



Time course of phthalate cumulative risks to male developmental health over a 27-year period: Biomonitoring samples of the German Environmental Specimen Bank



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ABSTRACT

In several human biomonitoring surveys, changes in the usage patterns of phthalates have come to light, but their influence on the risks associated with combined exposures is insufficiently understood. Based on the largest study to date, the 27-year survey of urinary phthalate metabolite levels in 24-hour urine samples from the German Environmental Specimen Bank, we present a deep analysis of changing phthalate exposures on mixture risks. This analysis adopts the Hazard Index (HI) approach based on the five phthalates DBP, DIBP, BBP, DEHP and DINP. Calculations of the hazard index for each study participant included updated phthalate reference doses for anti-androgenicity (RfD_{AA}) that take account of new evidence of phthalates' developmental toxicity.

The Maximum Cumulative Ratio (MCR) approach was used to establish whether a subject's combined exposure was dominated by one phthalate or was influenced by several phthalates simultaneously. Generally, over the years there was a shift towards lower HIs and higher MCRs, reflecting an increased complexity of the combined exposures. The decade from 1988 to about 1999 was characterised by rather high HIs of between 3 and 7 (95th percentile) which were driven by exposure to DBP and DEHP, often exceeding their single acceptable exposures. Traditional single phthalate risk assessments would have underestimated these risks by up to 50%. From 2006 onwards, no study participant experienced exposures above acceptable levels for a single phthalate, but combined exposures were still in excess of HI = 1. From 2011 onwards most individuals stayed below HI = 1. In interpreting these results, we caution against the use of HI = 1 as an acceptable limit and develop proposals for improved and more realistic mixture risk assessments that take account of co-exposures to other anti-androgenic substances also capable of disrupting the male reproductive system. From this perspective, we regard HIs between 0.1 and 0.2 as more appropriate for evaluating combined phthalate exposures. Assessed against lowered HIs of 0.1 – 0.2, the combined phthalate exposures of most study participants exceeded acceptable levels in all study years, including 2015. Continued monitoring efforts for phthalate combinations are required to provide the basis for appropriate risk management measures.

1. Introduction

Due to their uses as additives and plasticisers in a multitude of

consumer articles such as plastic bags, polyvinyl flooring, personal care products, pharmaceuticals, medical devices, cleaning materials and children's toys, there is widespread human exposure to multiple

Abbreviations: DI, daily intake; BBP, butylbenzyl phthalate; DEHP, di(2-ethylhexyl) phthalate; DEHTP, di(2-ethylhexyl) terephthalate; DEP, di-ethyl phthalate; DBP, di-n-butyl phthalate; DIBP, di-iso-butyl phthalate; DINCH, di-iso-nonyl cyclohexane; DINP, di-iso-nonyl phthalate; DPP, di-n-pentyl phthalate; Fue, fractional urinary excretion (= molar fraction of excreted metabolite relative to total intake at 24/48h post-dosing); HI, hazard index; MCR, maximum cumulative ratio; P95, 95th percentile; RQ, risk quotient; RfD_{AA}, reference dose for anti-androgenicity; TDI, tolerable daily intake

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phthalates. This has led to concerns about possible health impacts, especially of combined exposures.

Phthalates and their metabolites can cross the placental barrier and reach the foetus (Heudorf et al., 2007) where they act during a specific time period in pregnancy when the programming of male sexual development is established (late 1st to early 2nd trimester in humans). This developmental step is driven by androgens and a host of other factors. Certain phthalate metabolites can suppress InsL3 peptide hormone production and testosterone synthesis in foetal Leydig cells (Gray et al., 2000). Without InsL3, the gubernacular cord cannot develop properly, leading to the disruption of testis descent. Suppression of testosterone synthesis alters the entire developmental trajectory of the male reproductive tract with long-lasting and often irreversible effects on male reproductive health. These include increased risks of non-descending testicles, hypospadias, poor semen quality and testis cancer (for an authoritative review see Skakkebaek et al., 2016). From studies in animals it is well known that phthalates with a backbone chain length between three and six carbon atoms and a total carbon count of the alkyl chain between 4 (DBP and DIBP) and 9 carbon atoms (DINP) can suppress foetal testicular testosterone production. As a result, both, structural and functional impairments of male reproduction and development have been observed, termed the “phthalate syndrome” (Foster, 2006; Gray et al., 2006; National Research Council, 2008; Danish EPA, 2011; ECHA, 2009; 2014a; 2014b; Furr et al., 2014). These anti-androgenic properties are considered to be of human health relevance (Albert and Jégou, 2014), and accordingly, DBP, DIBP, BBP, DPP, and DEHP have been classified as reproductive toxicants in Europe.

The importance of considering combined phthalate exposures is underlined by experimental evidence showing that several phthalates together produce adverse reproductive and developmental effects, which are usually stronger than any single phthalate effect in the mixture (reviewed by Kortenkamp, 2020; Howdeshell et al., 2017). In the light of these findings, the US National Academy of Sciences called for mixture risk assessments of phthalates and suggested the use of the Hazard Index (HI) approach to achieve this goal (USNAS, 2008).

For all chemicals considered in a mixture risk assessment, the HI sums risk quotients (RQ) of estimated daily intakes (DI) and reference doses (RfD) for relevant health endpoints (Teuschler and Hertzberg, 1995). The utility of this approach for combined phthalate exposures was first shown by Benson (2009) and then expanded by Kortenkamp and Faust (2010) to include exposures to other substances capable of producing reproductive and developmental toxicity by anti-androgenic modes of action. Since then, several phthalate mixture risk assessments have been published (Table 1). To varying degrees, these studies revealed exceedances both of acceptable single and combined phthalate exposures. Due to their high prevalence and high potency in disrupting male sexual development, DBP and DEHP generally contributed most to the HI.

However, the outcomes of these various phthalate mixture risk assessments are difficult to compare. Not only were different phthalates investigated and evaluated using different reference doses, there is also evidence that phthalate exposures have undergone changes over the years. Covering a period of 27 years, from 1988 to 2015, the survey of changing phthalate exposures by Koch et al. (2017) is the largest of its kind to date. Urinary phthalate metabolite levels in 24-hour urine samples from the Environmental Specimen Bank (ESB) of the German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) (Kolossa-Gehring et al., 2012) were monitored. During this period, exposures to DEP, DBP, DIBP, BBP, and DEHP declined, while there was an increase in the levels of DINP metabolites. In a survey of morning spot urine samples from first-time mothers in Sweden decreases of DEP, DBP, BBP and DEHP metabolites were also noticed between 2009 and 2014 (Gyllenhammar et al., 2017), while DINP metabolite levels remained unchanged. Shu et al. (2018) saw declines in DEP and DEHP in spot urine samples from the Swedish

SELMA cohort between 2007 and 2010. The levels of DINP increased, while DBP and BBP metabolites showed fluctuations, with no clear overall trend. Declining exposures to DEP, DBP, BBP and DEHP were also found in an Italian study that compared the urinary metabolite levels in 2011 and 2016 (Tranfo et al., 2018). Similar temporal trends became apparent in analyses of spot urine samples from the NHANES programme in the USA covering the time between 2001 and 2010 (Zota et al., 2014) and 2004 to 2014 (Reyes and Price, 2018).

The implications of these trends for cumulative risks have not been investigated. The declining exposures to most classical phthalates shown by Koch et al. (2017), Gyllenhammar et al. (2017), Tranfo et al. (2018), Shu et al. (2018), Zota et al. (2014) and Reyes and Price (2018) can be expected to have a decreasing impact on combined risks, but mixture risk assessments that consider the impact of changing exposure patterns are comparatively rare. To our knowledge, Reyes and Price (2018) is the only study of its kind. They observed generally declining HIs during the period of 2005 to 2014 but also shifts in the contributing phthalates.

Here, we present a comprehensive analysis of the impact of changing phthalate exposures on mixture risks in Germany by using the HI approach, based on the study by Koch et al. (2017). This survey has several advantages. Not only does it cover the longest time period studied to date (27 years), it is also based on 24-hour urine samples. The collection of 24-hour urine samples decreases uncertainties in exposure assessments by eliminating the need to apply creatinine- or urinary volume-based corrections to metabolite concentrations. This is of importance as phthalates are rapidly metabolised, leading to considerable variations in the metabolite levels found in individual subjects, with diurnal and weekly changes. As they diminish the influence of diurnal changes, 24-hour samples are also less likely to overestimate inter-individual variations in phthalate metabolite concentrations. Spot urine samples, most widely used in phthalate biomonitoring studies (Table 1), are sensitive to such variations. Analyses of temporal trends based on spot samples may therefore overlook some changes in exposure patterns over time as these may be obscured (Lermen et al., 2019).

Our interest was to establish whether a subject's combined exposure was dominated by one phthalate or was influenced by several phthalates simultaneously. This will show the extent of cumulative risks that is missed in traditional single chemical risk assessments. A convenient way of addressing this issue is to calculate the ratio of an individual's HI (HI_p) and the maximum RQ among the RQs that sum to the HI, called Maximum Cumulative Ratio (MCR, here termed MCR_p , see Materials and Methods) (Price and Han 2011). By definition, the MCR cannot exceed the number of mixture components, in our case five. The MCR equals 5 when the RQs of all phthalates contribute equally to the HI. The value of MCR approaches 1 where only one phthalate makes up virtually 100% of the HI.

The ratio of the total impact of a combined exposure (equivalent to the HI) to the largest single-chemical impact (equivalent to RQ_{max}) was originally used by Könemann (1981) to distinguish types of joint action of chemicals in fish, and by Junghans et al. (2006) to establish the factors that determine the degree of divergent predictions of mixture effects derived from the assessment concepts of dose addition and independent action. Price et al. (2012) employed the MCR to group exposure scenarios into categories that can support risk management decisions. By creating scatter plots of MCR_p versus HI_p different groupings can be distinguished (Fig. 1).

We used these groupings and the labelling introduced by Price et al. (2012) to characterise how changing phthalate exposures evolved in terms of: exceedances of acceptable combined and single exposures (Region I in Fig. 1), exceedances of acceptable combined exposures (Region III) and combined exposures where multiple phthalates contribute to exceedances of the HI (Regions IIIb and Ib).

The quality of phthalate mixture risk assessments depends on the quality of the reference doses utilised, but there are issues with the

Table 1
Overview of phthalate mixture risk assessments.

Study	Country	Phthalates considered for HI	Number of phthalates included	Urine sampling	Population	EFSA (2005a, 2005b, 2005c, 2005d) HI (95th Percentile)	Kortenkamp and Faust (2010) HI(95th Percentile)	Kortenkamp and Koch (2020) Revised RfD _{AA} HI(95th Percentile)
Beko et al., 2013	Denmark	DBP; DIBP; DEHP	3	Morning urine	Children	2.3		3.6
Chang et al., 2017	Taiwan	DBP; DIBP; BBP; DEHP	4	Morning urine	General population	> 1		
Chen et al., 2019	China	DBP; DEHP	2	Morning urine	Pregnant women	3		
Christensen et al., 2014	USA	DBP, BBP, DEHP, DINP	4	Spot sample	General population	0.87		4
Dewalque et al., 2014	Belgium	DBP; DIBP; BBP; DEHP	4	Spot sample	Adults	1.22	0.31	1.53
Dong et al., 2018	China	DBP; DIBP; BBP; DEHP	4	Spot sample	Women 20–44 y	0.46	0.24	1
Frederiksen et al., 2014	Denmark	DBP; DIBP; BBP; DEHP	4	Spot sample	Infants < 14 months	> 1		
Gao et al., 2016	China	DBP; DIBP; DEHP	3	Morning urine	Young adults	> 1	> 1	
Gao et al., 2017	China	DEP; DBP; BBP; DEHP	4	Morning urine	Mother-neonate pairs	1.85		
Garf et al., 2019	Poland	DBP; DIBP; BBP; DEHP	4	Spot sample	Children 7 y		~ 1	
Hartmann et al., 2015	Austria	DBP; DIBP; BBP; DEHP	4	Spot sample	Children, adults, seniors	0.15–2.7	0.05–0.69	0.44
Jeddi et al., 2018	Iran	DBP; BBP; DEHP	3	Spot sample	Children and adolescents	0.44–0.65	0.4–0.6	
Kim et al., 2017	South Korea	DBP; DIBP; DEHP; DEP	4	Cloth diapers	Infants < 15 months	> 1	> 1	
Kranich et al., 2014	Denmark	DBP; BBP; DEHP; DINP	4	24 h sample	Men	0.5–0.88	0.32–1.19	2.76
Liroy et al., 2015	USA	DBP; DIBP; BBP; DEHP; DINP	5	Spot sample	Pregnant women		6.1	
Liroy et al., 2015	USA	DBP; DIBP; BBP; DEHP; DINP	5	Spot sample	Infants		0.96	
Reyes & Price, 2018	USA	DBP; DIBP; BBP; DEHP; DINP, DIDP	6	Spot sample	General population	> 1		
Rocha et al., 2017	Brazil	DBP; DIBP; DEHP	3	Spot sample	Children 6–14 y	3.4	2.1	
Seeborg et al., 2012	Denmark	DBP; DIBP; BBP; DEHP	4	unclear	Children, adolescents	1.3	0.43	
Wang et al., 2015	China	DBP; DIBP; BBP; DEHP	4	Morning urine	Children 8–11 y	3		
Zhang et al., 2019	China	DBP; DIBP; DEHP	3	Morning urine	All ages, e-recycling sites	> 1		

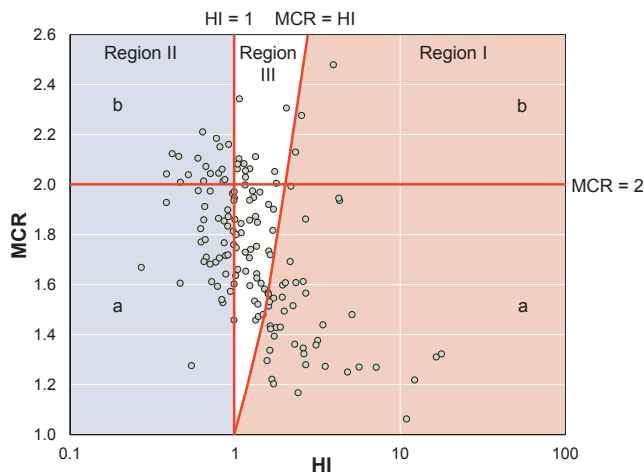


Fig. 1. Example scatter plot of Maximum Cumulative Ratio (MCR) versus Hazard Index (HI) with categories for risk management. Each study participant in this example is depicted by a data point (the data shown here are fictitious and have no further meaning). The blue segment to the left of the vertical line marking an acceptable HI (here = 1) contains individuals who experienced combined exposures that do not present concerns (Region II; we follow the labelling introduced by Price et al., 2012). The white segment defined by the vertical line for acceptable HIs and the curved line depicting MCR = HI shows subjects with combined exposures above HI = 1, but without exceeding acceptable levels for any single phthalate (Region III). The red segment to the right of the MCR = HI line is for subjects exceeding acceptable combined exposures and with phthalate exposures above acceptable levels for at least one phthalate (Region I). Data points below the horizontal line corresponding to MCR = 2 show subjects in whom one phthalate contributed 50% or more to the HI (Regions Ia, IIa and IIIa). Above this line are study participants who experienced combined exposures where multiple phthalates contributed to the HI (Regions Ib, IIb and IIIb).

values employed in previous assessments. The TDIs for individual phthalates derived by EFSA in 2005 and the reference doses for anti-androgenic effects (RfD_{AA}) proposed by Kortenkamp and Faust (2010) were most widely used, often side-by-side (see HI, Table 1). Both sets of values require updates and revisions because new evidence of anti-androgenic effects of phthalates has emerged after 2010. Both, the EFSA values and those by Kortenkamp and Faust (2010), are based on partly outdated toxicity information and should no longer be used in phthalate mixture risk assessments. Recently, Kortenkamp and Koch (2020) have derived new RfD_{AA}s for DBP, DIBP, BBP, DEHP and DINP (Table 2) and we employ these new values for our analysis of temporal trends of phthalate exposures in Germany.

As much as possible, the new RfD_{AA}s are based on effect doses for common endpoints of the phthalate syndrome, with the same effect magnitude (benchmark doses). This ensures consistency and removes some of the uncertainties inevitably introduced by the HI method through the mixing of reference doses based on different toxicity endpoints, effect magnitudes, species and varying uncertainty factors. The new values strike a balance between the need for consistency in terms of these principles and the requirement of realising a reasonable degree of protection. This was achieved by relying as much as possible on data related to suppression of foetal testicular testosterone synthesis, an effect common for many phthalates, including DIBP, BBP and DINP. For these three phthalates, other effects that make up the phthalate syndrome occurred at higher doses. However, in the case of DBP and DEHP, reliance on testosterone suppression would have been insufficiently protective, as effects that are also part of the phthalate syndrome (reduced spermatocyte development for DBP and mild dysgenesis of genitalia for DEHP), occur at lower doses than those necessary for producing suppressions of foetal testosterone synthesis. The data quality for these endpoints made it difficult to estimate benchmark doses for DBP and DEHP. For this reason, it was necessary to derive RfD_{AA}s from lowest-observed-adverse-effect-levels in these cases (Table 2). The details of derivation of the new RfD_{AA}s are described in Kortenkamp and Koch (2020).

Due to the need for accommodating the consistency required for mixture risk assessments, we wish to emphasise that the RfD_{AA} values

Table 2
Points-of-Departure (POD) and Reference Doses (RfD) for phthalate mixture risk assessments.

	POD (mg/kg/day)	UF	Adjustment	POD adjusted (mg/kg/day)	Revised RfD _{AA} (µg/kg/day)*	EFSA (2005a, 2005b, 2005c, 2005d) TDI (µg/kg/day)	Kortenkamp and Faust (2010) RfD _{AA} (µg/kg/day)
DBP	2 (LOAEL)	3	LOAEL - NOAEL	0.67	6.7	10	100
Endpoint	Spermatocyte development					Spermatocyte development	T suppression
Species	Rat					Rat	Rat
Reference	Lee et al., 2004					Lee et al., 2004	NRC, 2008
DIBP	10 (BMDL)	1		10	100	no value	200
Endpoint	T suppression						T suppression
Species	Rat						Rat
Reference	Hannas et al., 2011						NRC, 2008
BBP	1 (BMDL)	1		1	10	500	330
Endpoint	T suppression					AGD reduction	T suppression
Species	Rat					Rat	Rat
Reference	Furr et al., 2014					Tyl et al., 2004	NRC, 2008
DEHP	3 (LOAEL)	3	LOAEL - NOAEL	1	10	50	30
Endpoint	Dysgenesis of genitalia					Testicular toxicity	Nipple retention
Species	Rat					Rat	Rat
Reference	Christiansen et al., 2010					Wolfe and Layton, 2003	Christiansen et al., 2009
DINP	5.9 (BMDL)	1		5.9	59	150	1500
Endpoint	T suppression					Hepatic effects	T suppression
Species	Rat					Dog	Rat
Reference	Clewell et al., 2013						Gray et al., 2000

* with UF = 100 from adjusted POD

for all phthalates included in our mixture risk assessment may not be suitable for risk assessments with an orientation on single phthalates, as these may show low dose effects relating to endpoints other than those belonging to the phthalate syndrome.

2. Materials and methods

2.1. Provenance of urine samples

All 24-hour urine samples collected between 1988 and 2015 were from students of the University of Münster (Germany). For each year, samples from 30 males and 30 females were collected. In a few cases one or two samples were excluded for further analysis in order to maintain age consistency (age range 20–29 years). There were no statistically significant differences between males and females (Koch et al., 2017). We therefore did not stratify the analysis according to gender, and there was no need to exclusively focus on females, considering that the risk assessment concerns vulnerable periods in foetal life and women of reproductive age. Detailed information for all study years, together with ethical approvals are given by Koch et al. (2017).

2.2. Quantification of phthalate metabolites

The quantification of phthalate metabolites was carried out by on-line high-performance liquid chromatography and tandem mass spectrometry (HPLC-MS/MS) using internal isotope-labelled standards as described by Koch et al. (2017). Metabolite concentrations below the limit of quantification (LOQ) were set as LOQ/2. None of our analytical findings were sensitive to this decision. For the phthalates DIBP and DBP all samples had levels above the LOQ, for BBP 99.7% were above LOQ. With DEHP, all three oxidised metabolites showed levels above the LOQ, while the simple monoester MEHP was found above the LOQ in 96.3% of the samples. For DINP, all three oxidised metabolites were present at levels above the LOQ in 97.0 to 99.7% of the samples.

2.3. Estimation of daily intakes

For each study subject, we estimated daily intakes (DI) for DBP, DIBP, BBP, DEHP and DINP based on the urinary metabolite levels reported in Koch et al. (2017). We employed the reverse toxicokinetic model described by Koch et al. (2007). For DBP, DIBP and BBP the calculations utilized urinary concentrations of one metabolite, as follows:

$$DI_p \left[\frac{\mu\text{g}}{\text{kg bw} \times \text{day}} \right] = \frac{uc_m \left[\frac{\mu\text{g}}{\text{l}} \right]}{MW_m \left[\frac{\text{g}}{\text{mol}} \right]} \times \frac{MW_p \left[\frac{\text{g}}{\text{mol}} \right] \times uv \left[\frac{\text{l}}{\text{day}} \right]}{F_{ue} \times bw [\text{kg}]}$$

DI_p ($\mu\text{g}/\text{kg bw}/\text{day}$) is the daily intake of the unmetabolised parent phthalate, uc_m the urinary concentration of the metabolite (expressed as $\mu\text{g}/\text{l}$), MW_m the molecular weight of the metabolite (in g/mol), MW_p the molecular weight of the parent phthalate (in g/mol), uv the 24-hour urine volume (l/day), F_{ue} the molar urinary excretion factor for the metabolite, and bw the body weight of the study subject (in kg).

For DEHP and DINP we estimated the daily intake by considering a combination of several metabolites:

$$DI_p \left[\frac{\mu\text{g}}{\text{kg bw} \times \text{day}} \right] = \left(\frac{uc_{m1} \left[\frac{\mu\text{g}}{\text{l}} \right]}{MW_{m1} \left[\frac{\text{g}}{\text{mol}} \right]} + \frac{uc_{m2} \left[\frac{\mu\text{g}}{\text{l}} \right]}{MW_{m2} \left[\frac{\text{g}}{\text{mol}} \right]} \right) \times \frac{MW_p \left[\frac{\text{g}}{\text{mol}} \right] \times uv \left[\frac{\text{l}}{\text{day}} \right]}{\sum F_{ue(m1,m2)} \times bw [\text{kg}]}$$

Here, the subscripts m_1 and m_2 refer to the respective metabolites. The molar urinary excretion factors F_{ue} of all metabolites were summed. All parameters for calculation are given in Table 3.

2.4. Mixture risk assessment

For each study participant and year, we built risk quotients for DBP, DIBP, BBP, DEHP and DINP by division of estimated daily intakes by the revised RfD_{AA} values proposed by Kortenkamp and Koch (2020), Table 2:

$$RQ_p = \frac{DI_p \left[\frac{\mu\text{g}}{\text{kg bw} \times \text{day}} \right]}{RfD_{AA} \left[\frac{\mu\text{g}}{\text{kg bw} \times \text{day}} \right]}$$

For each study subject and year, we then calculated the HI_p by summing the RQ_p derived for each single phthalate:

$$HI_p = RQ_{DBP} + RQ_{DIBP} + RQ_{BBP} + RQ_{DEHP} + RQ_{DINP}$$

We further analysed the contribution of single phthalates to the sum of RQ by calculating the Maximum Cumulative Ratio (MCR) for each study subject. The MCR_p is the ratio of the HI_p and the RQ_p with the highest numerical value among RQ_{DBP} , RQ_{DIBP} , RQ_{BBP} , RQ_{DEHP} and RQ_{DINP} :

$$MCR_p = HI_p / RQ_{p,phthalate\ max}$$

For every study year, the MCR_p were then used to create scatter plots of MCR_p versus HI_p which yielded data points representing each study participant.

By creating these scatter plots of MCR_p versus HI_p several groupings can be distinguished (Fig. 1) which we have labelled following Price et al. (2012). While their labelling is not intuitive, we have adopted it here to align our work with several publications on MCR by Price and associates. Data points to the left of a vertical line demarcating an acceptable HI (commonly $HI = 1$, but values < 1 are possible, see Discussion) depict individuals who experienced combined exposures that do not present concerns (Region II). Conversely, data points to the right of that line show subjects who exceeded their acceptable combined exposures. These individuals fall into two separate categories: Data points that sit in the segment defined by the vertical line for acceptable HIs and the curved line depicting $MCR = HI$ signify individuals that have experienced unacceptable combined exposures without exceeding acceptable levels for any single phthalate (Region III). Conversely, data points to the right of the $MCR = HI$ line show study participants with phthalate exposures above acceptable levels for at least one phthalate (Region I). In turn, each of these three categories can be divided into two subgroups according to their MCR. Data points below the horizontal line corresponding to $MCR = 2$ show individuals where one phthalate contributed 50% or more to the HI (Regions Ia, IIa and IIIa). Above this line are subjects who experienced combined exposures where multiple phthalates contributed to the HI (Regions Ib, IIb and IIIb).

With these groupings, Price et al. (2012) identified the following risk management options: Regions I and III signal concerns as acceptable combined exposures are exceeded. For Regions Ia and IIIa these issues can be mitigated by targeting one phthalate with exposure reduction measures. The unacceptable exposures to several phthalates experienced by Region Ib subjects can be addressed by reducing exposures to several phthalates. In contrast, Region IIIb represents subjects with unacceptable risks which would have gone unnoticed during conventional single phthalate risk assessment and can only be addressed through cumulative risk assessment.

We also analysed the degree to which single phthalates drive cumulative exposures by preparing plots of $\log(MCR - 1)$ versus $\log HI$ (Reyes and Price 2018). Such plots are a convenient way of separating exposures where one phthalate contributed at least 50% to the combined exposures ($MCR \leq 2$; $\log(MCR - 1) < 0$) from those with more complex patterns. Study participants with $MCR > 2$ and falling into Regions Ib, IIb or IIIb are visualised by data points above the zero line in these plots.

Table 3
Parameters for the estimation of daily intakes (DI) from urinary phthalate metabolites.

Phthalate	Molecular weight [g/mol]	Specific metabolite	Molecular weight metabolite [g/mol]	Fue (molar excretion factor)	Sum of molar excretion factors, if more than one metabolite is considered
DBP	278.34	MBP	222.24	0.691 (24 h) ^{*1}	All 4 metabolites: 0.471
DIBP	278.34	MIBP	222.24	0.707 (48 h) ^{*2}	
BBP	312.36	MBzP	256.25	0.73 (24 h) ^{*1}	
DEHP	390.56	MEHP	278.34	0.063 (48 h) ^{*3}	
		5OH-MEHP	294.34	0.156 (48 h) ^{*3}	All 3 metabolites: 0.298
		5oxo-MEHP	292.33	0.113 (48 h) ^{*3}	
		5cx-MEPP	308.33	0.139 (48 h) ^{*3}	
DINP	418.61	cx-MINP	322.35	0.109 (48 h) ^{*3}	
		OH-MINP	308.37	0.123 (48 h) ^{*3}	
		oxo-MINP	306.36	0.066 (48 h) ^{*3}	

MBP: mono-n-butyl phthalate, MIBP: mono-iso-butyl phthalate, MBzP: mono benzyl phthalate, MEHP: mono(2-ethylhexyl) phthalate, 5OH-MEHP: mono(2-ethyl-5-hydroxy-hexyl) phthalate, 5oxo-MEHP: mono(2-ethyl-5-oxo-hexyl) phthalate, 5cx-MEPP: mono(2-ethyl-5-carboxy-pentyl) phthalate, cx-MINP: 7-Carboxy-(mono-methyl-heptyl) phthalate; OH-MINP: 7-OH-(Mono-methyl-octyl) phthalate, oxo-MINP: 7-Oxo-(Mono-methyl-octyl) phthalate, ^{*1}: Anderson et al., 2001, ^{*2}: Koch et al., 2012, ^{*3}: Anderson et al., 2011

3. Results

3.1. Daily intakes

Table 4 presents the daily intakes (DIs) estimated for DBP, BBP, DIBP, DEHP and DINP from 1988 to 2015. The period between 1988 and 1993 generally saw the highest exposures, with DBP and DEHP contributing most to the DIs. From then on, their DIs steadily declined. By 2015, the exposure patterns had changed markedly, with overall declines for all phthalates except DINP. In 2015, DINP and DEHP, but not DBP, were the most significant contributors. For each phthalate, there were specific changes, as follows:

In 1988, DBP was by far the most prominent phthalate, with DIs that in 1993 reached a peak of 42.3 µg/kg bw/day at the 95th percentile. After 1993, exposures began to decline steadily to a value of 0.92 µg/kg bw/day in 2015.

BBP had the highest DIs at the 95th percentile in the year 1996 (5.12 µg/kg bw/day) which fell to 0.63 µg/kg bw/day in 2015.

Similar to DBP, the DI of DEHP at the 95th percentile was highest between 1991 and 1996, with a maximum of 22.2 µg/kg bw/day in the year 1991. After 1996, it decreased to 3.07 µg/kg bw/day in 2015 (95th percentile).

The DI of DIBP increased until 1991, then entered a slow decline until it peaked at the 95th percentile in the years 2006 and 2008, with

9.23 and 8.78 µg/kg bw/day, respectively. Since then, exposures dropped to 1.64 µg/kg bw/day in 2015.

The DI of DINP at the 95th percentile was highest in 1998 (11.2 µg/kg bw/day) and then dropped to 3.7 µg/kg bw/day in 2015. Similar declining trends became apparent for the median DIs of all phthalates, except for DINP which showed an increasing tendency.

3.2. Hazard Index (HI) and Maximum Cumulative Ratio (MCR)

Table 5 presents the Hazard Indices, Risk Quotients and Maximum Cumulative Ratios for the years 1988 to 2015. The decreasing phthalate exposures led to declining HIs. After an initial rise from 1988 until 1993, the HIs dropped, both at the 95th percentile and as geometric means (Fig. 2a). This development can be attributed to the falling RQs for DBP and DEHP over time. By contrast, the RQs for the other phthalates fluctuated or even increased slightly (DINP) between 1988 and 2015 (Fig. 2b). As a result, the more recent HIs were driven by a greater number of phthalates, reflected in the slight upwards gradient of the regression lines of MCR versus study year (Fig. 2a).

Scatter plots of MCR_p versus HI_p for each year are presented in the Supplementary Material. They show clouds of data points which progressively shift leftwards towards lower HIs and upwards towards higher MCRs as the years advance. Here we focus on three years which mark key stages of the trajectory of changing phthalate exposures

Table 4
Daily Intakes [µg/kg bw/day] for 5 phthalates described with sample size n, range, median (P50 = 50th percentile) and P95 (95th percentile) for the years 1988–2015.

Year	n	DBP			BBP			DIBP			DEHP			DINP		
		Range	P50	P95	Range	P50	P95	Range	P50	P95	Range	P50	P95	Range	P50	P95
1988	60	0.72–27.8	6.97	22.9	0.01–6.58	0.25	0.76	0.26–6.02	1.09	3.44	0.99–52.1	4.89	12.1	0.09–3.29	0.30	1.93
1989	60	1.48–70.1	7.54	21.3	0.07–2.82	0.30	1.77	0.30–12.6	0.98	3.78	1.07–42.2	5.19	11.9	0.04–19.8	0.35	2.97
1991	60	2.13–28.7	6.42	14.2	0.11–2.84	0.43	1.54	0.35–19.7	1.21	8.31	1.46–29.8	5.08	22.2	0.07–30.9	0.33	5.62
1993	60	1.45–56.3	6.61	42.3	0.07–2.19	0.27	1.63	0.38–4.70	1.14	2.68	1.58–18.0	5.49	17.0	0.11–3.96	0.42	2.53
1996	145	1.05–90.2	3.68	15.1	0.04–27.3	0.29	5.12	0.43–28.3	1.54	7.90	0.91–38.3	4.53	16.9	0.09–5.24	0.51	2.46
1998	68	0.22–20.3	3.15	11.2	0.01–4.03	0.22	1.14	0.10–11.9	1.40	5.60	0.23–12.1	3.87	9.71	0.07–17.9	0.46	11.2
1999	60	0.83–32.8	2.77	15.5	0.03–10.9	0.21	3.49	0.40–14.7	1.46	4.12	1.29–18.5	3.46	10.7	0.05–4.81	0.50	2.65
2001	60	0.81–116	2.53	15.7	0.02–0.99	0.22	0.75	0.28–12.2	1.61	4.38	1.33–27.0	3.90	9.25	0.14–6.81	0.52	3.11
2002	57	0.71–121	2.47	5.69	0.08–2.31	0.27	1.38	0.43–4.42	1.23	3.58	1.67–22.1	3.63	7.29	0.03–11.9	0.94	2.37
2003	59	0.49–71.8	1.87	5.08	0.05–1.74	0.22	0.86	0.44–5.11	1.34	3.59	0.96–9.36	2.93	7.25	0.13–4.90	0.61	2.21
2004	58	0.50–56.2	1.54	4.51	0.07–6.51	0.24	0.74	0.37–3.43	1.04	2.58	1.28–17.8	3.52	13.7	0.17–9.59	0.84	3.00
2006	57	0.31–4.99	1.31	3.30	0.08–0.76	0.16	0.53	0.45–14.6	1.24	9.23	1.22–7.45	3.00	7.01	0.11–7.52	1.08	7.15
2007	60	0.13–2.52	0.74	1.61	0.02–1.90	0.14	0.79	0.21–10.1	0.93	3.62	0.47–47.6	2.44	12.0	0.08–6.89	0.55	4.57
2008	54	0.45–4.81	1.03	2.52	0.01–0.65	0.18	0.55	0.52–14.0	1.27	8.78	0.72–7.16	2.43	5.18	0.16–12.	1.24	6.01
2009	60	0.09–1.88	0.88	1.76	0.02–1.36	0.15	0.84	0.30–3.88	0.99	2.77	0.55–21.1	2.06	7.94	0.07–13.7	0.69	3.59
2011	60	0.21–1.83	0.64	1.29	0.02–2.29	0.13	0.55	0.37–6.59	0.88	2.00	0.50–4.47	1.54	3.16	0.19–34.9	0.72	4.47
2013	60	0.11–2.67	0.53	1.01	0.02–0.82	0.09	0.47	0.14–3.29	0.74	1.75	0.13–4.64	1.29	2.99	0.04–9.86	0.74	2.09
2015	60	0.07–0.97	0.43	0.92	0.01–5.15	0.05	0.63	0.11–33.0	0.47	1.64	0.35–15.6	0.95	3.07	0.23–10.1	0.57	3.70

Table 5
Hazard Indices, Maximum Cumulative Ratios (MCR) and Risk Quotients for single phthalates for the years 1988 to 2015.

Year	n	% female	Hazard Index		MCR		Risk quotient for single phthalate									
			GM*	P95	GM	P95	DEHP		DBP		DIBP		BBP		DINP	
							GM	P95	GM	P95	GM	P95	GM	P95	GM	P95
1988	60	50	1.71	4.39	1.52	1.94	0.52	1.19	1.04	3.02	0.01	0.03	0.03	0.08	0.01	0.03
1989	60	50	1.76	4.27	1.56	2.02	0.52	1.15	1.10	3.06	0.01	0.03	0.03	0.09	0.01	0.04
1991	60	50	1.67	3.67	1.65	2.05	0.56	1.90	0.95	2.09	0.01	0.08	0.04	0.15	0.01	0.05
1993	60	50	1.84	7.50	1.56	1.98	0.57	1.60	1.11	5.71	0.01	0.03	0.03	0.10	0.01	0.04
1996	145	47	1.32	4.59	1.75	2.14	0.54	1.69	0.62	2.14	0.02	0.08	0.04	0.42	0.01	0.04
1998	68	44	0.98	2.37	1.75	2.15	0.38	1.00	0.49	1.56	0.02	0.06	0.03	0.08	0.01	0.16
1999	60	50	0.94	3.11	1.75	2.16	0.36	0.99	0.47	2.10	0.02	0.04	0.03	0.30	0.01	0.04
2001	60	50	0.99	3.11	1.72	2.14	0.39	0.86	0.46	1.25	0.02	0.04	0.02	0.07	0.01	0.04
2002	57	47	0.89	1.63	1.81	2.17	0.37	0.75	0.39	0.83	0.01	0.04	0.03	0.10	0.02	0.04
2003	59	49	0.69	1.29	1.79	2.17	0.31	0.71	0.29	0.68	0.01	0.03	0.02	0.08	0.01	0.04
2004	58	48	0.70	1.93	1.73	2.12	0.36	1.20	0.25	0.56	0.01	0.03	0.02	0.06	0.02	0.05
2006	57	49	0.57	1.12	1.85	2.31	0.28	0.63	0.21	0.48	0.02	0.05	0.02	0.05	0.02	0.11
2007	60	50	0.44	1.29	1.60	2.33	0.27	1.20	0.10	0.23	0.01	0.03	0.01	0.06	0.01	0.07
2008	54	46	0.48	0.82	1.80	2.25	0.24	0.52	0.15	0.38	0.01	0.04	0.02	0.05	0.02	0.10
2009	60	50	0.39	1.00	1.78	2.28	0.21	0.60	0.12	0.25	0.01	0.03	0.02	0.08	0.02	0.05
2011	60	50	0.30	0.62	1.87	2.27	0.15	0.29	0.09	0.17	0.01	0.02	0.01	0.05	0.02	0.07
2013	60	50	0.25	0.54	1.87	2.26	0.13	0.29	0.08	0.15	0.01	0.02	0.01	0.04	0.01	0.04
2015	60	50	0.21	0.55	1.88	2.51	0.10	0.28	0.06	0.13	0.01	0.02	0.01	0.06	0.01	0.07

* Geometric mean.

(Fig. 3): The pollution peak in 1993, compliance with acceptable levels for single phthalates but exceedance of combined exposures with HI > 1 (2006), and finally general compliance with HI = 1 (2011).

In 1993, most of the study population exceeded acceptable combined exposures; some participants even reached HIs close to 10. Furthermore, the exposures of over half of the participants also did not comply with the acceptable levels for at least one phthalate, as is apparent from the cloud of data points to the right of the line depicting MCR = HI. Exposures in excess of acceptable levels for DBP, and to a lesser degree to DEHP, were drivers of this situation. Strikingly

however, no participant showed MCRs larger than 2. For all study subjects, at least 50% of the HI were attributable to only 1 phthalate, in most cases DBP. Thus, in 1993, risks from phthalates could have been significantly reduced by diminishing exposures to DBP. As shown in the [Supplementary Material](#), the years between 1993 and 1999 showed similar characteristics.

The period after 1999 is characterised by a shift towards lower HIs and higher MCRs, until in 2006 no study participant experienced exposures that exceeded acceptable levels for a single phthalate (indicated by the absence of data points to the right of the MCR = HI line, Fig. 3).

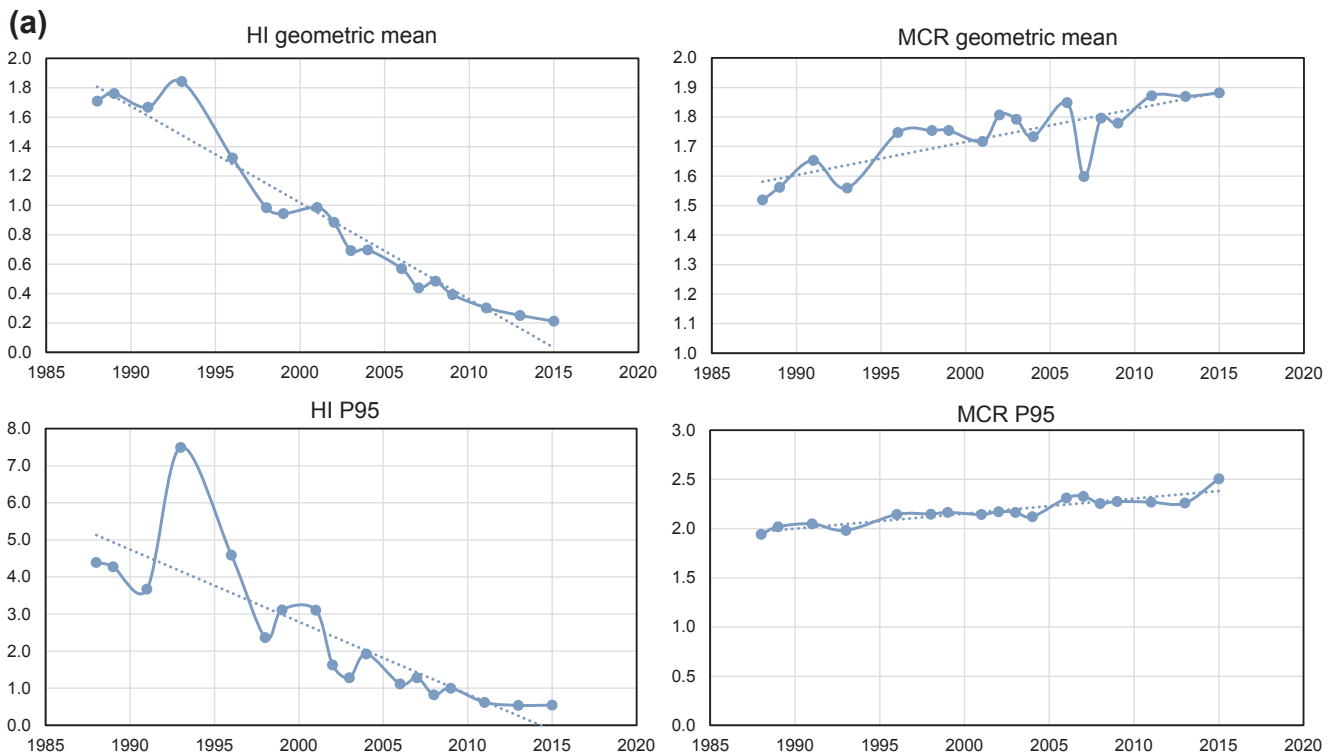


Fig. 2a. Temporal trends for Hazard Index and Maximum Cumulative Ratio 1988–2015. Trends for HI and MCR, with box plots showing the geometric mean and the 95th percentile.

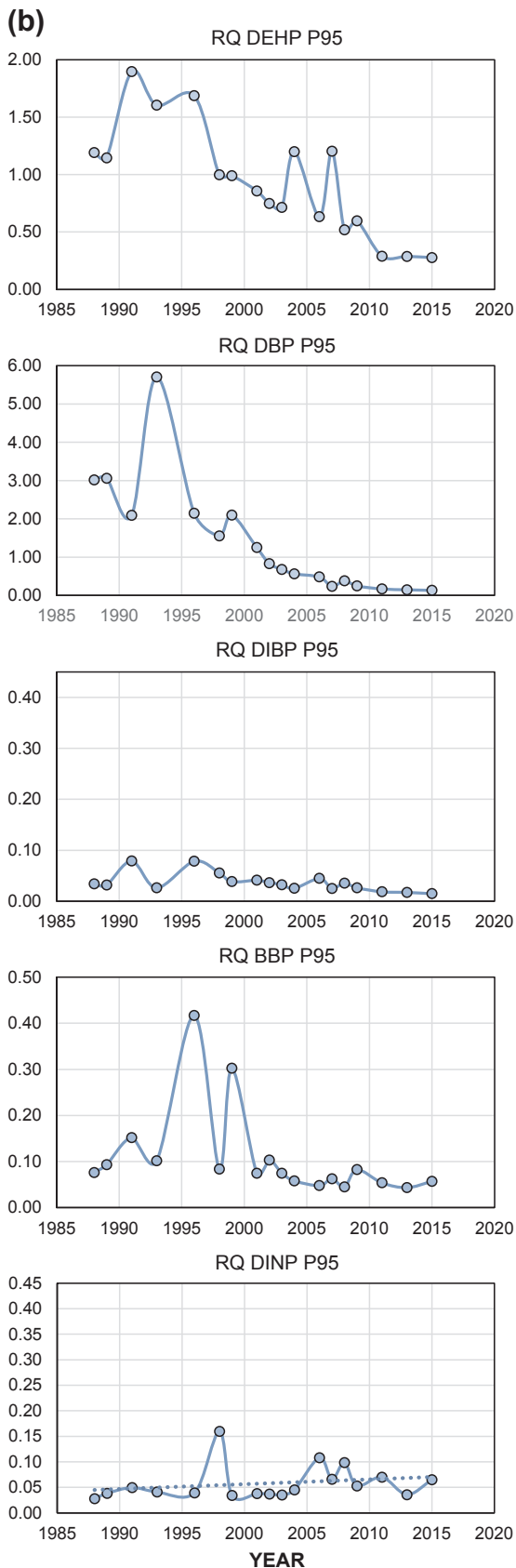


Fig. 2b. Temporal trends for single phthalate Risk Quotients 1988-2015. Trends for single DEHP, DBP, DIBP, BBP, and DINP Risk Quotients, with box plots showing the 95th percentile.

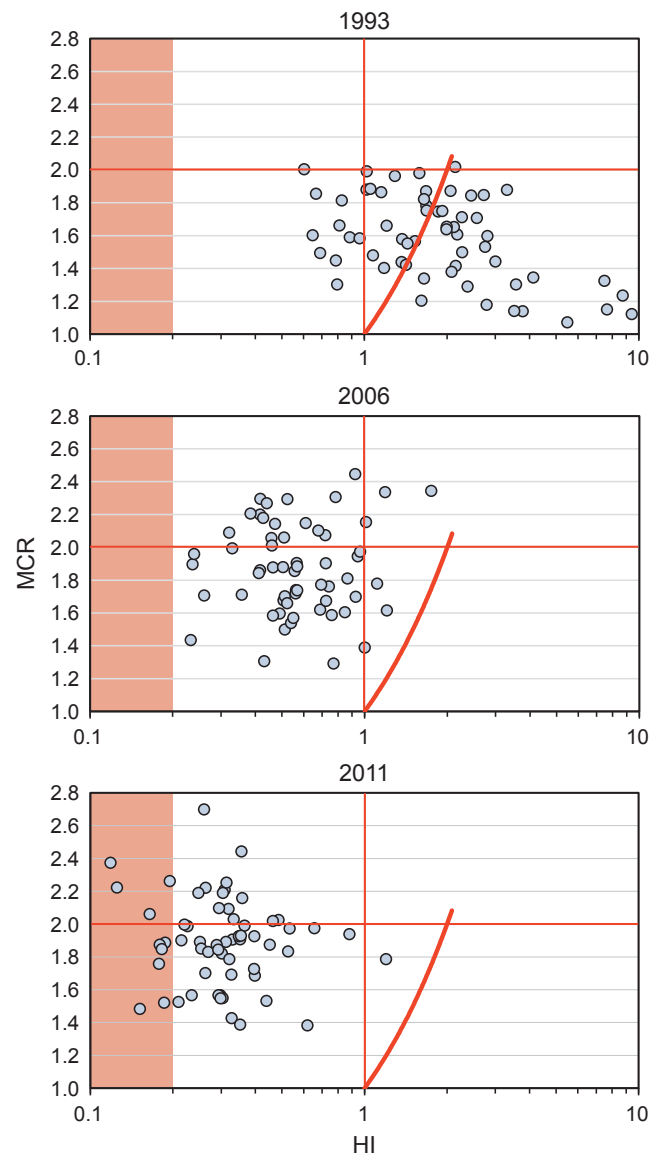


Fig. 3. Analysis of combined phthalate exposures with MCR versus HI scatter plots for 1993, 2006 and 2011. The results for individual study participants are shown as blue dots. The vertical red line shows HI = 1, the horizontal red line is for MCR = 2. The curved red line depicts MCR = HI. The red box in each plot shows the range of HI between 0.1 and 0.2 as suggested values for evaluation of combined phthalate exposures that can accommodate substances also contributing to male reproductive risks.

However, in 2006, 7% of all subjects still exceeded combined exposures of HI = 1. In continuation of the developments that set in after 1993, a significant number of data points appeared above the MCR = 2 line. For these participants combined risks are no longer due to only one phthalate as the main contributor to the HI. Of particular concern are those subjects in 2006 who fall above the MCR = 2 line, to the right of the vertical HI = 1 line and to the left of the curved line MCR = HI. These individuals experienced unacceptable combined exposures that would have gone unnoticed in traditional single phthalate risk assessment. At the same time, they could also not have been protected by controlling exposure to one single phthalate.

By 2011, the lower exposures to DBP and DEHP that produced the shift towards smaller HIs and larger MCRs after 1993 culminated in a situation where most subjects stayed below combined acceptable phthalate exposures; only one individual exceeded HI = 1. The remainder of participants showed HIs between 0.1 and 1. A significant

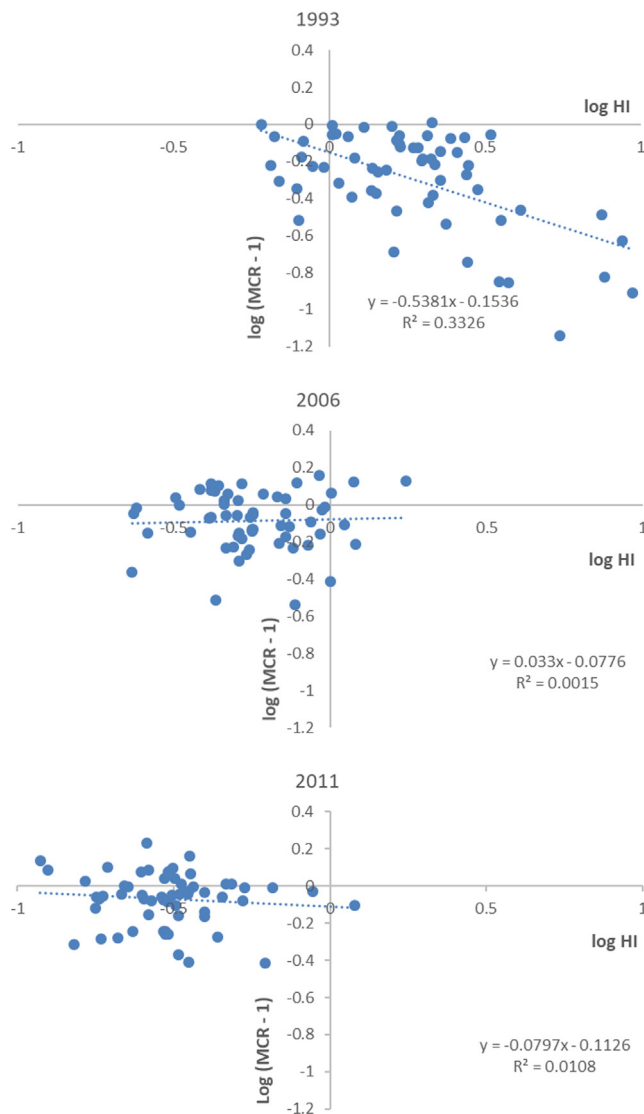


Fig. 4. Plots of $\log(\text{MCR}_p - 1)$ versus $\log \text{HI}_p$ for 1993, 2006 and 2011. Results for individual study participants are represented by dots, together with the best fitting linear regression line.

proportion of subjects experienced increasingly diverse phthalate exposures, as indicated by the large number of data points above the $\text{MCR} = 2$ line, with some reaching MCRs between 2.4 and 2.6. These trends continued in 2015, with the largest MCR around 3, reflecting an increased diversity of the combined exposures.

To further analyse the degree by which single phthalates have driven cumulative exposures during the years between 1988 and 2015, we investigated correlations between MCR and HI by preparing plots of $\log(\text{MCR} - 1)$ versus $\log \text{HI}$ (Reyes and Price, 2018). During the pollution peak in 1993, increasing HI_p were associated with decreasing MCR_p (Fig. 4). This correlation disappeared in 2006 and 2011. However, as depicted in the graphs in the Supplementary Material, these study years were an exception. In almost all other years there was an inverse relationship between MCR and HI, demonstrating that subjects with high combined exposures tended to experience relatively large exposures to a smaller number of phthalates. Conversely, study participants with relatively low combined phthalate exposures showed more complex exposure patterns.

4. Discussion

4.1. Changes in the regulatory landscape as a contributory factor to changing exposure patterns

Our analysis shows that declines in phthalate exposures in the German Environmental Specimen Bank study population became noticeable already at the end of the 1980s, with corresponding decreases in the HIs. The continuation of the initial declines was supplanted by a curious pollution peak around 1993, but after this episode HIs diminished year on year, which might be firstly attributable to the rating of some phthalates as priority substances according to Council Regulation (EEC) No 793/93 of 23 March 1993 on the evaluation and control of the risks of existing substances. A further reason for an altered production and usage of specific phthalates might be the Commission Decision 1999/815/EC of December 1999 on adopting measures prohibiting the placing on the market of toys and childcare articles intended to be placed in the mouth by children under three years of age and made of soft PVC containing one or more of the substances DEHP, DBP, BBP, DINP, DIDP, and DOP. Although this decision was restricted to special toys only and was initially temporary, it can be assumed that there was increasing awareness of risks associated with the use of the respective phthalates. After multiple renewals the more general Directive 2005/84/EC came into force. From 2006 onwards, the Directive restricts the use of DEHP, DBP, and BBP in all toys and childcare articles with a concentration limit of 0.1% by weight (entry 51 of Annex XVII to REACH). DINP, DIDP, and DOP have only been restricted in toys that can be taken into the mouth (0.1% mass percent of the plasticised part of the toy, entry 52 of Annex XVII to REACH). Additionally, Commission Directive 2004/93/EC led to a ban on DEHP and DBP in cosmetics from 2005 onwards. In 2011 then, restrictions followed in food contact materials (Commission Regulation (EU) No 10/2011 of 14 January 2011).

Due to the classification as reproductive toxicants, category 1B, under Annex VI to the Classification, Labelling and Packaging of substances and mixtures (CLP) regulation ((EC) No 1272/2008 and amendments) DEHP, DBP, DIBP, and BBP are substances of very high concern and were added via the Candidate List of Substances for Authorisation under REACH (in 2008/2009) to the Authorisation List (Annex XIV) in 2012. This means that from February 2015 they are not allowed to be produced in the EU unless authorisation has been granted for a specific use, however they still may be imported in consumer products. Further efforts for restriction of DEHP, DBP, DIBP, and BBP in products have already been initiated (COMMISSION REGULATION (EU) 2018/2005 of 17 December 2018 amending Annex XVII to Regulation (EC) No 1907/2006).

Considering that the main route of exposure to medium- and long chain phthalates is via food (Koch et al., 2013; Correia-Sá et al., 2018; Giovanoulis et al., 2018; Husøy et al., 2019), lifestyle changes could also have played a role. But these are possibly of minor importance, as the prevalence of phthalates in food items is not immediately obvious to the consumer, making rational choices for individual avoidance behaviour difficult. It seems that political pressure and the anticipation of regulatory action has played a dominant role in substitution decisions by industry, but only where it was possible to replace the more toxic DBP and DEHP with alternative phthalates or non-ortho-phthalate substitutes. The increasing trends in DINP exposures seen here and in DINCH and DEHTP exposures observed by us and others (Gyllenhammer et al., 2017; Silva et al., 2017; Kasper-Sonnenberg et al., 2019; Lessmann et al., 2019) strongly point in this direction.

Although the use of different RfDs in constructing RQs complicates direct comparisons with our values, similar trends were seen in the USA (Reyes and Price, 2018; Zota et al., 2014). This suggests that the changes we observed took place beyond the EU and are relevant internationally.

4.2. Changing exposure patterns and Maximum Cumulative Ratio

The rather high HIs experienced by study subjects in the earlier years of our time series study could have been lessened by reducing exposures to a single phthalate, DBP. The rather low MCR values, especially among subjects with high HIs to the right of the $MCR = HI$ line in Fig. 3, indicate that the main issue was exceedance of acceptable exposures to a single phthalate (DBP and, to a lesser degree, DEHP). But even with MCR values as low as 1.2 to 1.4, the combined exposures missed by neglecting to conduct a mixture risk assessment are between 17 and 30%.

The high exposures that characterised the decade from 1988 to about 1999 fuel concerns about adverse health effects in males born during this time. Only from 2011 onwards was a situation reached where most individuals did not experience phthalate exposures in excess of $HI = 1$. It will be timely to confirm or refute these concerns in epidemiological studies.

The declining DIs of DBP and DEHP led to a development characterised by an increasing complexity of combined phthalate exposures. The consequence are lower HIs but with correspondingly increasing MCRs. This becomes obvious from a leftward and upward shift of the data clouds in MCR versus HI plots as the years advance (Fig. 3 and Supplementary Material). As shown by the inverse relationship between MCR and HI, the high combined phthalate exposures experienced by some study participants tended to be attributable to a relatively small number of phthalates. Most of the gradients in the $\log(MCR - 1)$ versus $\log HI$ plots (-0.2 to -0.6) were similar to those reported for NHANES data (Reyes and Price 2018). It would seem that the emerging exposure patterns will become more and more difficult to manage as any attempt to reduce risks further cannot be achieved other than by targeting multiple phthalates.

4.3. Exposures to other anti-androgens, beyond phthalates

With a focus on 5 phthalates, our analysis is limited as it can only capture a fraction of the potential risks to male reproductive health. First, there are other phthalates, such as DIDP or the linear or branched side chain pentyl and hexyl phthalates that could also contribute to risks. Furthermore, experimental evidence shows that phthalates produce combination effects with a wide variety of other substances also capable of interfering with hormone action (reviewed by Kortenkamp, 2020; Howdeshell et al., 2017). These include androgen receptor antagonists (certain dicarboximide pesticides, parabens, bisphenol A), chemicals that inhibit steroidogenic and steroid-converting enzymes (certain imidazole and phenylurea pesticides, and the drug finasteride), substances interfering with the transport of androgen precursors (lipid-lowering drugs), and those capable of disrupting prostaglandin signaling by inhibition of Cox enzymes (certain analgesics including paracetamol and a wide variety of phenolic substances). Polychlorinated dioxins and biphenyls also contribute to risks via poorly defined pathways. Thus, common adverse outcomes overlapping with the effect spectrum of the phthalate syndrome can be induced through multiple interacting and converging pathways that involve numerous chemicals with diverse structural features. Human exposure to many of these substances is as widespread and common as to phthalates (Kortenkamp, 2020).

4.4. Risk assessment options for dealing with co-exposures to other anti-androgens

This evidence calls for caution in applying a $HI = 1$ as the benchmark for evaluating the outcome of phthalate mixture risk assessments. $HI = 1$ leaves no room for co-exposures to other substances that also disrupt the normal development of the male reproductive system. Evaluating combined phthalate exposures against $HI = 1$ tacitly assumes that phthalates are emitted into a pristine environment with no

background exposure to other chemicals that also contribute to disruptions of male reproductive health. This is clearly not the case.

There are two options for dealing with this situation. First, a more comprehensive mixture risk assessment that includes the substances also contributing to combined exposures could be conducted. However, this requires the assembly of adequate exposure data and the derivation of reference doses for use in the HI approach, a task well beyond the scope of this paper, but which is tackled within the framework of the European Initiative HBM4EU under work package 15 (<https://www.hbm4eu.eu/>).

Alternatively, combined phthalate exposures could be evaluated against a lowered HI, in recognition of the fact that the “risk cup” for male reproductive disorders is not solely made up by phthalates. The question is what should be regarded as an acceptable HI and to what degree the $HI = 1$ should be lowered.

An answer to this question requires knowledge of the number of chemicals, apart from phthalates, that also contribute to male reproductive risks, together with the relative contribution of each corresponding RQ to the HI. However, this information is currently not available. Thus, the choice of an acceptable HI below 1 is at present arbitrary. Even so, informed guesses can be made. Considering that in addition to the group of phthalates as a whole at least 10 further substances are likely to contribute to the combined exposures (Kortenkamp, 2020), it is not unrealistic to assume that phthalates alone make up 10% of the exposure of the entire risk cup. Accordingly, the group of phthalates alone would have to be evaluated using a lowered HI of 0.1. If however some of the non-phthalates with anti-androgenic properties make a disproportionately large contribution to the HI, while others add little, the phthalate share of the risk cup could increase to perhaps 20%. In this case, the HI of phthalates alone would have to be evaluated against a less stringent value of 0.2.

We emphasise that these considerations are speculative, but not implausible. They are equivalent to proposals of Mixture Assessment Factors of 10 by the Swedish KEMI (2015) and the Dutch RIVM (van Broekhuizen et al., 2016) and agree with very recent recommendations of a Swedish Government enquiry into how to improve the group-wise management of hazardous chemicals (Swedish Government Enquiries 2019). We therefore recommend 0.1 to 0.2 for the assessment of phthalate exposures until more information about exposures to other anti-androgens becomes available that allows upwards revisions of this value.

Evaluated against these lowered HIs of 0.1–0.2, the combined phthalate exposures of most study participants exceed levels that can be regarded as acceptable. This gives reason to continue monitoring potential exceedances of health-based guidance values in order to provide the basis for appropriate risk management measures.

CRedit authorship contribution statement

Petra Apel: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Andreas Kortenkamp:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Visualization. **Holger M. Koch:** Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Visualization. **Nina Vogel:** Formal analysis. **Maria Rùthers:** Data curation, Writing - review & editing. **Monika Kasper-Sonnenberg:** Investigation, Validation. **Andre Conrad:** Formal analysis. **Thomas Brüning:** Funding acquisition, Resources, Supervision. **Marika Kolossa-Gehring:** Project administration, Conceptualization, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105467>.

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