high risk surgery or trauma	2.75 [-3.73;9.22]	0.39	0.45 [-2.49;3.40]	0.75
Neurological medical disorders	-2.09 [-10.17;5.98]	0.60	-0.92 [-6.30;4.46]	0.73
Infectious medical diseases	-3.24 [-10.08;3.60]	0.34	2.50 [-1.87;6.86]	0.25
Other medical disorders	-0.86 [-7.70;5.98]	0.80	1.48 [-2.63;5.59]	0.47
Solid organ transplants			0.05 [-5.70;5.79]	0.98
PeLOD score first 24 hrs (per point added)	-0.85 [-2.93;1.24]	0.41	0.30 [-1.69;2.28]	0.76
PICU stay (per day added)	2.54 [-7.33;12.42]	0.60	6.83 [-9.72;23.39]	0.41
Extracorporeal circulation versus no extracorporeal circulation ^a	0.88 [-1.22;2.98]	0.40	2.09 [0.29;3.90]	0.02
Aortic clamp time (per min added)	0.76 [-0.92;2.45]	0.36	-2.45 [-4.93;0.04]	0.05
Duration of mechanical ventilation (per day added)	1.65 [-5.64;8.95]	0.65	5.80 [-10.36;21.96]	0.47
Peak creatinine (per mg/dl added)	0.53 [-3.19;4.26]	0.77	0.20 [-3.73;4.14]	0.91
Peak bilirubine (per mg/dl added)	-1.43 [-4.21;1.36]	0.30	-2.63 [-5.29;0.04]	0.05
Infection vs. no infection	0.31 [-1.09;1.71]	0.65	2.70 [1.11;4.28]	0.001
Antibiotics (per day added)	-4.47 [-10.69;1.74]	0.15	-21.54 [-38.57;4.51]	0.01
Duration of hemodynamic support (per day added)	0.95 [-2.40;4.30]	0.57	2.71 [-4.83;10.26]	0.47
Duration of corticosteroid treatment (per day added)	1.11 [-2.73;4.94]	0.56	-0.35 [-10.69;9.99]	0.94
Cumulative dose of opioids (per mg morphine-equivalent added)	-3.71 [-6.98;-0.44]	0.02	3.43 [-0.93;7.79]	0.12
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-1.08 [-4.29;2.14]	0.50	-0.98 [-3.65;1.68]	0.46
Received hypnotics versus no hypnotics	-1.08 [-7.11;4.94]	0.72	1.21 [-1.15;3.57]	0.30
Exceeding potentially harmful threshold for phthalate exposure	-0.75 [-1.64;0.13]	0.09	0.63 [-0.19;1.46]	0.12

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-22. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-11.92 [-46.89;23.05]	0.50	-2.42 [-37.56;32.73]	0.89
Age at sampling (per year added)	-420.17 [-493.50;-346.84]	<0.001	-384.54 [-474.95;-294.13]	<0.001
Caucasian vs. other race	28.86 [-98.08;155.81]	0.65	83.39 [-33.64;200.43]	0.16
Exclusively European vs. other origin	-10.27 [-115.75;95.21]	0.84	-124.94 [-245.38;-4.50]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	56.55 [1.22;111.88]	0.04	51.06 [-12.54;114.67]	0.11
Socioeconomic status (per category of 1 to 66)	-104.72 [-187.18;-22.26]	0.01	-61.41 [-146.58;23.76]	0.15
Pre-existing syndrome vs. no pre-existing syndrome	36.49 [-8.65;81.63]	0.11	51.15 [4.94;97.36]	0.03
History vs. no history of malignancy	-23.61 [-151.02;103.80]	0.71	9.21 [-98.04;116.46]	0.86
History vs. no history of diabetes	-11.53 [-189.80;166.73]	0.89		
Randomization to strict glycemic control vs. conventional therapy	2.80 [-31.63;37.24]	0.87	-12.71 [-48.11;22.70]	0.47
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	64.84 [-49.53;179.20]	0.26	217.54 [107.00;328.08]	<0.001
randomized for glycemic control postoperatively	-55.30 [-138.87;28.27]	0.19	82.87 [-7.65;173.40]	0.07
Complicated/high risk surgery or trauma	-44.31 [-169.38;80.77]	0.48	-94.16 [-232.80;44.47]	0.18
Neurological medical disorders	228.79 [-3.25;460.84]	0.05	12.28 [-238.20;262.75]	0.92
Infectious medical diseases	-191.14 [-349.37;-32.90]	0.01	-62.19 [-286.61;162.23]	0.58
Other medical disorders	-86.69 [-252.32;78.93]	0.30	-76.95 [-251.30;97.39]	0.38
Solid organ transplants	83.81 [-171.34;338.96]	0.51	-79.39 [-309.02;150.25]	0.49
PeLOD score first 24 hrs (per point added)	-62.69 [-155.68;30.30]	0.18	9.37 [-83.00;101.74]	0.84
PICU stay (per day added)	-0.62 [-113.73;112.49]	0.99	84.62 [-90.58;259.82]	0.34
Exceeding potentially harmful threshold for phthalate exposure	82.72 [34.77;130.66]	0.0008	100.67 [59.92;141.41]	0.000002

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-22. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-15.69 [-52.85;21.46]	0.40	-16.08 [-51.09;18.93]	0.36
Age at sampling (per year added)	-419.89 [-510.28;-329.49]	<0.001	-348.42 [-445.18;-251.65]	<0.001
Caucasian vs. other race	6.45 [-126.56;139.47]	0.92	80.88 [-34.83;196.59]	0.16
Exclusively European vs. other origin	-0.74 [-111.00;109.52]	0.98	-118.95 [-237.20;-0.70]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	51.15 [-8.46;110.76]	0.09	62.88 [0.21;125.54]	0.04
Socioeconomic status (per category of 1 to 66)	-113.21 [-200.77;-25.65]	0.01	-79.04 [-163.90;5.82]	0.06
Pre-existing syndrome vs. no pre-existing syndrome	41.52 [-7.18;90.21]	0.09	60.08 [14.53;105.63]	0.01
History vs. no history of malignancy	-31.32 [-166.66;104.02]	0.64	-11.78 [-117.12;93.57]	0.82
History vs. no history of diabetes	-28.38 [-211.94;155.18]	0.76		
Randomization to strict glycemic control vs. conventional therapy	0.03 [-36.92;36.98]	0.99	-4.11 [-40.47;32.25]	0.82
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	263.20 [35.21;491.20]	0.02	155.24 [-8.80;319.29]	0.06
randomized for glycemic control postoperatively	143.91 [-67.43;355.24]	0.18	52.82 [-83.43;189.07]	0.44
Complicated/high risk surgery or trauma	67.90 [-156.56;292.36]	0.55	-70.19 [-224.76;84.37]	0.37
Neurological medical disorders	83.43 [-281.09;447.95]	0.65	-68.05 [-347.06;210.95]	0.63
Infectious medical diseases	-393.22 [-673.38;-113.06]	0.006	24.65 [-218.31;267.60]	0.84
Other medical disorders	-219.38 [-443.54;4.77]	0.05	-26.24 [-267.37;214.89]	0.83
Solid organ transplants	54.16 [-329.26;437.59]	0.78	-68.23 [-331.39;194.94]	0.60
PeLOD score first 24 hrs (per point added)	-61.39 [-171.09;48.30]	0.27	-9.56 [-105.12;86.00]	0.84
PICU stay (per day added)	-402.95 [-895.14;89.24]	0.10	-527.75 [-1377.75;322.25]	0.22
Extracorporeal circulation versus no extracorporeal circulation ^a	-39.55 [-121.89;42.78]	0.34	-35.39 [-99.36;28.58]	0.27
Aortic clamp time (per min added)	8.67 [-100.21;117.54]	0.87	118.75 [-25.08;262.58]	0.10
Duration of mechanical ventilation (per day added)	404.64 [7.21;802.07]	0.04	819.49 [40.14;1598.85]	0.03
Peak creatinine (per mg/dl added)	15.03 [-220.08;250.15]	0.89	-102.72 [-328.55;123.11]	0.37
Peak bilirubine (per mg/dl added)	-65.20 [-240.02;109.61]	0.46	401.90 [75.84;727.97]	0.01
Infection vs. no infection	9.87 [-53.49;73.23]	0.75	14.11 [-39.89;68.11]	0.60
Antibiotics (per day added)	17.77 [-233.96;269.50]	0.88	-396.44 [-1013.76;220.88]	0.20
Duration of hemodynamic support (per day added)	5.18 [-214.62;224.98]	0.96	193.06 [-428.44;814.56]	0.54
Duration of corticosteroid treatment (per day added)	282.70 [-101.57;666.96]	0.14	179.92 [-248.66;608.49]	0.40
Cumulative dose of opioids (per mg morphine-equivalent added)	53.97 [-222.35;330.28]	0.70	-185.97 [-432.53;60.58]	0.13
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	38.49 [-240.68;317.67]	0.78	-136.16 [-313.39;41.07]	0.13
Received hypnotics versus no hypnotics	-148.17 [-342.37;46.04]	0.13	27.97 [-116.37;172.30]	0.70
Exceeding potentially harmful threshold for phthalate exposure	88.28 [35.89;140.66]	0.001	108.20 [66.91;149.49]	0.0000006

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-23. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-21.37 [-52.99;10.25]	0.18	10.75 [-22.33;43.82]	0.52
Age at sampling (per year added)	-364.69 [-431.05;-298.34]	<0.001	-377.60 [-462.68;-292.51]	<0.001
Caucasian vs. other race	-14.13 [-129.69;101.44]	0.80	25.31 [-84.83;135.45]	0.65
Exclusively European vs. other origin	-16.42 [-112.38;79.54]	0.73	-100.63 [-213.98;12.71]	0.08
Exclusively Dutch language vs. non-exclusively Dutch language	50.92 [0.67;101.16]	0.04	64.27 [4.42;124.13]	0.03
Socioeconomic status (per category of 1 to 66)	-52.92 [-127.48;21.65]	0.16	-100.33 [-180.48;-20.18]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	21.85 [-18.62;62.32]	0.28	46.94 [3.45;90.42]	0.03
History vs. no history of malignancy	-9.79 [-125.78;106.21]	0.86	28.73 [-72.21;129.66]	0.57
History vs. no history of diabetes	24.27 [-138.01;186.55]	0.76		
Randomization to strict glycemic control vs. conventional therapy	1.00 [-30.08;32.07]	0.94	-5.26 [-38.57;28.06]	0.75
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	33.51 [-70.56;137.58]	0.52	198.68 [94.65;302.70]	<0.001
randomized for glycemic control postoperatively	-16.91 [-92.54;58.73]	0.65	68.70 [-16.49;153.89]	0.11
Complicated/high risk surgery or trauma	-3.54 [-117.41;110.33]	0.95	-193.82 [-324.29;-63.35]	0.003
Neurological medical disorders	112.50 [-98.53;323.54]	0.29	99.79 [-135.92;335.51]	0.40
Infectious medical diseases	-118.96 [-262.99;25.07]	0.10	-55.44 [-266.64;155.76]	0.60
Other medical disorders	-114.24 [-264.99;36.51]	0.13	-66.78 [-230.86;97.29]	0.42
Solid organ transplants	107.63 [-124.61;339.87]	0.36	-51.12 [-267.23;164.98]	0.64
PeLOD score first 24 hrs (per point added)	-31.16 [-115.31;52.99]	0.46	-9.06 [-95.99;77.87]	0.83
PICU stay (per day added)	-54.62 [-155.58;46.35]	0.28	140.44 [-24.43;305.32]	0.09
Exceeding potentially harmful threshold for phthalate exposure	92.93 [50.07;135.79]	0.00003	73.85 [35.51;112.20]	0.0002

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-23. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-21.84 [-54.24;10.56]	0.18	2.18 [-31.23;35.58]	0.89
Age at sampling (per year added)	-370.46 [-449.43;-291.49]	<0.001	-351.27 [-443.60;-258.94]	<0.001
Caucasian vs. other race	-41.17 [-157.86;75.53]	0.48	30.85 [-79.56;141.25]	0.58
Exclusively European vs. other origin	-6.97 [-103.62;89.68]	0.88	-98.39 [-211.21;14.44]	0.08
Exclusively Dutch language vs. non-exclusively Dutch language	50.61 [-1.52;102.74]	0.05	74.49 [14.70;134.28]	0.01
Socioeconomic status (per category of 1 to 66)	-60.27 [-136.51;15.96]	0.12	-119.78 [-200.75;-38.81]	0.004
Pre-existing syndrome vs. no pre-existing syndrome	23.46 [-18.52;65.44]	0.27	50.95 [7.49;94.42]	0.02
History vs. no history of malignancy	-7.32 [-126.01;111.37]	0.90	8.38 [-92.14;108.89]	0.86
History vs. no history of diabetes	2.95 [-158.02;163.92]	0.97		
Randomization to strict glycemic control vs. conventional therapy	-0.23 [-32.29;31.83]	0.98	5.26 [-29.43;39.96]	0.76
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	238.74 [40.04;437.44]	0.01	150.92 [-5.60;307.45]	0.05
randomized for glycemic control postoperatively	176.94 [-7.34;361.23]	0.05	40.60 [-89.41;170.60]	0.53
Complicated/high risk surgery or trauma	61.75 [-134.43;257.92]	0.53	-203.40 [-350.88;-55.92]	0.007
Neurological medical disorders	9.03 [-310.35;328.41]	0.95	101.58 [-164.64;367.79]	0.45
Infectious medical diseases	-300.65 [-546.19;-55.10]	0.01	-19.22 [-251.03;212.60]	0.87
Other medical disorders	-297.61 [-494.03;-101.18]	0.003	32.13 [-197.94;262.20]	0.78
Solid organ transplants	111.79 [-224.63;448.21]	0.51	-102.61 [-353.71;148.49]	0.42
PeLOD score first 24 hrs (per point added)	-27.81 [-123.32;67.69]	0.56	-16.41 [-107.59;74.77]	0.72
PICU stay (per day added)	-280.76 [-704.43;142.92]	0.19	-699.85 [-1510.88;111.18]	0.09
Extracorporeal circulation versus no extracorporeal circulation ^a	-48.75 [-118.67;21.18]	0.17	-58.05 [-119.09;2.98]	0.06
Aortic clamp time (per min added)	-37.26 [-132.21;57.68]	0.43	94.49 [-42.74;231.72]	0.17
Duration of mechanical ventilation (per day added)	279.52 [-62.86;621.91]	0.10	526.41 [-217.21;1270.03]	0.16
Peak creatinine (per mg/dl added)	53.18 [-152.46;258.82]	0.61	-54.93 [-270.41;160.55]	0.61
Peak bilirubine (per mg/dl added)	-185.50 [-338.46;-32.54]	0.01	296.36 [-14.75;607.47]	0.06
Infection vs. no infection	-1.60 [-56.97;53.77]	0.95	10.64 [-40.88;62.17]	0.68
Antibiotics (per day added)	-51.91 [-272.58;168.76]	0.64	-1.99 [-591.01;587.03]	0.99
Duration of hemodynamic support (per day added)	24.70 [-167.70;217.10]	0.80	341.20 [-251.80;934.21]	0.25
Duration of corticosteroid treatment (per day added)	226.17 [-109.48;561.82]	0.18	236.16 [-172.76;645.08]	0.25
Cumulative dose of opioids (per mg morphine-equivalent added)	174.71 [-67.72;417.14]	0.15	-151.85 [-387.10;83.40]	0.20
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	139.09 [-105.57;383.75]	0.26	-116.59 [-285.70;52.51]	0.17
Received hypnotics versus no hypnotics	-129.10 [-299.48;41.27]	0.13	80.41 [-57.31;218.13]	0.25
Exceeding potentially harmful threshold for phthalate exposure	107.79 [62.64;152.93]	0.000005	83.31 [43.91;122.71]	0.00004

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-24. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-18.09 [-48.89;12.72]	0.24	5.43 [-26.93;37.78]	0.74
Age at sampling (per year added)	-388.84 [-453.44;-324.24]	<0.001	-380.48 [-463.71;-297.26]	<0.001
Caucasian vs. other race	7.50 [-104.34;119.34]	0.89	54.06 [-53.67;161.79]	0.32
Exclusively European vs. other origin	-13.28 [-106.21;79.65]	0.77	-112.01 [-222.88;-1.14]	0.04
Exclusively Dutch language vs. non-exclusively Dutch language	51.90 [3.15;100.64]	0.03	56.91 [-1.64;115.46]	0.05
Socioeconomic status (per category of 1 to 66)	-74.94 [-147.59;-2.29]	0.04	-83.00 [-161.39;-4.60]	0.03
Pre-existing syndrome vs. no pre-existing syndrome	27.09 [-12.68;66.85]	0.18	46.44 [3.90;88.97]	0.03
History vs. no history of malignancy	-17.06 [-129.31;95.18]	0.76	19.78 [-78.94;118.51]	0.69
History vs. no history of diabetes	8.37 [-148.67;165.42]	0.91		
Randomization to strict glycemic control vs. conventional therapy	1.40 [-28.94;31.74]	0.92	-9.80 [-42.39;22.79]	0.55
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	48.55 [-52.21;149.30]	0.34	205.69 [103.93;307.44]	<0.001
randomized for glycemic control postoperatively	-39.59 [-113.21;34.03]	0.29	72.36 [-10.97;115.69]	0.08
Complicated/high risk surgery or trauma	-23.88 [-134.07;86.32]	0.66	-143.67 [-271.29;-16.05]	0.02
Neurological medical disorders	173.79 [-30.64;378.22]	0.09	59.87 [-170.69;290.44]	0.60
Infectious medical diseases	-154.48 [-293.88;-15.07]	0.03	-59.80 [-266.38;146.78]	0.56
Other medical disorders	-102.42 [-248.33;43.50]	0.16	-70.35 [-230.83;90.14]	0.38
Solid organ transplants	98.02 [-126.77;322.80]	0.39	-64.11 [-275.49;147.27]	0.55
PeLOD score first 24 hrs (per point added)	-45.17 [-127.10;36.75]	0.27	-2.13 [-87.16;82.90]	0.96
PICU stay (per day added)	-24.78 [-124.43;74.87]	0.62	113.35 [-47.93;274.62]	0.16
Exceeding potentially harmful threshold for phthalate exposure	87.12 [44.88;129.37]	0.00007	88.60 [51.10;126.11]	0.000006

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-24. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	-20.19 [-52.29;11.90]	0.21	-5.46 [-37.77;26.85]	0.73
Age at sampling (per year added)	-391.65 [-469.74;-313.57]	<0.001	-348.19 [-437.51;-258.88]	<0.001
Caucasian vs. other race	-17.10 [-132.00;97.80]	0.76	55.50 [-51.30;162.30]	0.30
Exclusively European vs. other origin	-3.80 [-99.04;91.45]	0.93	-108.18 [-217.32;0.96]	0.05
Exclusively Dutch language vs. non-exclusively Dutch language	49.01 [-2.48;100.50]	0.06	68.00 [10.15;125.83]	0.02
Socioeconomic status (per category of 1 to 66)	-83.05 [-158.69;-7.42]	0.03	-101.47 [-179.79;-23.14]	0.01
Pre-existing syndrome vs. no pre-existing syndrome	30.79 [-11.28;72.85]	0.15	52.52 [10.48;94.56]	0.01
History vs. no history of malignancy	-19.79 [-136.70;97.11]	0.73	-0.63 [-97.86;96.60]	0.98
History vs. no history of diabetes	-11.75 [-170.31;146.82]	0.88		
Randomization to strict glycemic control vs. conventional therapy	-0.16 [-32.08;31.76]	0.99	-0.44 [-34.01;33.12]	0.97
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	254.45 [57.51;451.40]	0.01	151.70 [0.28;303.12]	0.04
randomized for glycemic control postoperatively	161.53 [-21.03;344.09]	0.08	44.10 [-81.66;169.86]	0.48
Complicated/high risk surgery or trauma	64.50 [-129.39;258.38]	0.51	-137.33 [-280.00;5.33]	0.05
Neurological medical disorders	44.12 [-270.76;359.00]	0.78	19.67 [-237.85;277.20]	0.88
Infectious medical diseases	-349.36 [-591.37;-107.36]	0.004	0.49 [-223.76;224.74]	0.99
Other medical disorders	-261.64 [-455.27;-68.01]	0.008	3.76 [-218.80;226.33]	0.97
Solid organ transplants	86.40 [-244.80;417.61]	0.60	-82.40 [-325.30;160.51]	0.50
PeLOD score first 24 hrs (per point added)	-44.07 [-138.83;50.69]	0.35	-15.74 [-103.95;72.46]	0.72
PICU stay (per day added)	-344.83 [-769.99;80.32]	0.11	-611.27 [-1395.83;173.29]	0.12
Extracorporeal circulation versus no extracorporeal circulation ^a	-46.80 [-117.92;24.32]	0.19	-47.12 [-106.17;11.92]	0.11
Aortic clamp time (per min added)	-12.01 [-106.06;82.03]	0.80	105.97 [-26.78;238.72]	0.11
Duration of mechanical ventilation (per day added)	346.37 [3.06;689.67]	0.04	687.27 [-32.09;1406.62]	0.06
Peak creatinine (per mg/dl added)	37.15 [-165.95;240.24]	0.71	-77.36 [-285.80;131.08]	0.46
Peak bilirubine (per mg/dl added)	-122.21 [-273.22;88.80]	0.11	337.48 [36.52;638.43]	0.02
Infection vs. no infection	5.25 [-49.48;59.98]	0.85	13.30 [-36.54;63.14]	0.59
Antibiotics (per day added)	-15.08 [-232.52;202.37]	0.89	-203.10 [-772.90;366.69]	0.48
Duration of hemodynamic support (per day added)	15.01 [-174.86;204.88]	0.87	263.64 [-310.01;837.29]	0.36
Duration of corticosteroid treatment (per day added)	252.33 [-79.61;584.26]	0.13	199.43 [-196.14;595.01]	0.32
Cumulative dose of opioids (per mg morphine-equivalent added)	112.93 [-125.76;351.61]	0.35	-169.44 [-397.01;58.13]	0.14
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	88.08 [-153.07;329.24]	0.47	-126.54 [-290.13;37.04]	0.12
Received hypnotics versus no hypnotics	-139.96 [-307.72;27.80]	0.10	54.62 [-78.61;187.84]	0.41
Exceeding potentially harmful threshold for phthalate exposure	96.98 [51.73;142.23]	0.00003	96.82 [58.71;134.93]	0.000001

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-25. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	15.85 [-13.86;45.56]	0.29	0.75 [-32.13;33.62]	0.96
Age at sampling (per year added)	-311.35 [-373.66;-249.04]	<0.001	-296.33 [-380.91;-211.75]	<0.001
Caucasian vs. other race	41.07 [-66.80;148.94]	0.45	68.89 [-40.59;178.37]	0.21
Exclusively European vs. other origin	-34.76 [-124.39;54.87]	0.44	-91.82 [-204.49;20.84]	0.10
Exclusively Dutch language vs. non-exclusively Dutch language	25.41 [-21.61;72.42]	0.28	28.18 [-31.32;87.68]	0.35
Socioeconomic status (per category of 1 to 66)	-82.69 [-152.76;-12.63]	0.02	-109.44 [-189.11;-29.77]	0.007
Pre-existing syndrome vs. no pre-existing syndrome	32.18 [-6.17;70.53]	0.09	64.00 [20.78;107.23]	0.003
History vs. no history of malignancy	-12.05 [-120.31;96.20]	0.82	48.66 [-51.67;148.99]	0.33
History vs. no history of diabetes	4.92 [-146.54;156.39]	0.94		
Randomization to strict glycemic control vs. conventional therapy	10.95 [-40.21;18.31]	0.46	-0.60 [-33.72;32.52]	0.97
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	75.58 [-21.60;172.76]	0.12	157.35 [53.95;260.76]	0.003
randomized for glycemic control postoperatively	-13.34 [-84.34;57.67]	0.71	63.16 [-21.52;147.84]	0.14
Complicated/high risk surgery or trauma	-12.97 [-119.25;93.31]	0.81	-94.76 [-224.44;34.93]	0.15
Neurological medical disorders	146.62 [-50.55;343.79]	0.14	7.39 [-226.91;241.70]	0.95
Infectious medical diseases	-139.97 [-274.42;-5.51]	0.04	-30.13 [-240.06;179.81]	0.77
Other medical disorders	-30.25 [-170.98;110.49]	0.67	-110.09 [-273.18;53.00]	0.18
Solid organ transplants	-25.68 [-242.48;191.12]	0.81	7.06 [-207.75;221.88]	0.94
PeLOD score first 24 hrs (per point added)	-29.90 [-108.92;49.11]	0.45	7.94 [-78.47;94.35]	0.85
PICU stay (per day added)	-10.04 [-106.14;86.07]	0.83	9.76 [-154.14;173.65]	0.90
Exceeding potentially harmful threshold for phthalate exposure	64.82 [24.07;105.56]	0.002	91.91 [53.80;130.03]	0.000004

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-25. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	10.56 [-21.37;42.49]	0.51	-13.58 [-46.49;19.32]	0.41
Age at sampling (per year added)	-317.99 [-395.68;-240.30]	<0.001	-267.55 [-358.51;-176.59]	<0.001
Caucasian vs. other race	33.82 [-80.49;148.14]	0.56	81.03 [-27.74;189.79]	0.14
Exclusively European vs. other origin	-36.35 [-131.11;58.41]	0.45	-105.00 [-216.16;6.15]	0.06
Exclusively Dutch language vs. non-exclusively Dutch language	23.80 [-27.43;75.02]	0.36	34.55 [-24.36;93.45]	0.24
Socioeconomic status (per category of 1 to 66)	-81.10 [-156.35;-5.85]	0.03	-123.42 [-203.19;-43.65]	0.002
Pre-existing syndrome vs. no pre-existing syndrome	38.55 [-3.30;80.39]	0.07	71.45 [28.64;114.27]	0.001
History vs. no history of malignancy	-14.58 [-130.89;101.74]	0.80	36.86 [-62.16;135.89]	0.46
History vs. no history of diabetes	-9.02 [-166.77;148.74]	0.91		
Randomization to strict glycemic control vs. conventional therapy	-10.21 [-41.97;21.54]	0.52	6.83 [-27.35;41.01]	0.69
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	209.12 [13.18;405.06]	0.03	67.55 [-86.66;221.76]	0.38
randomized for glycemic control postoperatively	119.38 [-62.25;301.01]	0.19	5.42 [-122.66;133.50]	0.93
Complicated/high risk surgery or trauma	48.10 [-144.80;241.00]	0.62	-121.09 [-266.38;24.20]	0.10
Neurological medical disorders	15.08 [-298.20;328.35]	0.92	-7.30 [-269.58;254.97]	0.95
Infectious medical diseases	-234.98 [-475.76;5.80]	0.05	45.25 [-183.13;273.64]	0.69
Other medical disorders	-101.07 [-293.71;91.57]	0.30	-45.04 [-271.71;181.62]	0.69
Solid organ transplants	-55.63 [-385.15;273.89]	0.73	55.21 [-192.18;302.59]	0.66
PeLOD score first 24 hrs (per point added)	-43.62 [-137.89;50.66]	0.36	-32.37 [-122.20;57.46]	0.47
PICU stay (per day added)	-244.42 [-667.41;178.58]	0.25	477.94 [-321.09;1276.96]	0.23
Extracorporeal circulation versus no extracorporeal circulation ^a	-18.85 [-89.61;51.91]	0.59	-4.77 [-64.91;55.36]	0.87
Aortic clamp time (per min added)	-12.23 [-105.80;81.33]	0.79	152.51 [17.31;287.71]	0.02
Duration of mechanical ventilation (per day added)	204.71 [-136.85;546.27]	0.23	441.02 [-291.59;1173.64]	0.23
Peak creatinine (per mg/dl added)	47.46 [-154.60;249.52]	0.64	18.00 [-194.28;230.29]	0.86
Peak bilirubine (per mg/dl added)	0.23 [-150.01;150.47]	0.99	323.15 [16.64;629.66]	0.03
Infection vs. no infection	23.54 [-30.92;77.99]	0.39	33.30 [-17.46;84.05]	0.19
Antibiotics (per day added)	15.43 [-200.92;231.77]	0.88	-787.96 [-1368.26;-207.66]	0.008
Duration of hemodynamic support (per day added)	-7.89 [-196.79;181.02]	0.93	-251.50 [-835.72;332.73]	0.39
Duration of corticosteroid treatment (per day added)	168.31 [-161.94;498.55]	0.31	50.58 [-352.29;453.45]	0.80
Cumulative dose of opioids (per mg morphine-equivalent added)	69.67 [-167.80;307.15]	0.56	-258.90 [-490.66;-27.13]	0.02
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	48.97 [-190.96;288.90]	0.68	-82.52 [-249.12;84.09]	0.32
Received hypnotics versus no hypnotics	-77.74 [-244.64;89.17]	0.35	73.62 [-62.06;209.29]	0.28
Exceeding potentially harmful threshold for phthalate exposure	63.76 [18.74;108.78]	0.005	87.75 [48.93;126.56]	0.00001

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-26. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time nondominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	-2.40 [-30.94;26.13]	0.86	5.11 [-27.37;37.59]	0.75
Age at sampling (per year added)	-255.86 [-315.75;-195.98]	<0.001	-289.76 [-373.30;-206.21]	<0.001
Caucasian vs. other race	14.26 [-90.02;118.54]	0.78	20.49 [-87.65;128.64]	0.70
Exclusively European vs. other origin	-46.44 [-133.03;40.15]	0.29	-84.45 [-195.75;26.84]	0.13
Exclusively Dutch language vs. non-exclusively Dutch language	44.55 [-0.79;89.89]	0.05	49.66 [-9.12;108.43]	0.09
Socioeconomic status (per category of 1 to 66)	-34.13 [-101.42;33.15]	0.31	-87.83 [-166.53;-9.13]	0.02
Pre-existing syndrome vs. no pre-existing syndrome	22.93 [-13.60;59.45]	0.21	44.23 [1.53;86.92]	0.04
History vs. no history of malignancy	-46.05 [-150.72;58.63]	0.38	16.44 [-82.67;115.54]	0.74
History vs. no history of diabetes	20.50 [-125.94;166.94]	0.78		
Randomization to strict glycemic control vs. conventional therapy	-9.59 [-37.63;18.45]	0.50	3.36 [-29.36;36.08]	0.83
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	29.46 [-64.45;123.38]	0.53	168.26 [66.12;270.41]	0.001
randomized for glycemic control postoperatively	27.95 [-40.30;96.20]	0.42	48.93 [-34.72;132.58]	0.25
Complicated/high risk surgery or trauma	55.70 [-47.06;158.45]	0.28	-217.05 [-345.16;-88.94]	0.001
Neurological medical disorders	44.90 [-145.53;235.34]	0.64	156.42 [-75.03;387.87]	0.18
Infectious medical diseases	-133.75 [-263.72;-3.78]	0.04	-109.72 [-317.10;97.66]	0.29
Other medical disorders	-76.52 [-212.55;59.51]	0.26	-66.30 [-227.41;98.80]	0.41
Solid organ transplants	52.26 [-157.31;261.83]	0.62	19.45 [-192.74;231.65]	0.85
PeLOD score first 24 hrs (per point added)	-13.45 [-89.38;62.49]	0.72	21.15 [-64.21;106.50]	0.62
PICU stay (per day added)	-12.77 [-103.88;78.34]	0.78	52.71 [-109.19;214.61]	0.52
Exceeding potentially harmful threshold for phthalate exposure	56.30 [17.62;94.97]	0.004	48.76 [11.11;86.41]	0.01

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-26. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time nondominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	1.21 [-28.37;30.79]	0.93	-0.42 [-34.20;33.35]	0.98
Age at sampling (per year added)	-276.98 [-349.08;-204.89]	<0.001	-282.75 [-376.10;-189.40]	<0.001
Caucasian vs. other race	-4.73 [-111.27;101.81]	0.93	23.45 [-88.17;135.08]	0.67
Exclusively European vs. other origin	-43.70 [-131.93;44.54]	0.32	-81.51 [-195.59;32.56]	0.16
Exclusively Dutch language vs. non-exclusively Dutch language	48.82 [1.23;96.41]	0.04	58.02 [-2.44;118.47]	0.05
Socioeconomic status (per category of 1 to 66)	-42.77 [-112.36;26.83]	0.22	-110.70 [-192.56;-28.83]	0.008
Pre-existing syndrome vs. no pre-existing syndrome	26.25 [-12.08;64.58]	0.17	46.33 [2.39;90.27]	0.03
History vs. no history of malignancy	-62.65 [-171.01;45.71]	0.25	1.97 [-99.65;103.60]	0.96
History vs. no history of diabetes	11.98 [-134.98;158.94]	0.87		
Randomization to strict glycemic control vs. conventional therapy	-13.58 [-42.85;15.68]	0.36	11.86 [-23.22;46.93]	0.50
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	138.72 [-42.69;320.13]	0.13	195.52 [37.27;353.78]	0.01
randomized for glycemic control postoperatively	134.68 [-33.56;302.93]	0.11	81.84 [-49.60;213.29]	0.22
Complicated/high risk surgery or trauma	116.85 [-62.25;295.95]	0.19	-234.56 [-383.67;-85.45]	0.002
Neurological medical disorders	15.40 [-276.18;306.98]	0.91	164.43 [-104.73;433.59]	0.22
Infectious medical diseases	-201.17 [-425.34;23.00]	0.07	-102.22 [-336.60;132.17]	0.39
Other medical disorders	-172.88 [-352.21;6.45]	0.05	-10.22 [-242.84;222.40]	0.93
Solid organ transplants	-31.60 [-338.74;275.53]	0.83	-94.80 [-348.68;159.08]	0.46
PeLOD score first 24 hrs (per point added)	-18.75 [-105.94;68.44]	0.67	9.75 [-82.44;101.93]	0.83
PICU stay (per day added)	-251.37 [-638.17;135.43]	0.20	-557.89 [-1377.90;262.12]	0.18
Extracorporeal circulation versus no extracorporeal circulation ^a	-24.01 [-87.85;39.83]	0.45	-65.00 [-126.71;-3.29]	0.03
Aortic clamp time (per min added)	-13.02 [-99.70;73.66]	0.76	114.42 [-24.33;253.17]	0.10
Duration of mechanical ventilation (per day added)	267.49 [-45.09;580.07]	0.09	429.37 [-322.49;1181.22]	0.26
Peak creatinine (per mg/dl added)	115.74 [-71.99;303.48]	0.22	28.85 [-189.02;246.71]	0.79
Peak bilirubine (per mg/dl added)	-175.77 [-315.42;-36.13]	0.01	148.07 [-166.48;462.63]	0.35
Infection vs. no infection	-19.69 [-70.24;30.87]	0.44	17.82 [-34.27;69.91]	0.50
Antibiotics (per day added)	-53.19 [-254.65;148.28]	0.60	-80.61 [-676.15;514.93]	0.78
Duration of hemodynamic support (per day added)	52.27 [-123.38;227.92]	0.55	111.91 [-487.66;711.48]	0.71
Duration of corticosteroid treatment (per day added)	319.64 [13.20;626.07]	0.04	366.24 [-47.21;779.69]	0.08
Cumulative dose of opioids (per mg morphine-equivalent added)	159.91 [-61.42;381.24]	0.15	-55.57 [-293.43;182.28]	0.64
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	122.10 [-101.27;345.46]	0.28	-64.26 [-235.24;106.72]	0.45
Received hypnotics versus no hypnotics	-63.71 [-219.25;91.84]	0.42	58.59 [-80.66;197.83]	0.40
Exceeding potentially harmful threshold for phthalate exposure	69.11 [27.89;110.32]	0.001	51.40 [11.57;91.24]	0.01

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-27. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time overall

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	6.16 [-19.48;31.79]	0.63	0.86 [-27.93;29.64]	0.95
Age at sampling (per year added)	-291.71 [-345.47;-237.95]	<0.001	-296.68 [-370.45;-222.91]	<0.001
Caucasian vs. other race	29.78 [-63.29;122.85]	0.52	44.42 [-51.08;139.91]	0.36
Exclusively European vs. other origin	-40.63 [-117.96;36.70]	0.30	-88.86 [-187.13;9.42]	0.07
Exclusively Dutch language vs. non-exclusively Dutch language	37.75 [-2.81;78.32]	0.06	42.39 [-9.52;94.30]	0.10
Socioeconomic status (per category of 1 to 66)	-52.54 [-112.99;7.92]	0.08	-99.16 [-168.76;-29.56]	0.005
Pre-existing syndrome vs. no pre-existing syndrome	27.46 [-5.63;60.55]	0.10	53.01 [14.98;91.05]	0.006
History vs. no history of malignancy	-30.68 [-124.08;62.73]	0.51	33.04 [-54.49;120.57]	0.45
History vs. no history of diabetes	5.61 [-125.08;136.29]	0.93		
Randomization to strict glycemic control vs. conventional therapy	-9.20 [-34.45;16.05]	0.47	-1.48 [-30.44;27.47]	0.91
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	54.02 [-29.83;137.86]	0.20	157.88 [67.53;248.22]	<0.001
randomized for glycemic control postoperatively	1.14 [-60.13;62.40]	0.97	57.46 [-16.69;131.61]	0.12
Complicated/high risk surgery or trauma	20.26 [-71.44;111.96]	0.66	-143.41 [-256.53;-30.29]	0.01
Neurological medical disorders	108.37 [-61.75;278.49]	0.21	82.70 [-121.76;287.17]	0.42
Infectious medical diseases	-130.34 [-246.34;-14.33]	0.02	-74.68 [-257.79;108.44]	0.42
Other medical disorders	-48.20 [-169.62;73.23]	0.43	-90.32 [-232.60;51.97]	0.21
Solid organ transplants	-5.25 [-192.31;181.81]	0.95	10.37 [-177.02;197.75]	0.91
PeLOD score first 24 hrs (per point added)	-16.72 [-84.90;51.45]	0.62	13.81 [-61.64;89.26]	0.71
PICU stay (per day added)	-9.20 [-92.12;73.72]	0.82	27.89 [-115.06;170.84]	0.70
Exceeding potentially harmful threshold for phthalate exposure	62.34 [27.19;97.50]	0.0006	74.64 [41.32;107.96]	0.00001

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-27. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and inconsistency of reaction time overall (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	4.86 [-22.27;31.99]	0.72	-9.19 [-38.67;20.29]	0.53
Age at sampling (per year added)	-311.43 [-377.44;-245.43]	<0.001	-277.95 [-359.11;-196.80]	<0.001
Caucasian vs. other race	15.74 [-81.38;112.87]	0.74	51.39 [-45.63;148.41]	0.29
Exclusively European vs. other origin	-40.88 [-121.39;39.63]	0.31	-93.69 [-192.84;5.47]	0.06
Exclusively Dutch language vs. non-exclusively Dutch language	38.68 [-4.84;82.20]	0.08	50.18 [-2.37;102.73]	0.06
Socioeconomic status (per category of 1 to 66)	-54.67 [-118.61;9.27]	0.09	-118.64 [-189.91;-47.37]	0.001
Pre-existing syndrome vs. no pre-existing syndrome	32.88 [-2.67;68.44]	0.06	57.89 [19.28;96.49]	0.003
History vs. no history of malignancy	-42.04 [-140.86;56.78]	0.40	19.56 [-68.80;107.93]	0.66
History vs. no history of diabetes	-6.39 [-140.43;127.64]	0.92		
Randomization to strict glycemic control vs. conventional therapy	-10.73 [-37.71;16.26]	0.43	6.47 [-24.11;37.04]	0.67
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	178.84 [12.36;345.32]	0.03	133.61 [-3.94;271.17]	0.05
randomized for glycemic control postoperatively	125.31 [-29.01;279.63]	0.11	51.35 [-62.94;165.64]	0.37
Complicated/high risk surgery or trauma	87.77 [-76.13;251.67]	0.29	-163.27 [-292.88;-33.66]	0.01
Neurological medical disorders	3.55 [-262.62;269.72]	0.97	70.87 [-163.13;304.86]	0.55
Infectious medical diseases	-220.02 [-424.59;-15.45]	0.03	-39.56 [-243.35;164.24]	0.70
Other medical disorders	-131.48 [-295.15;32.20]	0.11	-39.84 [-242.02;162.34]	0.69
Solid organ transplants	-43.98 [-323.95;235.99]	0.75	-13.16 [-233.90;207.58]	0.90
PeLOD score first 24 hrs (per point added)	-33.92 [-114.02;46.18]	0.40	-12.49 [-92.76;67.77]	0.75
PICU stay (per day added)	-268.87 [-628.26;90.52]	0.14	-42.10 [-754.83;670.62]	0.90
Extracorporeal circulation versus no extracorporeal circulation ^a	-16.95 [-77.07;43.17]	0.57	-35.38 [-89.04;18.28]	0.19
Aortic clamp time (per min added)	-15.88 [-95.37;63.62]	0.69	131.84 [11.25;252.44]	0.03
Duration of mechanical ventilation (per day added)	254.83 [-35.37;545.03]	0.08	417.01 [-236.97;1070.99]	0.20
Peak creatinine (per mg/dl added)	113.17 [-58.51;284.85]	0.19	13.83 [-175.58;203.23]	0.88
Peak bilirubine (per mg/dl added)	-81.96 [-209.61;45.69]	0.20	260.25 [-13.42;533.91]	0.06
Infection vs. no infection	3.63 [-42.64;49.89]	0.87	26.43 [-18.87;71.74]	0.25
Antibiotics (per day added)	-9.93 [-193.74;173.89]	0.91	-406.59 [-924.23;111.05]	0.12
Duration of hemodynamic support (per day added)	11.33 [-149.17;171.83]	0.88	-79.38 [-600.78;442.01]	0.76
Duration of corticosteroid treatment (per day added)	236.68 [-43.90;517.27]	0.09	194.21 [-165.32;553.74]	0.28
Cumulative dose of opioids (per mg morphine-equivalent added)	107.59 [-94.17;309.36]	0.29	-152.64 [-359.37;54.10]	0.14
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	81.45 [-122.40;285.31]	0.43	-87.64 [-236.25;60.97]	0.24
Received hypnotics versus no hypnotics	-78.82 [-220.63;62.99]	0.27	56.12 [-64.91;177.14]	0.36
Exceeding potentially harmful threshold for phthalate exposure	67.80 [29.55;106.05]	0.0006	74.42 [39.74;109.10]	0.00003

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-28. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and tapping dominant hand

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.28 [-0.65;1.20]	0.55	-0.01 [-1.21;1.18]	0.98
Age at sampling (per year added)	18.86 [16.92;20.80]	<0.001	19.65 [16.59;22.71]	<0.001
Caucasian vs. other race	2.04 [-1.34;5.42]	0.23	-1.53 [-5.48;2.43]	0.44
Exclusively European vs. other origin	-2.11 [-4.92;0.70]	0.14	2.73 [-1.41;6.87]	0.19
Exclusively Dutch language vs. non-exclusively Dutch language	-0.68 [-2.15;0.79]	0.36	-0.79 [-3.09;1.50]	0.49
Socioeconomic status (per category of 1 to 66)	1.31 [-0.90;3.51]	0.24	-1.93 [-4.79;0.93]	0.18
Pre-existing syndrome vs. no pre-existing syndrome	0.48 [-0.71;1.68]	0.42	-1.11 [-2.69;0.47]	0.16
History vs. no history of malignancy	-0.31 [-3.68;3.06]	0.85	0.22 [-3.38;3.82]	0.90
History vs. no history of diabetes	1.34 [-3.41;6.09]	0.57		
Randomization to strict glycemic control vs. conventional therapy	0.24 [-0.68;1.15]	0.60	0.45 [-0.75;1.64]	0.46
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	1.32 [-1.73;4.36]	0.39	-2.30 [-6.02;1.41]	0.22
randomized for glycemic control postoperatively	2.77 [0.54;4.99]	0.01	-0.82 [-3.89;2.26]	0.60
Complicated/high risk surgery or trauma	-0.81 [-4.07;2.45]	0.62	-1.73 [-6.27;2.82]	0.45
Neurological medical disorders	-3.53 [-9.70;2.64]	0.26	-0.31 [-8.78;8.15]	0.94
Infectious medical diseases	-2.11 [-6.32;2.10]	0.32	-0.44 [-8.02;7.14]	0.90
Other medical disorders	2.15 [-2.26;6.56]	0.33	2.75 [-3.14;8.64]	0.35
Solid organ transplants	0.23 [-6.57;7.02]	0.94	2.85 [-4.88;10.58]	0.46
PeLOD score first 24 hrs (per point added)	0.89 [-1.59;3.36]	0.48	0.50 [-2.59;3.60]	0.74
PICU stay (per day added)	0.58 [-2.44;3.59]	0.70	-1.03 [-6.87;4.80]	0.72
Exceeding potentially harmful threshold for phthalate exposure	-1.89 [-3.17;-0.61]	0.004	-0.93 [-2.30;0.45]	0.18

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-28. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and tapping dominant hand (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.40 [-0.58;1.37]	0.42	0.02 [-1.22;1.26]	0.97
Age at sampling (per year added)	17.47 [15.10;19.85]	<0.001	18.39 [14.97;21.81]	<0.001
Caucasian vs. other race	2.16 [-1.33;5.65]	0.22	-1.82 [-5.91;2.27]	0.38
Exclusively European vs. other origin	-2.27 [-5.16;0.63]	0.12	3.28 [-0.96;7.52]	0.12
Exclusively Dutch language vs. non-exclusively Dutch language	-0.74 [-2.30;0.81]	0.34	-0.81 [-3.19;1.58]	0.50
Socioeconomic status (per category of 1 to 66)	1.39 [-0.91;3.69]	0.23	-1.73 [-4.70;1.24]	0.25
Pre-existing syndrome vs. no pre-existing syndrome	0.64 [-0.63;1.91]	0.32	-1.10 [-2.73;0.54]	0.18
History vs. no history of malignancy	-0.89 [-4.41;2.63]	0.61	0.58 [-3.14;4.31]	0.75
History vs. no history of diabetes	1.95 [-2.87;6.76]	0.42		
Randomization to strict glycemic control vs. conventional therapy	0.12 [-0.85;1.09]	0.80	0.26 [-1.00;1.51]	0.68
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	-3.46 [-9.41;2.49]	0.25	-0.86 [-6.64;4.92]	0.76
randomized for glycemic control postoperatively	-1.39 [-6.91;4.12]	0.61	0.19 [-4.59;4.96]	0.93
Complicated/high risk surgery or trauma	-0.33 [-6.16;5.50]	0.91	0.04 [-5.38;5.46]	0.98
Neurological medical disorders	-3.18 [-12.74;6.38]	0.51	0.19 [-9.67;10.06]	0.96
Infectious medical diseases	0.11 [-7.25;7.46]	0.97	-0.18 [-8.51;8.16]	0.96
Other medical disorders	4.93 [-0.95;10.82]	0.09	0.98 [-7.52;9.48]	0.82
Solid organ transplants	3.33 [-6.72;13.37]	0.51	-0.37 [-9.58;8.85]	0.93
PeLOD score first 24 hrs (per point added)	0.06 [-2.80;2.93]	0.96	0.77 [-2.62;4.16]	0.65
PICU stay (per day added)	-2.47 [-15.38;10.44]	0.70	-17.77 [-44.70;9.17]	0.19
Extracorporeal circulation versus no extracorporeal circulation ^a	2.49 [0.37;4.60]	0.02	0.66 [-1.58;2.90]	0.55
Aortic clamp time (per min added)	0.93 [-1.94;3.81]	0.52	-2.28 [-7.41;2.84]	0.38
Duration of mechanical ventilation (per day added)	5.06 [-5.38;15.49]	0.34	2.67 [-23.69;29.02]	0.84
Peak creatinine (per mg/dl added)	3.86 [-2.30;10.01]	0.21	4.33 [-3.58;12.24]	0.28
Peak bilirubine (per mg/dl added)	1.30 [-3.28;5.88]	0.57	-0.10 [-12.20;11.99]	0.98
Infection vs. no infection	0.24 [-1.42;1.90]	0.77	-0.73 [-2.59;1.13]	0.43
Antibiotics (per day added)	-1.83 [-8.44;4.77]	0.58	6.07 [-15.08;27.23]	0.57
Duration of hemodynamic support (per day added)	-3.67 [-9.41;2.07]	0.20	-0.01 [-19.27;19.25]	0.99
Duration of corticosteroid treatment (per day added)	-1.67 [-11.75;8.42]	0.74	11.28 [-2.87;25.42]	0.11
Cumulative dose of opioids (per mg morphine-equivalent added)	-3.30 [-10.55;3.95]	0.37	3.44 [-5.08;11.95]	0.42
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	1.90 [-5.42;9.22]	0.60	4.39 [-1.86;10.63]	0.16
Received hypnotics versus no hypnotics	1.06 [-4.04;6.15]	0.68	-1.49 [-6.60;3.62]	0.56
Exceeding potentially harmful threshold for phthalate exposure	-2.16 [-3.53;-0.78]	0.002	-0.77 [-2.23;0.69]	0.29

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 5-29. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and no. of valid synchronous taps

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
A. Corrected for baseline risk factors and PICU stay				
Male vs. female gender	0.44 [-0.62;1.50]	0.41	-0.16 [-1.33;1.01]	0.78
Age at sampling (per year added)	15.82 [13.63;18.02]	<0.001	17.11 [14.05;20.17]	<0.001
Caucasian vs. other race	0.19 [-3.75;4.13]	0.92	-1.09 [-4.93;2.74]	0.57
Exclusively European vs. other origin	-1.61 [-4.81;1.59]	0.32	1.28 [-2.73;5.29]	0.52
Exclusively Dutch language vs. non-exclusively Dutch language	0.47 [-1.23;2.16]	0.58	0.00 [-2.23;2.23]	>0.99
Socioeconomic status (per category of 1 to 66)	1.14 [-1.37;3.66]	0.37	0.61 [-2.19;3.42]	0.66
Pre-existing syndrome vs. no pre-existing syndrome	-0.04 [-1.41;1.32]	0.95	-2.17 [-3.74;-0.61]	0.006
History vs. no history of malignancy	-0.97 [-4.78;2.85]	0.61	1.40 [-2.09;4.89]	0.43
History vs. no history of diabetes	2.41 [-2.98;7.81]	0.37		
Randomization to strict glycemic control vs. conventional therapy	0.17 [-0.87;1.21]	0.75	0.51 [-0.67;1.69]	0.39
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	4.91 [1.43;8.38]	0.005	1.49 [-2.17;5.15]	0.42
randomized for glycemic control postoperatively	1.58 [-0.95;4.11]	0.21	2.29 [-0.71;5.29]	0.13
Complicated/high risk surgery or trauma	2.22 [-1.46;5.91]	0.23	3.67 [-0.74;8.08]	0.10
Neurological medical disorders	-3.53 [-10.51;3.45]	0.31	-5.30 [-13.54;2.93]	0.20
Infectious medical diseases	0.20 [-4.57;4.97]	0.93	-0.36 [-7.72;7.00]	0.92
Other medical disorders	0.04 [-4.95;5.02]	0.98	6.03 [0.33;11.74]	0.03
Solid organ transplants	-5.41 [-13.11;2.29]	0.16	-7.82 [-15.32;-0.32]	0.04
PeLOD score first 24 hrs (per point added)	1.61 [-1.19;4.41]	0.25	1.59 [-1.44;4.62]	0.30
PICU stay (per day added)	-1.52 [-4.81;1.77]	0.36	-2.41 [-8.03;3.22]	0.39
Exceeding potentially harmful threshold for phthalate exposure	-1.76 [-3.12;-0.41]	0.01	-0.35 [-1.73;1.04]	0.62

CI: confidence interval; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

eTable 5-29. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating 5oxo-MEHP exposure and no. of valid synchronous taps (continued)

VARIABLE	DEVELOPMENT COHORT		VALIDATION COHORT	
	Estimate (95% CI)	P value	Estimate (95% CI)	P value
B. Corrected for baseline risk factors, PICU stay, extracorporeal circulation, aortic clamp time and complications/treatments during PICU stay				
Male vs. female gender	0.56 [-0.56;1.68]	0.32	-0.25 [-1.44;0.94]	0.67
Age at sampling (per year added)	15.95 [13.24;18.66]	<0.001	16.17 [12.84;19.50]	<0.001
Caucasian vs. other race	0.86 [-3.30;5.01]	0.68	-1.43 [-5.32;2.47]	0.47
Exclusively European vs. other origin	-1.23 [-4.54;2.09]	0.46	2.11 [-1.92;6.15]	0.30
Exclusively Dutch language vs. non-exclusively Dutch language	-0.21 [-2.03;1.60]	0.81	-0.41 [-2.69;1.86]	0.71
Socioeconomic status (per category of 1 to 66)	1.28 [-1.36;3.92]	0.33	0.86 [-2.01;3.73]	0.55
Pre-existing syndrome vs. no pre-existing syndrome	-0.42 [-1.91;1.06]	0.57	-2.20 [-3.79;-0.60]	0.007
History vs. no history of malignancy	-0.80 [-4.81;3.22]	0.69	2.01 [-1.54;5.55]	0.26
History vs. no history of diabetes	2.44 [-3.08;7.96]	0.38		
Randomization to strict glycemic control vs. conventional therapy	0.40 [-0.71;1.50]	0.47	-0.03 [-1.25;1.19]	0.95
Diagnostic category (as compared with all other categories)				
Cardiac surgery for congenital heart defects				
randomized for glycemic control preoperatively	3.10 [-3.78;9.99]	0.37	1.66 [-3.92;7.24]	0.55
randomized for glycemic control postoperatively	0.17 [-6.18;6.52]	0.95	2.55 [-2.05;7.15]	0.27
Complicated/high risk surgery or trauma	1.65 [-5.00;8.30]	0.62	5.17 [-0.05;10.39]	0.05
Neurological medical disorders	-3.13 [-14.08;7.82]	0.57	-6.44 [-15.89;3.01]	0.18
Infectious medical diseases	-0.78 [-9.21;7.65]	0.85	0.99 [-6.96;8.94]	0.80
Other medical disorders	2.41 [-4.30;9.13]	0.47	2.83 [-5.28;10.94]	0.49
Solid organ transplants	-3.43 [-15.01;8.15]	0.55	-6.76 [-15.57;2.05]	0.13
PeLOD score first 24 hrs (per point added)	1.50 [-1.82;4.82]	0.37	1.06 [-2.21;4.33]	0.52
PICU stay (per day added)	6.33 [-8.60;21.26]	0.40	-14.84 [-44.88;15.21]	0.33
Extracorporeal circulation versus no extracorporeal circulation ^a	1.11 [-1.37;3.60]	0.37	2.32 [0.12;4.52]	0.03
Aortic clamp time (per min added)	0.48 [-2.82;3.79]	0.77	-4.22 [-9.13;0.68]	0.09
Duration of mechanical ventilation (per day added)	-0.39 [-12.43;11.64]	0.94	22.88 [-3.77;49.53]	0.09
Peak creatinine (per mg/dl added)	-2.01 [-9.15;5.13]	0.57	7.58 [-0.01;15.16]	0.05
Peak bilirubine (per mg/dl added)	-1.45 [-6.75;3.85]	0.59	-6.19 [-17.84;5.46]	0.29
Infection vs. no infection	0.93 [-1.01;2.87]	0.34	-0.78 [-2.61;1.05]	0.40
Antibiotics (per day added)	-5.17 [-12.76;2.42]	0.18	-3.04 [-24.92;18.84]	0.78
Duration of hemodynamic support (per day added)	-5.34 [-11.89;1.21]	0.10	-6.39 [-24.94;12.15]	0.49
Duration of corticosteroid treatment (per day added)	-2.48 [-14.00;9.04]	0.67	-0.14 [-14.10;13.83]	0.98
Cumulative dose of opioids (per mg morphine-equivalent added)	-6.27 [-14.53;1.99]	0.13	4.81 [-3.31;12.93]	0.24
Cumulative dose of benzodiazepines (per mg midazolam-eqv added)	-2.36 [-10.74;6.03]	0.58	1.19 [-4.83;7.22]	0.69
Received hypnotics versus no hypnotics	0.38 [-5.47;6.22]	0.89	-2.01 [-6.89;2.86]	0.41
Exceeding potentially harmful threshold for phthalate exposure	-1.95 [-3.46;-0.45]	0.01	-0.30 [-1.76;1.16]	0.68

CI: confidence interval; eqv: equivalent; PeLOD score: pediatric logistic organ dysfunction score; PICU: pediatric intensive care unit.

^a with exposure to large bore tubings

eTable 6. Multivariable linear regression analyses determining significant and independent associations between exceeding a potentially harmful threshold of circulating DEHP metabolite exposure and deficits in alertness and motor coordination, further adjusted for number of indwelling medical devices

Phthalate exposure ^a	Neurocognitive functions from the development cohort, significantly affected in validation cohort ^b	Best threshold (μmol/l ×days) ^c of development cohort	R ² of the model	Estimate [95% CI]	P value
Total DEHP^d 0.72 (0.34-2.19) (μmol/l×days) ^e	Attention and motor coordination				
	<i>Alertness (msec)^f</i>				
	Reaction time dominant hand	>0.551	0.60	58.90 [13.78;104.02]	0.01
	Reaction time nondominant hand	>0.551	0.61	42.58 [0.24;84.91]	0.04
	Reaction time overall	>0.551	0.63	52.03 [10.49;93.58]	0.01
	<i>Inconsistency of alertness (msec)^g</i>				
	SD reaction time dominant hand	>0.551	0.54	56.43 [15.24;97.62]	0.007
	SD reaction time overall	>0.551	0.57	41.03 [4.08;77.97]	0.02
	<i>Motor coordination (No. of taps in 10s)^h</i>				
	No. of unimanual taps	>0.551	0.65	-1.53 [-3.01;-0.05]	0.04
5oxo-MEHP 0.03 (0.02-0.10) (μmol/l×days) ^e	Attention and motor coordination				
	<i>Alertness (msec)^f</i>				
	Reaction time dominant hand	>0.031	0.64	107.92 [63.87;151.96]	0.000003
	Reaction time nondominant hand	>0.031	0.64	81.04 [39.00;123.08]	0.0002
	Reaction time overall	>0.031	0.66	95.34 [54.62;136.06]	0.000007
	<i>Inconsistency of alertness (msec)^g</i>				
	SD reaction time dominant hand	>0.031	0.56	84.04 [42.91;125.16]	0.00008
	SD reaction time nondominant	>0.031	0.52	44.17 [2.03;86.31]	0.04
	SD reaction time overall	>0.031	0.60	70.18 [33.40;106.96]	0.0002

^a "Exposure" was defined as the product of the last day concentrations in μmol/l and the number of days exposed in PICU.

^b Neurocognitive functions, that were significantly associated with the phthalate exposure in the development cohort, were tested in the validation cohort. Only the remaining functions that were also significantly associated with the phthalate exposure in the validation cohort are listed.

^c Threshold values are rounded to three decimals.

^d Exposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5-OH-MEHP.

^e Distribution of metabolite exposures within the patient cohort (μmol/l ×days). Data are median (interquartile range).

^f For reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time, 562 (95% CI 524-600) for the nondominant hand reaction time and 560 (95% CI 524-600) for the overall reaction time.¹

^g For inconsistency of alertness, higher scores reflect worse performance. Mean scores for healthy children are 259 (95% CI 229-290) for the dominant hand, 262 (95% CI 232-292) for the nondominant hand and 275 (95% CI 246-304) for the overall SD, standard deviation.¹

^h For motor coordination, higher scores reflect better performance. Mean scores for healthy children are 36 (95% CI 34-38) for dominant hand unimanual taps, 32 (95% CI 30-33) for nondominant hand unimanual taps and 22 (95% CI 20-24) for valid synchronous taps.¹

eTable 7. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the subgroup of cardiac surgery patients and further corrected for the “Risk Adjusted classification for Congenital Heart Surgery” (RACHS) score

Phthalate exposure ^a	Neurocognitive functions affected, as determined by a multivariable bootstrap approach ^b	Potentially harmful threshold (μmol/l ×days) ^{c,d}	Development cohort				Validation cohort	
			R ² of the model	Estimate [95% CI]	P value	R ² of the model	Estimate [95% CI]	P value
Total DEHP ^e 0.78 (0.34-2.66) (μmol/l×days) ^g	Attention and motor coordination							
	Alertness (msec) ^h							
	Reaction time dominant hand	>0.551	0.57	86.99 [33.89;140.10]	0.001	0.59	73.07 [24.61;121.53]	0.003
	Reaction time nondominant hand	>0.551	0.56	74.64 [25.09;124.19]	0.003	0.61	58.58 [13.11;104.04]	0.01
	Reaction time overall	>0.551	0.60	79.57 [32.07;127.08]	0.001	0.62	67.35 [22.85;111.86]	0.003
	Inconsistency of alertness (msec) ⁱ							
	SD reaction time dominant hand	>0.551	0.51	58.00 [11.97;104.02]	0.01	0.56	68.66 [25.57;111.75]	0.002
	SD reaction time nondominant	>0.551	0.46	59.09 [15.60;102.58]	0.008	0.50	40.99 [-3.48;85.46]	0.07
	SD reaction time overall	>0.551	0.55	60.34 [20.50;100.17]	0.003	0.58	56.14 [17.14;95.14]	0.005
	Motor coordination (No. of taps in 10s) ^j							
	No. of valid synchronous taps	>0.551	0.70	-2.24 [-3.75;-0.74]	0.003	0.55	-1.15 [-2.72;0.42]	0.14
MEHP Metabolites ^f 0.47 (0.22-1.80) (μmol/l×days) ^g	Attention and motor coordination							
	Alertness (msec) ^h							
	Reaction time dominant hand	>0.365	0.57	100.26 [42.61;157.92]	0.0008	0.58	57.81 [7.84;107.78]	0.02
	Reaction time nondominant hand	>0.365	0.56	78.45 [24.46;132.44]	0.004	0.60	54.97 [8.51;101.44]	0.02
	Reaction time overall	>0.365	0.61	89.56 [37.89;141.22]	0.0008	0.62	58.18 [12.44;103.92]	0.01
	Inconsistency of alertness (msec) ⁱ							
	SD reaction time dominant hand	>0.365	0.52	72.10 [22.26;121.95]	0.004	0.55	56.81 [12.39;101.22]	0.01
	SD reaction time nondominant	>0.365	0.46	65.31 [18.06;112.57]	0.007	0.49	36.82 [-8.59;82.24]	0.11
	SD reaction time overall	>0.365	0.56	71.24 [28.04;114.43]	0.001	0.57	49.29 [9.23;89.35]	0.01
	Motor coordination (No. of taps in 10s) ^j							
	No. of valid synchronous taps	>0.365	0.70	-1.98 [-3.65;-0.31]	0.02	0.54	-0.33 [-1.94;1.28]	0.68

eTable 7. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the subgroup of cardiac surgery patients and further corrected for the “Risk Adjusted classification for Congenital Heart Surgery” (RACHS) score (continued)

MEHP		Attention and motor coordination							
0.23	<i>Alertness (msec)^h</i>								
(0.10-0.68)		Reaction time dominant hand	>0.157	0.56	66.73 [14.07;119.38]	0.01	0.58	51.91 [3.17;100.65]	0.03
($\mu\text{mol/l} \times \text{days}$)		Reaction time nondominant hand	>0.157	0.55	60.93 [11.94;109.93]	0.01	0.60	38.57 [-7.05;84.19]	0.09
^g		Reaction time overall	>0.157	0.59	62.39 [15.31;109.47]	0.009	0.61	46.55 [1.74;91.36]	0.04
	<i>Motor coordination (No. of taps in 10s)^j</i>								
		No. of valid synchronous taps	>0.157		-2.52 [-4.01;-1.04]	0.001	0.56	-1.51 [-3.06;0.03]	0.05
5oxo-MEHP		Attention and motor coordination							
0.03	<i>Alertness (msec)^h</i>								
(0.01-0.12)		Reaction time dominant hand	>0.031	0.59	123.93 [64.42;183.44]	0.00006	0.62	111.69 [62.31;161.07]	0.00001
($\mu\text{mol/l} \times \text{days}$)		Reaction time nondominant hand	>0.031	0.60	136.19 [82.78;189.60]	0.000001	0.62	88.83 [41.99;135.66]	0.0003
^g		Reaction time overall	>0.031	0.64	129.26 [77.11;181.41]	0.000002	0.65	101.46 [56.02;146.90]	0.00002
	<i>Inconsistency of alertness (msec)ⁱ</i>								
		SD reaction time dominant hand	>0.031	0.53	87.61 [35.81;139.41]	0.001	0.57	87.72 [42.94;132.49]	0.0002
		SD reaction time nondominant	>0.031	0.48	88.50 [40.07;136.93]	0.0004	0.51	58.02 [11.49;104.56]	0.01
		SD reaction time overall	>0.031	0.57	88.45 [43.81;133.09]	0.0001	0.59	76.11 [35.75;116.46]	0.0003
	<i>Motor coordination (No. of taps in 10s)^j</i>								
		No. of unimanual taps							
		Dominant hand	>0.031	0.78	-1.81 [-3.39;-0.23]	0.02	0.58	-1.02 [-2.77;0.73]	0.25

^a“Exposure” was defined as the product of the last day concentrations in $\mu\text{mol/l}$ and the number of days exposed in PICU.

^bOnly the neurocognitive functions that were significantly associated with the phthalate exposures as identified by bootstrapping are listed.

^cidentified via bootstrap resampling.

^dthreshold values are rounded to three decimals.

^eExposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^fExposure to the sum of 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^gDistribution of metabolite exposures within the patient cohort ($\mu\text{mol/l} \times \text{days}$). Data are median (interquartile range).

^hFor reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time, 562 (95% CI 524-600) for the nondominant hand reaction time and 560 (95% CI 524-600) for the overall reaction time (ref 1).

ⁱFor inconsistency of alertness, higher scores reflect worse performance. Mean scores for healthy children are 259 (95% CI 229-290) for the dominant hand, 262 (95% CI 232-292) for the nondominant hand and 275 (95% CI 246-304) for the overall SD, standard deviation (ref 1).

^jFor motor coordination, higher scores reflect better performance. Mean scores for healthy children are 36 (95% CI 34-38) for dominant hand unimanual taps, 32 (95% CI 30-33) for nondominant hand unimanual taps and 22 (95% CI 20-24) for valid synchronous taps (ref 1).

eTable 8. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions in the subgroup of patients in whom DEHP metabolite concentrations were higher on the last day in PICU than upon PICU admission

Phthalate exposure ^a	Neurocognitive functions affected, as determined by a multivariable bootstrap approach ^b	Potentially harmful threshold (μmol/l ×days) ^{c,d}	Development cohort			Validation cohort		
			R ² of the model	Estimate [95% CI]	P value	R ² of the model	Estimate [95% CI]	P value
Total DEHP ^e 0.78 (0.34-2.66) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.551	0.62	93.68 [43.92;143.43]	0.0003	0.63	75.98 [31.29;120.67]	0.001
	Reaction time nondominant hand	>0.551	0.62	78.93 [35.14;122.73]	0.0005	0.64	64.02 [22.65;105.39]	0.002
	Reaction time overall	>0.551	0.66	85.54 [43.07;128.01]	0.0001	0.66	71.74 [30.75;112.73]	0.0007
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.551	0.53	60.13 [16.60;103.66]	0.007	0.56	66.02 [22.06;109.97]	0.003
	SD reaction time nondominant hand	>0.551	0.53	56.13 [16.06;96.20]	0.006	0.52	51.34 [8.84;93.83]	0.01
	SD reaction time overall	>0.551	0.60	62.12 [25.46;98.78]	0.001	0.58	57.65 [18.56;96.73]	0.004
	Motor coordination (No. of taps in 10s) ⁱ							
	No. of unimanual taps							
	Dominant hand	>0.551	0.73	-1.10 [-2.54;0.35]	0.13	0.63	-0.81 [-2.54;0.92]	0.35
	Nondominant hand	>0.551	0.76	-0.83 [-2.06;0.40]	0.18	0.66	-1.88 [-3.56;-0.19]	0.02
	No. of valid synchronous taps	>0.551	0.65	-2.04 [-3.57;-0.51]	0.009	0.57	-1.75 [-3.37;-0.12]	0.03
5oxo-MEHP 0.03 (0.01-0.12) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.031	0.65	90.59 [36.89;144.30]	0.001	0.71	114.57 [70.46;158.68]	0.000001
	Reaction time nondominant hand	>0.031	0.66	124.74 [74.97;174.51]	0.000002	0.69	86.38 [44.72;128.04]	0.00007
	Reaction time overall	>0.031	0.70	106.96 [59.96;153.97]	0.00001	0.72	101.85 [61.46;142.23]	0.000002
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.031	0.52	58.76 [5.69;111.84]	0.03	0.62	88.06 [42.77;133.34]	0.0002
	SD reaction time nondominant hand	>0.031	0.56	84.12 [38.37;129.87]	0.0004	0.57	67.71 [22.61;112.81]	0.003
	SD reaction time overall	>0.031	0.62	72.24 [29.16;115.32]	0.001	0.65	82.15 [42.28;122.02]	0.00008
	Motor coordination (No. of taps in 10s) ⁱ							
	No. of unimanual taps							
	Dominant hand	>0.031	0.76	-2.50 [-4.19;-0.81]	0.004	0.66	-0.84 [-2.75;1.08]	0.38
	No. of valid synchronous taps	>0.024	0.65	-2.03 [-3.83;-0.23]	0.02	0.58	-0.69 [-2.62;1.24]	0.48

^a“Exposure” was defined as the product of the last day concentrations in $\mu\text{mol/l}$ and the number of days exposed in PICU.

^bOnly the neurocognitive functions that were significantly associated with the phthalate exposures as identified by bootstrapping are listed.

^cidentified via bootstrap resampling.

^dthreshold values are rounded to three decimals.

^eExposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^fDistribution of metabolite exposures within the patient cohort ($\mu\text{mol/l} \times \text{days}$). Data are median (interquartile range).

^gFor reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time, 562 (95% CI 524-600) for the nondominant hand reaction time and 560 (95% CI 524-600) for the overall reaction time (ref 1).

^hFor inconsistency of alertness, higher scores reflect worse performance. Mean scores for healthy children are 259 (95% CI 229-290) for the dominant hand, 262 (95% CI 232-292) for the nondominant hand and 275 (95% CI 246-304) for the overall SD, standard deviation (ref 1).

ⁱFor motor coordination, higher scores reflect better performance. Mean scores for healthy children are 36 (95% CI 34-38) for dominant hand unimanual taps, 32 (95% CI 30-33) for nondominant hand unimanual taps and 22 (95% CI 20-24) for valid synchronous taps (ref 1).

eTable 9. Multivariable linear regression analyses determining significant and independent associations between exposure to a potentially harmful threshold of circulating phthalate metabolites and neurocognitive functions with exposure calculated with the admission concentration when last day concentration is higher than admission concentration

Phthalate exposure ^a	Neurocognitive functions affected, as determined by a multivariable bootstrap approach ^b	Potentially harmful threshold (μmol/l ×days) ^{c,d}	Development cohort			Validation cohort		
			R ² of the model	Estimate [95% CI]	P value	R ² of the model	Estimate [95% CI]	P value
Total DEHP ^e 0.78 (0.34-2.66) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.551	0.57	58.50 [12.94;104.05]	0.01	0.60	62.44 [19.90;104.98]	0.004
	Reaction time nondominant hand	>0.551	0.58	56.11 [15.49;96.73]	0.007	0.61	56.18 [16.48;95.88]	0.005
	Reaction time overall	>0.551	0.61	56.26 [16.34;96.18]	0.006	0.63	60.65 [21.65;99.65]	0.002
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.551	0.50	36.81 [-2.32;75.94]	0.06	0.53	51.54 [12.05;91.04]	0.01
	SD reaction time nondominant hand	>0.551	0.47	44.70 [8.52;80.88]	0.01	0.49	38.59 [-0.83;78.00]	0.05
	SD reaction time overall	>0.551	0.56	43.54 [10.19;76.89]	0.01	0.56	45.79 [10.65;80.93]	0.01
	Motor coordination (No. of taps in 10s) ⁱ							
No. of unimanual taps								
Dominant hand	>0.551	0.76	-0.98 [-2.18;0.22]	0.10	0.65	-0.77 [-2.20;0.66]	0.28	
Nondominant hand	>0.551	0.78	-0.74 [-1.84;0.35]	0.18	0.66	-1.97 [-3.33;-0.61]	0.004	
No. of valid synchronous taps	>0.551	0.66	-2.07 [-3.42;-0.71]	0.003	0.62	-1.47 [-2.83;-0.11]	0.03	
5oxo-MEHP 0.03 (0.01-0.12) (μmol/l×days) ^f	Attention and motor coordination							
	Alertness (msec) ^g							
	Reaction time dominant hand	>0.031	0.57	55.31 [3.94;106.67]	0.03	0.63	105.97 [62.34;149.60]	0.000003
	Reaction time nondominant hand	>0.031	0.59	83.38 [39.01;127.74]	0.0003	0.62	77.95 [36.30;119.60]	0.0003
	Reaction time overall	>0.031	0.61	67.64 [23.01;112.27]	0.003	0.65	93.02 [52.68;133.36]	0.00001
	Inconsistency of alertness (msec) ^h							
	SD reaction time dominant hand	>0.031	0.50	27.96 [-16.17;72.08]	0.21	0.54	74.74 [33.33;116.15]	0.0005
	SD reaction time nondominant hand	>0.031	0.48	59.59 [19.71;99.48]	0.003	0.50	51.41 [9.65;93.17]	0.01
	SD reaction time overall	>0.031	0.55	42.61 [5.04;80.18]	0.02	0.58	65.75 [28.91;102.58]	0.0005
	Motor coordination (No. of taps in 10s) ⁱ							
No. of unimanual taps								
Dominant hand	>0.031	0.77	-1.56 [-2.90;-0.21]	0.02	0.65	-0.78 [-2.31;0.75]	0.31	
No. of valid synchronous taps	>0.024	0.65	-1.61 [-3.08;-0.14]	0.03	0.61	-0.67 [-2.15;0.82]	0.37	

^a“Exposure” was defined as the product of the last day concentrations in $\mu\text{mol/l}$ and the number of days exposed in PICU.

^bOnly the neurocognitive functions that were significantly associated with the phthalate exposures as identified by bootstrapping are listed.

^cidentified via bootstrap resampling.

^dthreshold values are rounded to three decimals.

^eExposure to the sum of MEHP and its metabolites 5cx-MEPP, 5oxo-MEHP and 5OH-MEHP.

^fDistribution of metabolite exposures within the patient cohort ($\mu\text{mol/l} \times \text{days}$). Data are median (interquartile range).

^gFor reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time, 562 (95% CI 524-600) for the nondominant hand reaction time and 560 (95% CI 524-600) for the overall reaction time (ref 1).

^hFor inconsistency of alertness, higher scores reflect worse performance. Mean scores for healthy children are 259 (95% CI 229-290) for the dominant hand, 262 (95% CI 232-292) for the nondominant hand and 275 (95% CI 246-304) for the overall SD, standard deviation (ref 1).

ⁱFor motor coordination, higher scores reflect better performance. Mean scores for healthy children are 36 (95% CI 34-38) for dominant hand unimanual taps, 32 (95% CI 30-33) for nondominant hand unimanual taps and 22 (95% CI 20-24) for valid synchronous taps (ref 1).

eTable 10. Percentage of neurocognitive deficit in critically ill children that can be explained by exposure above a potentially harmful threshold of circulating DEHP metabolites

	Total DEHP metabolites > 0.551 ($\mu\text{mol/l}$)xPICUdays			Total MEHP metabolites > 0.365 ($\mu\text{mol/l}$)xPICUdays			MEHP > 0.157 ($\mu\text{mol/l}$)xPICUdays			5-oxo-MEHP > 0.031 ($\mu\text{mol/l}$)xPICUdays*		
	Develop. cohort (N=228) %	Validation cohort (N=221) %	Average %	Develop. cohort (N=228) %	Validation cohort (N=221) %	Average %	Develop. cohort (N=228) %	Validation cohort (N=221) %	Average %	Develop. cohort (N=228) %	Validation cohort (N=221) %	Average %
<i>Alertness (msec)</i>												
Reaction time dominant hand	57	36	46	64	26	45	42	23	32	64	63	63
Reaction time nondominant hand	65	35	50	69	32	50	56	22	39	100	57	78
Reaction time overall	62	36	49	68	30	49	49	24	36	81	61	71
<i>Inconsistency of alertness (msec)</i>												
SD reaction time dominant hand	38	35	36	45	27	36	-	-	-	47	56	51
SD reaction time nondominant hand	56	-	-	62	-	-	-	-	-	81	37	59
SD reaction time overall	49	30	39	56	24	40	-	-	-	62	50	56
<i>Motor coordination (number of taps in 10s)</i>												
Number of unimanual taps												
Dominant hand	34	-	-	-	-	-	-	-	-	54	-	-
Nondominant hand	25	27	26	-	-	-	-	-	-	-	-	-
Number of valid alternating taps	-	-	-	-	-	-	-	-	-	-	-	-
Number of valid synchronous taps	59	-	-	54	-	-	68	32	50	49	-	-

The percentage of the deficit in the different neurocognitive functions explained by exceeding a potentially harmful threshold of phthalate exposure was calculated by dividing the scaled estimate for exceeding the potentially harmful threshold obtained in the respective multiple regression analyses (when independently associated with the respective test result, see Table 2 and Table 3) by the difference of the mean scores for critically ill and healthy children (see eTable 2A) and then multiplying by 100. * a lower potentially harmful threshold of 0.024 $\mu\text{mol/l}$ was identified for number of valid synchronous taps.

eTable 11-1. Identification of a potentially harmful threshold for circulating [total DEHP metabolite] at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
Total DEHP metabolites	228	227	0.265013879	0.13675816	0.523832112	0.387073952

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Memory span, numbers	0.075160868	0.066834676	0.102730937	9.27	0.450761084	0.0000568
Delayed memory, word pairs	0.079695249	0.075160868	0.097155165	5.68	0.481291106	0.000425228
Immediate memory, word pairs	0.102730937	0.075034689	0.165727907	23.43	0.423819688	0.030210072
Memory, learning word pairs	0.102730937	0.04457308	0.175194092	33.75	0.439595043	0.045707626
Memory, learning index	0.103106871	0.077428059	0.143670286	17.11	0.509902372	0.016584652
Memory, learning dots	0.110435775	0.103106871	0.341668494	61.63	0.384664643	0.005914816
Flexibility, no. of errors	0.111135028	0.058349635	0.527632752	121.24	0.203611521	0.095852657
Tapping dominant hand	0.141483083	0.088220903	0.346865883	66.82	0.762964783	0.14653212
Valid alternating taps	0.161007146	0.104960707	1.956240604	478.28	0.379919207	0.192656788
Visual-motor integration	0.199586618	0.165727907	0.305008801	35.98	0.372080754	0.031237881
Valid synchronous taps	0.220184303	0.07490851	0.443735314	95.29	0.65484027	0.034208916
Reaction time dominant hand	0.25320974	0.109406291	0.292874702	47.40	0.57720718	0.004416003
Overall reaction time	0.25320974	0.117833404	0.292874702	45.22	0.597024973	0.010376002
Reaction time nondominant hand	0.266870782	0.088547073	0.40673982	82.20	0.551250074	0.041935607
Delayed memory, dots	0.274719898	0.103106871	0.521530322	108.10	0.368531342	0.148491884
Verbal IQ	0.301949141	0.120570777	0.705184663	151.03	0.378483739	0.076227949
Memory span, pictures	0.319934118	0.116705456	0.473735273	92.24	0.497835324	0.057330213
Tapping nondominant hand	0.361228402	0.100183733	0.526133901	110.04	0.771116921	0.062010316
Flexibility, Δ reaction time	0.375782474	0.025943037	2.462670777	629.53	0.324073422	0.012810833
Externalizing problems	0.378009023	0.038386796	0.708691208	173.17	0.1940692	0.060360165
Working memory	0.391355678	0.115456693	0.40673982	75.25	0.418149206	0.00231869
Inhibition, no. of errors	0.504813466	0.093700709	0.67637121	150.53	0.134967283	0.049261525
Memory, recognition word pairs	0.557224262	0.169595807	0.627847002	118.39	0.383055108	0.028117649
Immediate memory, dots	0.677267751	0.391355678	1.195336789	207.71	0.377686778	0.068773091
Full-scale IQ	0.708691208	0.423471295	0.722133205	77.16	0.372434115	0.011748062
Total behavioral problems	0.708691208	0.386948102	0.715934537	84.99	0.221374219	0.11693596
Performance IQ	0.715934537	0.462316933	0.722133205	67.12	0.318763365	0.007582272
Internalizing problems	0.715934537	0.375782474	1.399357122	264.44	0.224939657	0.154304698
Inhibition, Δ reaction time	0.789868549	0.589287844	0.871546911	72.92	0.300226098	0.022151555

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.079695249	Delayed memory, word pairs	0.489567533	0.000189504	0.000128218	0.001087138
	Memory span, numbers	0.430052754	0.001415544	0.001118141	0.005809536
	Memory, learning index	0.488686124	0.023024307	0.016611423	0.057880771

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. The threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 11-2. Identification of a potentially harmful threshold for circulating [total MEHP metabolite] at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
Total MEHP metabolites	228	227	0.17510705	0.078694899	0.369338857	0.290643958

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Flexibility, Δ reaction time	0.02893957	0.024928618	0.564941319	185.80	0.32416967	0.029610968
Memory, learning index	0.029161952	0.020337293	0.071991914	17.77	0.489847708	0.094335423
Flexibility, no. of errors	0.031380998	0.0280355	0.282606213	87.59	0.202893746	0.122037318
Memory span, numbers	0.042563161	0.040273422	0.060708004	7.03	0.440298349	0.001161451
Memory, learning word pairs	0.042982854	0.0280355	0.116532846	30.45	0.427097094	0.176194587
Delayed memory, word pairs	0.058495772	0.044976832	0.05945961	4.98	0.445046614	0.004311239
Immediate memory, word pairs	0.058931959	0.042563161	0.081988321	13.56	0.421893796	0.052998697
Tapping dominant hand	0.068419367	0.022125146	0.191810036	58.38	0.763088188	0.24288781
Memory, learning dots	0.069642098	0.02223316	0.263655708	83.06	0.361597338	0.023495877
Tapping nondominant hand	0.081163992	0.047586096	0.3074486	89.41	0.768850415	0.104441224
Memory, recognition word pairs	0.101344386	0.048253821	0.438859879	134.39	0.383563937	0.027554948
Verbal IQ	0.108737178	0.082777238	0.483086495	137.73	0.38158156	0.027676425
Valid alternating taps	0.116532846	0.045932321	1.672173757	559.53	0.379511023	0.262718959
Visual-motor integration	0.124297778	0.033807673	0.236870876	69.87	0.368206515	0.092033649
Inhibition, no. of errors	0.124697649	0.027644982	0.363240017	115.47	0.135921713	0.096572873
Delayed memory, dots	0.159442314	0.033807673	0.302940772	92.60	0.366071027	0.234862055
Externalizing problems	0.166199901	0.037983683	0.56340115	180.78	0.194776645	0.070079194
Memory span, pictures	0.170983284	0.039584339	0.355686508	108.76	0.488378142	0.129014522
Working memory	0.208462249	0.112686201	0.282606213	58.46	0.407750993	0.002324747
Reaction time nondominant hand	0.2365302	0.041283597	0.317812249	95.14	0.551561551	0.024974509
Reaction time dominant hand	0.2517791	0.098452556	0.276108909	61.13	0.579010189	0.001976719
Overall reaction time	0.2517791	0.216293336	0.282606213	22.82	0.598366094	0.004702477
Valid synchronous taps	0.304799859	0.181001275	0.375326361	66.86	0.65349177	0.041479816
Performance IQ	0.317812249	0.02223316	0.585532451	193.81	0.315510553	0.011574361
Full-scale IQ	0.317812249	0.058495772	0.477211363	144.06	0.373195705	0.024623509
Internalizing problems	0.342723614	0.170983284	0.56340115	135.02	0.22644358	0.065079829
Total behavioral problems	0.447654943	0.170983284	0.56340115	135.02	0.221476971	0.077647172
Inhibition, Δ reaction time	0.483086495	0.040128633	0.651840249	210.47	0.30137977	0.014898837
Immediate memory, dots	0.585532451	0.137477722	0.916323626	267.97	0.381380924	0.058385939

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.042563161	Memory span, numbers	0.443131639	0.000696449	0.000630885	0.002066042
	Delayed memory, word pairs	0.434233046	0.014728026	0.010666136	0.031093607
0.245287147	Overall reaction time	0.599666995	0.002668944	0.001833563	0.010018913

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Both thresholds dichotomize the development cohort with at least 10 patients per group and are retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 11-3. Identification of a potentially harmful threshold for circulating MEHP concentration at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
MEHP	228	222	0.079267992	0.039457565	0.134696383	0.095238818

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Memory span, numbers	0.009224844	0.009224844	0.0154489	6.54	0.45033264	0.000503795
Memory, learning word pairs	0.028006302	0.020574938	0.068348771	50.16	0.44300905	0.045806893
Delayed memory, word pairs	0.032597707	0.007582544	0.274618049	280.39	0.443515178	0.005081461
Memory, learning index	0.033088839	0.027732961	0.257874614	241.65	0.511457172	0.006795703
Delayed memory, dots	0.038625297	0.031114957	0.161831278	137.25	0.389620411	0.034334606
Inhibition, no. of errors	0.041765526	0.023066662	0.327946181	320.12	0.127926018	0.302917722
Memory, learning dots	0.046420641	0.030448416	0.161831278	137.95	0.364764653	0.017595044
Verbal IQ	0.047937981	0.0232829	0.085203792	65.02	0.374629589	0.10243251
Full-scale IQ	0.049122499	0.0232829	0.185071104	169.88	0.357902193	0.198259988
Valid synchronous taps	0.05614508	0.051790198	0.059689498	8.29	0.664224976	0.000854805
Reaction time dominant hand	0.059126802	0.057896817	0.079952437	23.16	0.57959824	0.001887146
Overall reaction time	0.059126802	0.057896817	0.080125372	23.34	0.603085508	0.002910632
Visual-motor integration	0.065037288	0.035389154	0.123244148	92.25	0.369195446	0.056497063
Flexibility, no. of errors	0.095459093	0.031114957	0.103670159	76.18	0.204273671	0.058878578
Reaction time nondominant hand	0.097641947	0.057896817	0.101353746	45.63	0.557608588	0.005553527
Valid alternating taps	0.097641947	0.068348771	0.888650877	861.31	0.379705345	0.186781514
Inhibition, Δ reaction time	0.121437126	0.069440539	1.374668534	1370.48	0.281619207	0.170678232
Tapping nondominant hand	0.121466112	0.05473274	0.136286714	85.63	0.769262915	0.035463395
Memory span, pictures	0.126157873	0.04011091	0.211739871	180.21	0.484358957	0.136359659
Tapping dominant hand	0.135533629	0.051790198	0.136286714	88.72	0.764680658	0.046053251
Working memory	0.14137508	0.040669369	0.224331974	192.84	0.352652399	0.17543165
Performance IQ	0.193225922	0.065037288	0.888650877	864.79	0.302070424	0.174463647
Immediate memory, word pairs	0.224331974	0.023659609	0.274618049	263.50	0.42757841	0.025551499
Externalizing problems	0.22682206	0.109813264	0.28345916	182.33	0.208696336	0.007739372
Memory, recognition word pairs	0.274618049	0.116084275	0.327946181	222.45	0.386151274	0.026327984
Immediate memory, dots	0.279013163	0.202010192	0.327946181	132.23	0.410278731	0.001369197
Total behavioral problems	0.28006758	0.20219232	0.325959344	129.95	0.248175641	0.001936213
Internalizing problems	0.28006758	0.215310507	0.325959344	116.18	0.246042838	0.004289826
Flexibility, Δ reaction time	0.497150804	0.080125372	1.374668534	1359.26	0.316377025	0.089963309

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.009224844	Memory span, numbers	0.454031281	0.000226603	0.000173324	0.000957854
0.05614508	Valid synchronous taps	0.665824412	0.000502058	0.000322517	0.003032893
	Reaction time dominant hand	0.57580753	0.002193173	0.001558686	0.005270529
	Overall reaction time	0.600173168	0.001856856	0.001369492	0.005073703

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Only the green threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 11-4. Identification of a potentially harmful threshold for circulating 5cx-MEHP concentration at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5cx-MEPP	228	227	0.136783366	0.054936002	0.32299271	0.268056709

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Memory, learning index	0.015080876	0.00777936	0.047292114	14.74	0.489966961	0.0743
Flexibility, no. of errors	0.015080876	0.015080876	0.192565928	66.21	0.203162346	0.118664482
Flexibility, Δ reaction time	0.02064542	0.006162229	0.545848605	201.33	0.32172857	0.030350446
Memory span, numbers	0.029608537	0.021184412	0.046504986	9.45	0.435036714	0.002192874
Delayed memory, word pairs	0.032022208	0.030507951	0.042267165	4.39	0.456782583	0.003163658
Immediate memory, word pairs	0.032022208	0.030507951	0.052317063	8.14	0.428379643	0.030900855
Memory, learning dots	0.032022208	0.00777936	0.20758189	74.54	0.352783157	0.046336231
Memory, learning word pairs	0.034631472	0.015080876	0.134605035	44.59	0.425589923	0.171184516
Tapping dominant hand	0.04728603	0.009170522	0.178667379	63.23	0.762542945	0.310736001
Tapping nondominant hand	0.061221368	0.026210264	0.18612576	59.66	0.768199633	0.159858275
Inhibition, no. of errors	0.075100413	0.030356181	0.490483919	171.65	0.134204279	0.086268461
Memory, recognition word pairs	0.085535044	0.035299197	0.387490568	131.39	0.381890504	0.025899055
Valid alternating taps	0.090331004	0.032022208	1.45066713	529.23	0.379483362	0.174015775
Memory span, pictures	0.09124143	0.021591974	0.321805798	112.00	0.483541591	0.278991999
Visual-motor integration	0.117732529	0.030302621	0.199027753	62.94	0.369587648	0.059733403
Delayed memory, dots	0.140287245	0.021591974	0.321805798	112.00	0.365384248	0.230972245
Externalizing problems	0.143569783	0.017966963	0.498047678	179.10	0.194469532	0.073125193
Reaction time nondominant hand	0.157136201	0.022352712	0.294287148	101.45	0.549468279	0.079158081
Overall reaction time	0.163487193	0.156590985	0.20758189	19.02	0.597171599	0.008182309
Reaction time dominant hand	0.168539415	0.156590985	0.20758189	19.02	0.577944576	0.00232262
Internalizing problems	0.175923736	0.143345839	0.503406597	134.32	0.231618184	0.031001504
Working memory	0.189265176	0.11359402	0.244350808	48.78	0.405893384	0.002840406
Valid synchronous taps	0.201566383	0.156590985	0.354330162	73.77	0.654200025	0.024632028
Verbal IQ	0.263014222	0.066383338	0.461579972	147.43	0.384618972	0.0140168
Inhibition, Δ reaction time	0.297707674	0.156590985	0.594775102	163.47	0.303057073	0.013866932
Performance IQ	0.398814639	0.032022208	0.461579972	160.25	0.318846126	0.018102306
Full-scale IQ	0.404670082	0.179233313	0.461579972	105.33	0.375971553	0.005297722
Total behavioral problems	0.43615222	0.143457811	0.503406597	134.28	0.22491035	0.045156505
Immediate memory, dots	0.531538336	0.134605035	0.681307825	203.95	0.382409545	0.045002561

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.029608537	Memory span, numbers	0.439555957	0.000787319	0.000635054	0.00225929
	Delayed memory, word pairs	0.429435292	0.016284382	0.010508319	0.038975036
	Immediate memory, word pairs	0.408694892	0.081896219	0.053358674	0.162774828
	Memory, learning index	0.458098955	0.352534194	0.277911801	0.467286324
0.168539415	Reaction time dominant hand	0.58233023	0.000913681	0.000595235	0.003305614
	Overall reaction time	0.600174211	0.00513789	0.003167005	0.014935434

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Both thresholds dichotomize the development cohort with at least 10 patients per group and are retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 11-5. Identification of a potentially harmful threshold for circulating 5OH-MEHP concentration at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5OH-MEHP	228	185	0.019350548	0.008709822	0.044730445	0.036020623

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Tapping nondominant hand	0.004181393	0.004181393	0.012008082	21.73	0.77341636	0.00222
Memory span, numbers	0.010574613	0.00645512	0.035723481	81.25	0.375915825	0.145251716
Delayed memory, word pairs	0.012138002	0.008666983	0.019286538	29.48	0.412084018	0.074835123
Working memory	0.012495992	0.011677718	0.023228562	32.07	0.363307797	0.049486269
Valid alternating taps	0.015032343	0.008922871	0.271526335	729.04	0.379955421	0.148328021
Visual-motor integration	0.015426152	0.008666983	0.041274579	90.52	0.364056312	0.182216911
Memory, recognition word pairs	0.019350548	0.00645512	0.027083477	57.27	0.351384922	0.127928569
Memory, learning index	0.019414558	0.015102948	0.024412998	25.85	0.470495586	0.171984632
Memory, learning word pairs	0.019414558	0.01016529	0.058673535	134.67	0.415644394	0.341917231
Immediate memory, word pairs	0.01984075	0.008333629	0.035723481	76.04	0.400186582	0.296254057
Full-scale IQ	0.019940679	0.011536245	0.046929775	98.26	0.360586557	0.096663205
Verbal IQ	0.020049169	0.011536245	0.042870787	86.99	0.375187033	0.075837998
Memory, learning dots	0.022179911	0.019085561	0.024412998	14.79	0.356668158	0.024921518
Valid synchronous taps	0.023133233	0.022311957	0.024659232	6.52	0.654354547	0.018329301
Memory span, pictures	0.024412998	0.016377026	0.065699422	136.93	0.491063139	0.059575704
Tapping dominant hand	0.024412998	0.009072959	0.072942568	177.31	0.762654989	0.199296002
Reaction time dominant hand	0.025301007	0.024659232	0.025301007	1.78	0.596560755	0.0000231109
Overall reaction time	0.025301007	0.024659232	0.029897295	14.54	0.613677269	0.000148708
Delayed memory, dots	0.025301007	0.0202115	0.058673535	106.78	0.376411734	0.116149528
Reaction time nondominant hand	0.029897295	0.025947162	0.035723481	27.14	0.566425068	0.000830736
Performance IQ	0.03984983	0.013585416	0.239220817	626.41	0.304034604	0.068252089
Flexibility, no. of errors	0.065405492	0.028896812	0.1520641	341.94	0.201265497	0.125674022
Immediate memory, dots	0.065699422	0.029562165	0.125143638	265.35	0.382971223	0.017308081
Total behavioral problems	0.067929356	0.027083477	0.129849327	285.30	0.220808439	0.14005548
Internalizing problems	0.067929356	0.020867529	0.127496483	296.02	0.22450072	0.161440234
Externalizing problems	0.069675778	0.014850677	0.129849327	319.26	0.191371801	0.130431136
Inhibition, Δ reaction time	0.071460518	0.011167301	0.096095688	235.78	0.280817867	0.190989586
Inhibition, no. of errors	0.075604207	0.019105242	0.079907143	168.80	0.142409427	0.047817931
Flexibility, Δ reaction time	0.134026363	0.025177155	0.20312378	494.01	0.31711806	0.063976901

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.004181393	Tapping nondominant hand	0.774123614	0.001633652	0.00143229	0.002367302
0.025301007	Reaction time dominant hand	0.600940147	0.00000832	0.00000532	0.0000427
	Overall reaction time	0.618866671	0.0000323	0.0000238	0.000188346
	Valid synchronous taps	0.656171705	0.011159618	0.007735086	0.031461639
	Memory, learning dots	0.332517756	0.087818866	0.066284414	0.163898896

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. Only the green threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses. Neurocognitive tests are ordered from the lowest to the highest median exposure covariate P value found for comparison of patients according to the identified potentially harmful threshold.

eTable 11-6. Identification of a potentially harmful threshold for circulating 5oxo-MEHP concentration at last PICU day

A. Descriptive statistics

Concentration of	Number of patients	Number of unique values	Median	25th percentile	75th percentile	Interquartile range
5oxo-MEHP	228	148	0.009540407	0.006499504	0.020394375	0.013894871

B. Selection of significant and stable cut-offs

Neurocognitive test	Median cut-off	25th percentile cut-off	75th percentile cut-off	IQR cut-off / IQR exposure (%)	Median R ²	Median exposure covariate P value
Verbal IQ	0.006499504	0.006334561	0.013011503	48.05	0.375642332	0.0634
Delayed memory, word pairs	0.006895201	0.006196198	0.013766183	54.48	0.399104565	0.299855094
Memory span, numbers	0.007325794	0.006196198	0.020801823	105.12	0.365043253	0.37956931
Visual-motor integration	0.008529539	0.00489703	0.01338206	61.07	0.370206697	0.064878069
Working memory	0.008529539	0.006499504	0.012737636	44.90	0.350363039	0.13944208
Tapping dominant hand	0.008868966	0.006334561	0.024422765	130.18	0.762922308	0.111711179
Memory, learning dots	0.009910871	0.009856868	0.01120982	9.74	0.376143622	0.009768178
Inhibition, Δ reaction time	0.009910871	0.00489703	0.041620094	264.29	0.286258472	0.093858778
Memory, learning index	0.009942002	0.007325794	0.010205969	20.73	0.484096414	0.050195227
Memory, learning word pairs	0.009942002	0.007325794	0.024679015	124.89	0.417101882	0.187212616
Performance IQ	0.010205969	0.006334561	0.034663576	203.88	0.303445721	0.098281491
Memory, recognition word pairs	0.010205969	0.006895201	0.017671239	77.55	0.34242153	0.292475606
Valid synchronous taps	0.010402614	0.006499504	0.014558539	58.00	0.651919724	0.078277263
Full-scale IQ	0.010402614	0.006334561	0.024422765	130.18	0.364415745	0.09112564
Tapping nondominant hand	0.012233924	0.002383856	0.021319536	136.28	0.770314088	0.039666841
Memory span, pictures	0.012233924	0.009467712	0.028653806	138.08	0.485399068	0.094109172
Delayed memory, dots	0.012233924	0.00985449	0.036304458	190.36	0.370595206	0.109403706
Immediate memory, word pairs	0.013752617	0.006196198	0.024422765	131.17	0.402373362	0.221331663
Overall reaction time	0.013766183	0.010402614	0.017661309	52.24	0.609457019	0.000446171
Reaction time nondominant hand	0.013766183	0.010253254	0.015767544	39.69	0.564173665	0.002127026
Reaction time dominant hand	0.014230521	0.010402614	0.017661309	52.24	0.58890791	0.000306435
Flexibility, no. of errors	0.014420029	0.014300052	0.069485544	397.16	0.203774165	0.101576339
Inhibition, no. of errors	0.026604113	0.021319536	0.032494871	80.43	0.142534334	0.024824398
Valid alternating taps	0.032494871	0.009958553	0.125707462	833.03	0.376602738	0.318769842
Immediate memory, dots	0.036304458	0.024422765	0.098948686	536.36	0.394426932	0.004705647
Externalizing problems	0.0368674	0.00489703	0.037866754	237.28	0.199606469	0.03791726
Total behavioral problems	0.037464027	0.034184727	0.043641043	68.06	0.224822899	0.060294382
Internalizing problems	0.037665391	0.033222808	0.057563398	175.18	0.23112608	0.033670697
Flexibility, Δ reaction time	0.069485544	0.013049462	0.086354987	527.57	0.313218415	0.098418515

Criteria met for selection (stability and significance of the determined cut-off) are shown in bold. Responses grouped together around a similar cut-off are shown in the same color. Neurocognitive tests are ordered from the lowest to the highest median cut-off that was identified.

C. Determination of a potentially harmful threshold per grouped responses

Potentially harmful threshold	Neurocognitive test	Median R ²	Median exposure covariate P value	25th percentile exposure covariate P value	75th percentile exposure covariate P value
0.009910871	Memory, learning dots	0.383660057	0.00352465	0.002443359	0.010025297

Criteria met for selection (median, 25th and 75th percentile lower than or equal to 0.05) are shown in bold. The threshold dichotomizes the development cohort with at least 10 patients per group and is retained for further analyses.

eTable 12. Multivariable linear regression analyses determining significant and independent associations between a potentially harmful threshold of circulating phthalate metabolite concentrations on the last PICU day and neurocognitive functions in the development cohort (N=228)

Phthalate concentration ^c	Neurocognitive functions affected, as determined by a multivariable bootstrap approach ^d	Potentially harmful threshold (μmol/l) ^{a,b}	R ² of the model	Estimate [95% CI]	P value
Total DEHP^e 0.27 (0.14-0.52) (μmol/l) ^g	Memory <i>Verbal-auditory^h</i> Memory span, repeating numbers forward (up to 19 numbers)	>0.080	0.42	-1.60 [-2.46;-0.75]	0.0003
	Delayed memory, word pairs (proportion of (proportion of correct responses)	>0.080	0.45	-0.09 [-0.14;-0.04]	0.0002
	Immediate memory, word pairs (proportion of correct responses)	>0.080	0.39	-0.06 [-0.12;-0.01]	0.03
MEHP Metabolites^f 0.18 (0.08-0.37) (μmol/l) ^g	Attention and motor coordination <i>Alertness (msec)ⁱ</i> Reaction time overall	>0.245	0.58	49.61 [13.84;85.38]	0.007
	Memory <i>Verbal-auditory^h</i> Memory span, repeating numbers forward (up to 19 numbers)	>0.043	0.41	-1.36 [-2.16;-0.57]	0.001
	Delayed memory, word pairs (proportion of (proportion of correct responses)	>0.043	0.39	-0.06 [-0.10;-0.01]	0.02
MEHP 0.08 (0.04-0.14) (μmol/l) ^g	Attention and motor coordination <i>Alertness (msec)ⁱ</i> Reaction time dominant hand	>0.056	0.59	52.33 [19.32;85.35]	0.002
	Reaction time overall	>0.056	0.59	57.19 [21.24;93.15]	0.002
	<i>Motor coordination (No. of taps in 10s)^j</i> No. of valid synchronous taps	>0.056	0.66	-1.98 [-3.09;-0.88]	0.0005
5-cx-MEPP 0.14 (0.05-0.32) (μmol/l) ^g	Attention and motor coordination <i>Alertness (msec)ⁱ</i> Reaction time dominant hand	>0.169	0.57	65.76 [27.08;104.44]	0.001
	Reaction time overall	>0.169	0.59	52.82 [18.14;87.49]	0.003
	Memory <i>Verbal-auditory^h</i> Memory span, repeating numbers forward (up to 19 numbers)	>0.030	0.41	-1.36 [-2.16;-0.57]	0.001
	Delayed memory, word pairs (proportion of (proportion of correct responses)	>0.030	0.39	-0.06 [-0.10;-0.01]	0.02
5-OH-MEHP 0.02 (0.01-0.4) (μmol/l) ^g	Attention and motor coordination <i>Alertness (msec)ⁱ</i> Reaction time dominant hand	>0.025	0.59	93.17 [53.07;133.27]	0.000008
	Reaction time overall	>0.025	0.60	77.12 [41.10;113.15]	0.00003
	<i>Motor coordination (No. of taps in 10s)^j</i> No. of valid synchronous taps	>0.025	0.64	-1.62 [-2.88;-0.37]	0.01
5-oxo-MEHP 0.01 (0.01-0.02) (μmol/l) ^g	Memory <i>Nonverbal, visual-spatial^k</i> Dots: learning (proportion of correct responses)	>0.010	0.30	-0.05 [-0.09;-0.003]	0.04

^aidentified via bootstrap resampling. ^bcut-off values are rounded to three decimals. ^c“Concentration” was defined as the last day concentrations in μmol/l. ^dOnly these neurocognitive functions that were significantly associated with the phthalate exposures as identified by mining multivariable bootstrap approach are listed. ^eThe sum of MEHP and its metabolites 5-cx-MEPP, 5-oxo-MEHP and 5-OH-MEHP. ^fThe sum of 5-cx-MEPP, 5-oxo-MEHP and 5-OH-MEHP. ^gDistribution of metabolites within the patient cohort (μmol/l). Data are median (interquartile range). ^hFor verbal-auditory memory, higher scores reflect better performance. Mean scores for healthy children are children are 9 (95% CI 9-10) for memory span (repeating numbers forward), 0.42 (95% CI 0.38-0.45) for delayed memory and 0.50 (95% CI 0.46-0.53) for immediate memory. ⁱFor reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time and 560 (95% CI 524-596) for the overall reaction time. ^jFor motor coordination, higher scores reflect better performance. Mean scores for healthy children are 22 (95% CI 20-24) for valid synchronous taps. ^kVisual-spatial nonverbal memory, higher scores reflect better performance. Mean scores for healthy children are children are 0.86 (95% CI 0.84-0.89) for learning dots. ^{s1}

eTable 13. Multivariable linear regression analyses determining significant and independent associations between a potentially harmful threshold of circulating phthalate metabolite concentrations on the last PICU day and neurocognitive functions in the validation cohort (N=221)

Phthalate exposure ^b	Neurocognitive functions from the development cohort, significantly affected in validation cohort ^c	Best threshold (μmol/l) ^a of development cohort	R ² of the model	Estimate [95% CI]	P value
MEHP metabolites^d	Attention and motor coordination				
0.21 (0.08-0.47) (μmol/l) ^e	<i>Alertness (msec)^f</i> Reaction time overall	>0.245	0.57	35.41 [0.34;70.47]	0.05
MEHP	Attention and motor coordination				
0.07 (0.04-0.12) (μmol/l) ^e	<i>Alertness (msec)^f</i> Reaction time dominant hand	>0.056	0.53	40.81 [3.62;78.00]	0.03
5-OH-MEHP	Attention and motor coordination				
0.02 (0.01-0.05) (μmol/l) ^e	<i>Alertness (msec)^f</i> Reaction time dominant hand	>0.025	0.55	67.80 [27.5;108.1]	0.001
	Reaction time overall	>0.025	0.59	69.61 [32.98;106.2]	0.0002

^acut-off values are rounded to three decimal places. ^b"Exposure" was defined as the product of the last day concentrations in μmol/l and the number of days exposed in PICU. ^cNeurocognitive functions, that were significantly associated with the phthalate exposure in the development cohort, were tested in the validation cohort. Only the remaining functions that were also significantly associated with the phthalate exposure in the validation cohort are listed. ^dExposure to the sum of 5-cx-MEPP, 5-oxo-MEHP and 5-OH-MEHP. ^eDistribution of metabolites within the patient cohort (μmol/l). Data are median (interquartile range). ^fFor reaction times, higher scores reflect worse performance. Mean scores for healthy children are 558 (95% CI 521-595) for the dominant hand reaction time and 560 (95% CI 524-596) for the overall reaction time.^{S1}

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