TEMPLATE

for third party submission of information on alternatives for

Applications for Authorisation

NON-CONFIDENTIAL

Legal name of submitter(s): *Health and Environment Alliance (HEAL)*

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1. ALTERNATIVE ID AND PROPERTIES

The identification of an alternative that is only a substance as opposed to a material or technique is a central contention of this application. The applicant says

"Whilst a flexible PVC processor producing plastic articles could potentially consider a different plastic material to flexible PVC as a potential alternative, for the applicant, a chemical manufacturer, an alternative material (or technique) cannot be a technically or economically feasible alternative. Alternative materials, which could act as replacements to DEHP plasticised PVC are alien to the technical capabilities of the applicant and have not been considered;
And
Whilst the applicant could theoretically consider and potentially implement the manufacture of an alternative substance, the production of a range of alternative substances would be profoundly unfeasible from a practical and economic perspective and thus it has not been considered in this AoA (further justification for this approach is provided in Section 3.1)."

This is a completely tautological argument: in essence saying they won't consider alternative materials / designs, because they make only the one substance that has multiple uses; so the multiple uses must continue to be made by using a single plasticizer that works for all uses, and that doesn't cost differently to that substance.

The REACH legal text aims to promote safer alternatives for specific uses, whether materials, processes, designs or substances. REACH does allows applications for more than one use, but this applicant is using the argument of being a chemical manufacturer to avoid addressing the issue that a wide range of different consumer articles are made from the DEHP-plasticised PVC. In arguing that this chemical manufacturer can only have a single alternative that fulfils the all very same functions as DEHP for plasticising PVC, at an equivalent economic cost, it is tantamount to asking for an authorisation for business as usual, the examination of the various alternative plasticizers notwithstanding.

2. TECHNICAL FEASIBILITY

[Insert text here]

3. ECONOMIC FEASIBILITY

[Insert text here]

4. HAZARDS AND RISKS OF THE ALTERNATIVE

[Insert text here]

Given that the Chemical Safety Report which would reveal the purported risks for this substance was not available in this public consultation, it is impossible to give meaningful and constructive comments on the hazards and risks of the alternative that compare and contrast the risks of the applied-for substance. As such, the confidentiality constraints of this public consultation defeat some of the purpose of this public consultation.

5. AVAILABILITY

[Insert text here]

6. CONCLUSION ON SUITABILITY AND AVAILABILITY OF THE ALTERNATIVE

[Insert text here]

7. OTHER COMMENTS

Unproven assertion of adequate control
The applicant says

> "The CSR accompanying this AfA demonstrates adequate control - based on very conservative assumptions, exposure to DEHP is below the effect threshold (it should be noted that the recent RAC derived no-effect level document for DEHP has been taken into consideration. This is addressed further in the CSR). Therefore, the risks associated with the endpoint of concern, reproductive toxicity, (as well as other human health endpoints and the environment) are adequately controlled. Consequently, the use of any alternative (whether commercially proven or not) would not result in a discernible benefit to human health or the environment."

However, because the CSR is confidential and NOT available in the public consultation, it is impossible to make a meaningful contribution – whether critique or confirmation of the above statement, which becomes without the CSR purely an ASSERTION in the confines of this public consultation. As such, the statement

> "The CSR demonstrates that there is no risk from exposure to DEHP for Industrial/professional workers and to consumers. The risks are adequately controlled"

is in the absence of the levels of exposure and the total volumes of the substance, and any references to the scientific studies on which the judgements about risk are made, without merit.

The exposures arising from DEHP
It is generally recognised on the basis of the totality of human biomonitoring studies, that the general population all over Europe is widely exposed to multiple phthalates, including DEHP. The recent European Union co-financed research project on exposures COPHES/DEMOCOPHES demonstrated, however, that unanticipated and large variations in exposures to phthalates between different countries existed. *(Ref 1).* As a consequence, without significant and extensive biomonitoring data, any judgements on exposure of industrial workers, professional users, and most

especially consumers, are replete with significant uncertainties. It is possible that some sub-populations are above the risk characterisation ratios which have been calculated to date.

The applicant says in the summary of exposure scenarios:

"In addition to biomonitoring data, modelling of exposure from PVC products was also carried out in order to reflect exposure from all considered consumer articles under all circumstances. This step was performed to show that for consumers, even (and also) under very conservative modelling assumptions, there is no risk of exposure and there is therefore adequate control."

In combination with the above-noted points on the unknown and possibly highly variable exposures in the European population, it is important to note that recent science on phthalates exposure and on potential negative health effects, particularly for children covers a wide range of issues, for example, preterm birth, early puberty, attention deficit disorder and learning disabilities, and other disorders which derive from effects that have their origins in the reproductive stage. (Please see appendix, which has just taken a selection of recent articles). Considering these studies, it is therefore extremely doubtful whether this application, particularly via its exposure scenarios as part of the Alternatives Assessment, has satisfactorily proven 'adequate control' for the risks, and that any negative health and environmental impacts can be excluded.

REFERENCES

1) *EU Biomonitoring, Democophes,* http://www.eu-hbm.info/democophes

See also http://www.eu-hbm.info/euresult/media-corner/press-kit *and*

http://www.eu-hbm.info/euresult/democophes-short-technical-report

The national reports are available via the Member State project partners:

http://www.eu-hbm.info/democophes/project-partners

APPENDIXES

PHTHALATES AND PERFLUOROOCTANESULFONIC ACID IN HUMAN AMNIOTIC FLUID: TEMPORAL TRENDS AND TIMING OF AMNIOCENTESIS IN PREGNANCY

1.1 Abstract

Background: Measures of prenatal environmental exposures are important, and amniotic fluid levels may directly reflect fetal exposures during hypothesized windows of vulnerability.

Objectives: We aimed to detect various phthalate metabolites and perfluorooctanesulfonic acid (PFOS) in human amniotic fluid, to study temporal exposure trends, and to estimate potential associations with gestational week of amniocentesis and maternal age and parity at amniocentesis.

Methods: We studied 300 randomly selected second-trimester amniotic fluid samples from a Danish pregnancy-screening biobank covering 1980 through 1996. We used only samples from male offspring pregnancies. We assayed the environmental pollutants by liquid chromatography/triple quadrupole mass spectrometry and analyzed data using generalized linear regression models.

Results: We detected the di(2-ethylhexyl) phthalate (DEHP) metabolite mono(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP) at a median concentration of **0.27 ng/mL** [interquartile range (IQR): 0.20–0.37 ng/mL], the diisononyl phthalate (DiNP) metabolite mono(4-methyl-7-carboxyheptyl) phthalate (7cx-MMeHP) at 0.07 ng/mL (IQR: 0.05–0.11 ng/mL), and PFOS at 1.1 ng/mL (IQR: 0.66–1.60 ng/mL). An increase of 1 calendar year was associated with 3.5% lower [95% confidence interval (CI): –4.8%, –2.1%] 5cx-MEPP levels and with 7.1% higher (95% CI: 5.3%, 9.0%) 7cx-MMeHP levels. For each later gestational week of amniocentesis, 5cx-MEPP was 9.9% higher (95% CI: 4.8%, 15.2%), 7cx-MMeHP was 8.6% higher (95: CI: 2.7%, 14.9%), and PFOS was 9.4% higher (95: CI: 3.3%, 15.9%). We observed no associations with maternal age or parity.

Conclusions: **Measured metabolite levels appeared to parallel decreasing DEHP exposure and increasing DiNP exposure during the study period. The environmental pollutant levels were positively associated with later gestational age at amniocentesis during pregnancy weeks 12–22.**

http://dx.doi.org/10.1289/ehp.1104522

ESTIMATED DAILY INTAKE AND HAZARD QUOTIENTS AND INDICES OF PHTHTALATE DIESTERS FOR YOUNG DANISH MEN

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Environ. Sci. Technol., 2014, 48 (1), pp 706–712

DOI: 10.1021/es402569k

Publication Date (Web): November 14, 2013

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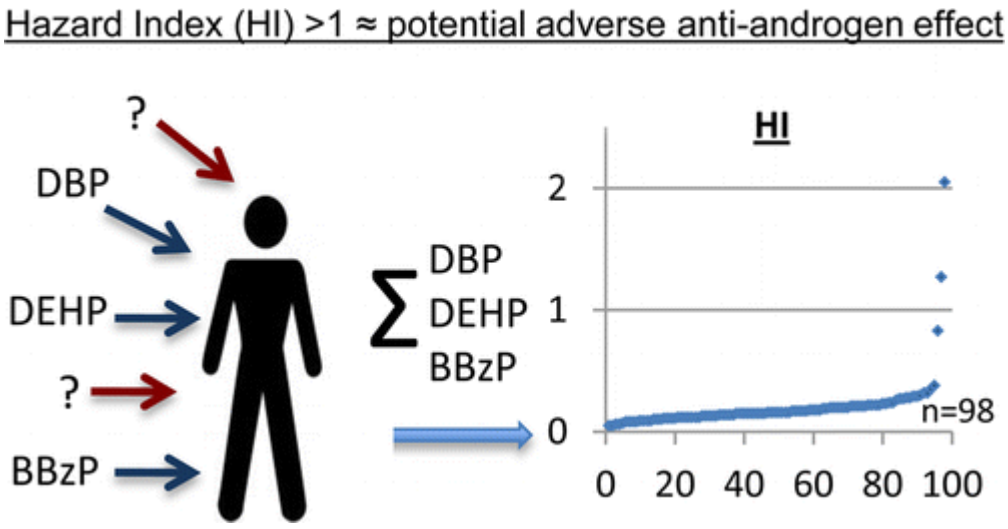
1.2 Abstract



Because of wide exposure to phthalates, we investigated whether simultaneous exposure to several phthalates reached levels that might cause adverse antiandrogenic effects. Thirty three healthy young Danish men each delivered three 24-h urine samples during a three months period. The daily intakes of the sum of di-*n*-butyl and di-iso-butyl phthalate, di(2-ethylhexyl) phthalate, di-iso-nonyl phthalate, and butylbenzyl phthalate were estimated based on urinary excretion of the metabolites. Based on a hazard quotient (HQ) of the individual phthalate (i.e., the ratio between the daily intake and an acceptable level of exposure), a hazard index (HI) for each man was calculated as the sum of HQs for the individual phthalates. All men were exposed to all phthalates during the urine collection periods. Median HIs were all below 1 (i.e., below an acceptable cumulative threshold) ranging from 0.11 to 0.17 over the three different sample collections. Of the 33 men, 2 men had HIs above 1 in one of their three samples, indicating that occasionally the combined exposure to the investigated phthalates reached a level that may not be considered safe. Besides the phthalates investigated here, humans are exposed to numerous other chemicals that also may contribute to a cumulative antiandrogenic exposure.

ENVIRONMENTAL PHTHALATE EXPOSURE AND PRETERM BIRTH

Kelly K. Ferguson, MPH[1]; Thomas F. McElrath, MD, PhD[2]; John D. Meeker, ScD[1]

[+] Author Affiliations

JAMA Pediatr. 2014;168(1):61-67. doi:10.1001/jamapediatrics.2013.3699.

1.3 ABSTRACT

ABSTRACT | METHODS | RESULTS | DISCUSSION | ARTICLE INFORMATION | REFERENCES

Importance Preterm birth is a leading cause of neonatal mortality, with a variety of contributing causes and risk factors. Environmental exposures represent a group of understudied, but potentially important, factors. Phthalate diesters are used extensively in a variety of consumer products worldwide. Consequently, exposure in pregnant women is highly prevalent.

Objective To assess the relationship between phthalate exposure during pregnancy and preterm birth.

Design, Setting, and Participants This nested case-control study was conducted at Brigham and Women's Hospital, Boston, Massachusetts. Women were recruited for a prospective observational cohort study from 2006-2008. Each provided demographic data, biological samples, and information about birth outcomes. From within this group, we selected 130 cases of preterm birth and 352 randomly assigned control participants, and we analyzed urine samples from up to 3 time points during pregnancy for levels of phthalate metabolites.

Exposure Phthalate exposure during pregnancy.

Main Outcomes and Measures We examined associations between average levels of phthalate exposure during pregnancy and preterm birth, defined as fewer than 37 weeks of completed gestation, as well as spontaneous preterm birth, defined as preterm preceded by spontaneous preterm labor or preterm premature rupture of the membranes (n = 57).

Results Geometric means of the di-2-ethylhexyl phthalate (DEHP) metabolites mono-(2-ethyl)-hexyl phthalate (MEHP) and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), as well as mono-*n*-butyl phthalate (MBP), were significantly higher in cases compared with control participants. In adjusted models, MEHP, MECPP, and Σ DEHP metabolites were associated with significantly increased odds of preterm birth. When spontaneous preterm births were examined alone, MEHP, mono-(2-ethyl-5-oxohexyl) phthalate, MECPP, Σ DEHP, MBP, and mono-(3-carboxypropyl) phthalate metabolite levels were all associated with significantly elevated odds of prematurity.

Conclusions and Relevance Women exposed to phthalates during pregnancy have significantly increased odds of delivering preterm. Steps should be taken to decrease maternal exposure to phthalates during pregnancy.

http://archpedi.jamanetwork.com/article.aspx?articleid=1769137

1.4 Urinary phthalates linked to early puberty in boys

ACTUAL Pub Med http://www.ncbi.nlm.nih.gov/pubmed/23824423

URINARY PHTHALATES FROM 168 GIRLS AND BOYS MEASURED TWICE A YEAR DURING A 5-YEAR PERIOD: ASSOCIATIONS WITH ADRENAL ANDROGEN LEVELS AND PUBERTY.

Mouritsen A, Frederiksen H, Sørensen K, Aksglaede L, Hagen C, Skakkebaek NE, Main KM, Andersson AM, Juul A.

1.4.1 Abstract

1.4.1.1 BACKGROUND:

Little is known about the possible deleterious effects of phthalate exposure on endogenous sex steroid levels in children.

1.4.1.2 OBJECTIVE:

Our objective was to investigate whether urinary phthalate metabolite levels are associated with circulating adrenal androgen levels and age at puberty.

1.4.1.3 METHODS:

This was a longitudinal study of 168 healthy children (84 girls) examined every 6 months for 5 years. Serum levels of dehydroepiandrostenedione sulfate (DHEAS), Δ4-androstenedione, testosterone, and urinary morning excretion of 14 phthalate metabolites, corresponding to 7 different phthalate diesters were determined. A variation in urinary excretion of phthalates was evident in each child, which made a mean of repetitive samples more representative for long-term excretion than a single determination.

1.4.1.4 RESULTS:

We found that girls with excretion of monobutyl phthalate isomers (MBP) and di(2-ethylhexyl) phthalate metabolites above the geometric group mean (795 and 730 ng/kg, respectively) had lower levels of DHEAS and Δ4-androstenedione, although statistically significant only at 13 years of age. In boys, we found that excretion of monobenzyl phthalate above the geometric group mean (346 ng/kg) was associated with lower levels of DHEAS at 11 years of age but higher levels of testosterone at 13 years of age. The same trend was observed for MBP excretion, albeit not statistically significant. A lower age at pubarche was observed in boys with excretion of MBP above the geometric group mean (11.0 vs 12.3 years, P = 0.005).

1.4.1.5 CONCLUSION:

Our data indicate that **exposure to dibutyl phthalate isomers (DBP) (in girls) and butylbenzyl phthalate (in boys) are negatively associated with adrenal androgen levels and in boys positively associated with testosterone level at 13 years of age. High exposure to DBP was associated with earlier age at pubarche in boys. In girls, no associations between phthalate exposure and age at pubertal milestones were observed.**

ASSOCIATION BETWEEN PHTHALATES AND ATTENTION DEFICIT DISORDER AND LEARNING DISABILITY IN U.S. CHILDREN, 6-15 YEARS.

Environ Res. 2013 Nov 19. pii: S0013-9351(13)00179-5. doi: 10.1016/j.envres.2013.10.004. [Epub ahead of print]

Chopra V, Harley K, Lahiff M, Eskenazi B.

http://www.ncbi.nlm.nih.gov/pubmed/24267794

1.4.2 Abstract

1.4.2.1 OBJECTIVE:

This study investigates the association between urinary phthalate metabolite levels and attention deficit disorder (ADD), learning disability (LD), and co-occurrence of ADD and LD in 6-15-year-old children.

1.4.2.2 METHODS:

We used cross-sectional data from the National Health and Nutrition Examination Survey (NHANES, 2001-2004). Phthalate metabolites with ≥75% detection in urine samples were examined. The study population comprised 1493 children with parent-reported information on ADD or LD diagnosis and phthalate concentrations in urine. Phthalate concentrations were creatinine-adjusted and $\log_{10}$-transformed for analysis. All models controlled for child sex, age, race, household income, blood lead, and maternal smoking during pregnancy.

1.4.2.3 RESULTS:

There were 112 ADD cases, 173 LD cases, and 56 ADD and LD cases in the sample. After adjusting for potential confounders, we found **increased odds of ADD with increasing urinary concentration of di-2-ethylhexyl phthalates (OR: 2.1; 95% CI: 1.1, 3.9) and high molecular weight phthalates (OR: 2.7; 95% CI: 1.2, 6.1).** In addition, dibutyl phthalates (OR: 3.3; 95% CI: 0.9, 12.7) and high molecular weight phthalates (OR: 3.7; 95% CI: 0.9, 14.8) were marginally associated with increased odds of co-occurring ADD and LD. We did not find associations for any phthalate and LD alone. We observed stronger associations between phthalates and ADD and both ADD and LD in girls than boys in some models.

1.4.2.4 CONCLUSIONS:

We found cross-sectional evidence that certain phthalates are associated with increased odds of ADD and both ADD and LD. Further investigations with longitudinal data are needed to confirm these results.

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EARLY LIFE PHTHALATE EXPOSURE AND ATOPIC DISORDERS IN CHILDREN: A PROSPECTIVE BIRTH COHORT STUDY.

http://www.ncbi.nlm.nih.gov/pubmed/24161446?dopt=Abstract

Wang IJ, Lin CC, Lin YJ, Hsieh WS, Chen PC.

1.4.3 Abstract

The role of phthalate exposure at different stages in the immune system and atopic disorders is not well-known. This study aims to evaluate the effects of prenatal and postnatal phthalate exposures on immunoglobulin E (IgE) levels and atopic dermatitis (AD) in children by objective biomarkers. We conducted a prospective Taiwan Birth Panel cohort study with 483 mother/infant pairs. Finally, 161 urine specimens at 3rd trimester of pregnancy, 219 urine specimens from children at age 2, and 192 urine specimens at age 5 were analyzed after excluding missing data and loss to follow-up. Urine monoethyl phthalate (MEP), monobutyl phthalate (MBP), monobenzyl phthalate (MBzP), and mono-(2-ethylhexyl) phthalate (MEHP) at 3rd trimester of pregnancy and at ages 2 and 5 were measured by ultra-performance liquid chromatography coupled with tandem mass spectrometry. At ages 2 and 5, information on the development of AD and serum total IgE was collected. The association between urine phthalate metabolite levels at different stages and serum IgE and AD was evaluated by multivariate linear regression and logistic regression. Urine phthalate metabolite levels were higher at age 2 than those at pregnancy and age 5. At each period, urine MBP levels were higher than MEP, MEHP, and MBzP. MEHP levels at age 2 positively correlated with serum IgE levels (per ln-unit: β=0.191, p=0.02). Analyses stratified by gender revealed that MEHP levels positively correlated with serum IgE levels only in boys (per ln-unit: β=0.256, p=0.03). When dividing into quartiles, urine MBzP levels at age 2 had a significant association with AD. We found no statistically significant association of other phthalate metabolites with IgE and AD. Early life phthalate exposure may increase the risk of allergic sensitization and atopic disorders.

PHTHALATES: STUDY LINKS CHEMICALS WIDELY FOUND IN PLASTICS, PROCESSED FOOD TO ELEVATED BLOOD PRESSURE IN CHILDREN, TEENS

http://medicalxpress.com/news/2013-05-phthalates-links-chemicals-widely-plastics.html

Journal of Pediatrics

J Pediatr. 2013 Sep;163(3):747-53.e1. doi: 10.1016/j.jpeds.2013.03.072. Epub 2013 May 24.

URINARY PHTHALATES ARE ASSOCIATED WITH HIGHER BLOOD PRESSURE IN CHILDHOOD.

Trasande L, Sathyanarayana S, Spanier AJ, Trachtman H, Attina TM, Urbina EM.

1.4.4 **http://www.ncbi.nlm.nih.gov/pubmed/23706605**

1.4.5

1.4.6 Abstract

1.4.6.1 OBJECTIVE:

To examine associations of urinary phthalate levels with blood pressure (BP) and serum triglyceride and lipoprotein levels in children.

1.4.6.2 STUDY DESIGN:

We performed a cross-sectional analysis of a subsample of US children aged 6-19 years who participated in the National Health and Nutrition Examination Survey between 2003 and 2008. We quantified exposure to 3 families of phthalates--low molecular weight, high molecular weight and di-2-ethylhexylphthalate (DEHP)--based on molar concentration of urinary metabolites. We assessed descriptive, bivariate, and multivariate associations with BP and lipid levels.

1.4.6.3 RESULTS:

Controlling for an array of sociodemographic and behavioral factors, as well as diet and body mass index, levels of metabolites of DEHP, a phthalate commonly found in processed foods, were associated with higher age-, sex-, and height-standardized BP. For each log unit (roughly 3-fold) increase in DEHP metabolites, a 0.041 SD unit increase in systolic BP z-score was identified (P = .047). Metabolites of low molecular weight phthalates commonly found in cosmetics and personal care products were not associated with BP. Phthalate metabolites were not associated with triglyceride levels, high-density lipoprotein level, or prehypertension.

1.4.6.4 CONCLUSIONS:

Dietary phthalate exposure is associated with higher systolic BP in children and adolescents. Further work is needed to confirm these associations, as well as to evaluate opportunities for intervention.

Carlstedt, F., Jönsson, B.A., Bornehag, C.G. **PVC flooring is related to human uptake of phthalates in infants**. *Indoor Air*, (accepted May 7, 2012) DOI: 10.1111/j.1600-0668.2012.00788

URINARY CONCENTRATIONS OF PHTHALATES AND PHENOLS IN A POPULATION OF SPANISH PREGNANT WOMEN AND CHILDREN.

http://www.ncbi.nlm.nih.gov/pubmed/21440302?dopt=Abstractplus

Casas L, Fernández MF, Llop S, Guxens M, Ballester F, Olea N, Irurzun MB, Rodríguez LS, Riaño I, Tardón A, Vrijheid M, Calafat AM, Sunyer J; INMA Project.

1.4.7 Author information

1.4.8 Abstract

1.4.8.1 BACKGROUND:

Phthalate and phenol exposure is prevalent among the general population and of potential concern for pregnant women and children because of their suspected susceptibility to endocrine effects.

1.4.8.2 OBJECTIVES:

To evaluate the extent of exposure to several phthalates and phenols in a sample of Spanish pregnant women - according to their individual characteristics (age, social class, education, and body mass index) - and children who participated in the INMA - Infancia y Medio Ambiente (Environment and Childhood) project.

1.4.8.3 METHODS:

One spot urine sample was taken during the third trimester of pregnancy from 120 pregnant women and from 30 4-year old children belonging to 5 Spanish birth cohorts, and analyzed for 11 phthalate metabolites and 9 phenols.

1.4.8.4 RESULTS:

Three metabolites of di(2-ethylhexyl) phthalate, mono-2-ethyl-5-carboxypentyl phthalate, mono-2-ethyl-5-hydroxyhexyl phthalate, and mono-2-ethyl-5-oxohexyl phthalate; two metabolites of dibutyl phthalates, mono-isobutyl phthalate and mono-n-butyl phthalate; monoethyl phthalate (MEP), the main metabolite of diethyl phthalate; and two phenols, methyl paraben (M-PB) and 2,5-dichlorophenol **were detected in the urine samples of all women**. The highest urinary concentrations were for MEP and M-PB. Urinary concentrations of all phthalate metabolites and of 2,4-dichlorophenol, 2,5-dichlorophenol, and bisphenol A were lower in the pregnant women than in the children. Among women, a positive relationship with social class and education was shown for most of the phthalate metabolites and phenols. **Almost all phthalate metabolites varied by region even after adjusting for social class and education.**

1.4.8.5 CONCLUSIONS:

Phthalate and phenol exposures are prevalent in a group of pregnant women and young children, two susceptible populations, and these exposures might be positively related to social class.

Toxicol Lett. 2013 Dec 24. pii: S0378-4274(13)01468-9. doi: 10.1016/j.toxlet.2013.12.012. [Epub ahead of print]

PHTHALATE INTAKE BY INFANTS CALCULATED FROM BIOMONITORING DATA.

Völkel W[1], Kiranoglu M[2], Schuster R[2], Fromme H[2]; HBMnet.

1.4.9 http://www.ncbi.nlm.nih.gov/pubmed/24374175

1.4.10 Abstract

Urine samples (n=207) of 47 infants between 1- and 5-month of age were quantitated for 12 metabolites of 7 phthalates and compared with samples collected from the mothers of the infants at different time points. Median and 95-percentile were lower for all metabolites in urine samples of infants compared to mothers. For di-2-ethylhexyl phthalate (DEHP) the 95-percentile daily intake was 23.3µg/kg b.w. for mothers and 5.4µg/kg b.w. for infants and for di-isobutyl phthalate (DiBP) 10.1µg/kg b.w. and 8.5µg/kg b.w. Some values exceeded the corresponding tolerable daily intake (TDI) for DiBP for infants and mothers and for DEHP and di-n-butyl phthalate (DnBP) only for mothers. Both, infants and mothers are able to efficiently form phase II metabolites but infants with a slightly lower degree. **Therefore, a distinguished risk assessment with respect to the formed toxic metabolites of phthalates would be necessary in combination with a reduction of the most toxic phthalates.**

CONSIDERATIONS FOR ESTIMATING DAILY INTAKE VALUES OF NON-PERSISTENT ENVIRONMENTAL ENDOCRINE DISRUPTORS BASED ON URINARY BIOMONITORING DATA.

Søeborg T, Frederiksen H, Andersson AM.

1.4.11 Author information

1.4.12 Abstract

IntroductionHuman exposure to chemicals may be estimated by back-calculating urinary concentrations resulting from biomonitoring studies if knowledge of the chemical's toxicokinetic

properties is available.AimTo review available toxicokinetic data for back-calculating urinary concentrations into daily intake values for bisphenol A, phthalates, parabens and triclosan, and to identify knowledge gaps.MethodsHuman data was evaluated and supplied with relevant animal data. Focus was on recovery of the administered dose, the route of administration and on differences between humans and animals.ResultsTwo human toxicokinetic studies are currently used to conclude that an oral dose of bisphenol A is recoverable in urine and that no free bisphenol A is present in plasma in spite of several contradicting biominotoring studies.Urinary recovery of an oral dose of phthalates in humans is complicated to assess due to extensive metabolism. In animals using 14C-marked phthalates, near-complete recovery is observed. An oral dose of 14C-marked parabens is also almost completely recovered in animals. In both humans and animals however, two unspecific metabolites are formed, which complicates the back-calculation of parabens in humans. The recovery of both oral and dermal triclosan in humans has been studied, but due to background levels of triclosan, the back-calculation is difficult to perform.ConclusionDue to limited data, reasonable estimates of daily intake values based on urinary data are often not possible to obtain. Several knowledge gaps were identified and new studies were suggested. The route of administration used in toxicokinetic studies often does not match realistic scenarios.

http://www.ncbi.nlm.nih.gov/pubmed/24287425

PHTHALATES IN GERMAN DAYCARE CENTERS: OCCURRENCE IN AIR AND DUST AND THE EXCRETION OF THEIR METABOLITES BY CHILDREN (LUPE 3).

Fromme H, Lahrz T, Kraft M, Fembacher L, Dietrich S, Sievering S, Burghardt R, Schuster R, Bolte G, Völkel W.

1.4.13 http://www.ncbi.nlm.nih.gov/pubmed/24103347

1.4.14 Abstract

Phthalates have been used for decades in large quantities, leading to the ubiquitous exposure of the population. In an investigation of 63 German daycare centers, indoor air and dust samples were analyzed for the presence of 10 phthalate diesters. Moreover, 10 primary and secondary phthalate metabolites were quantified in urine samples from 663 children attending these facilities. In addition, the urine specimens of 150 children were collected after the weekend and before they went to daycare centers. Di-isobutyl phthalate (DiBP), dibutyl phthalate (DnBP), and di-2-ethylhexyl phthalate (DEHP) were found in the indoor air, with median values of 468, 227, and 194ng/m(3), respectively. In the dust, median values of 888mg/kg for DEHP and 302mg/kg for di-isononyl phthalate (DiNP) were observed. DnBP and DiBP were together responsible for 55% of the total phthalate concentration in the indoor air, whereas DEHP and DiNP were responsible for 70% and 24% of the total phthalate concentration in the dust. Median concentrations in the urine specimens were 44.7µg/l for the DiBP monoester, 32.4µg/l for the DnBP monoester, and 16.5µg/l and 17.9µg/l for the two secondary DEHP metabolites. For some phthalates, we observed significant correlations between their concentrations in the indoor air and dust and their corresponding metabolites in the urine specimens using bivariate analyses. In multivariate analyses, the concentrations in dust were not associated with urinary metabolite excretion after controlling for the concentrations in the indoor air. The total daily "high" intake levels based on the 95th percentiles calculated from the biomonitoring data were 14.1µg/kg b.w. for DiNP and 11.9µg/kg b.w. for DEHP. Compared with tolerable daily intake (TDI) values, our "high" intake was 62% of the TDI value for DiBP, 49% for

DnBP, 24% for DEHP, and 9% for DiNP. For DiBP, the total daily intake exceeded the TDI value for 2.4% of the individuals. Using a cumulative risk-assessment approach for the sum of DEHP, DnBP, and DiBP, 20% of the children had concentrations exceeding the hazard index of one. Therefore, a further reduction of the phthalate exposure of children is needed.

Int J Hyg Environ Health. 2013 Jun;216(3):271-9. doi: 10.1016/j.ijheh.2012.12.005. Epub 2013 Feb 8.

EXPOSURE ASSESSMENT OF PHTHALATES IN FRENCH PREGNANT WOMEN: RESULTS OF THE ELFE PILOT STUDY.

Zeman FA, Boudet C, Tack K, Floch Barneaud A, Brochot C, Péry AR, Oleko A, Vandentorren S.

1.4.15 http://www.ncbi.nlm.nih.gov/pubmed/23394847

1.4.16 Abstract

The ubiquitous use of phthalate esters in plastics, building material, medical devices, personal care products and food packaging materials results in a widespread exposure of general population. This study reports measurement of urinary concentration of phthalate metabolites in France and provides a first assessment of the exposure of French pregnant women to this chemical class. For the majority of the phthalate metabolites, concentrations measured in urine were similar to those reported in previous studies except for two phthalates that were characterized by high concentrations of metabolites if compared to previous European and American studies: DiNP (Di-iso-nonylphthalate) and DEHP (Di(2-ethylhexyl)phthalate). In a second part of the study, a pharmacokinetic model was used in order to gain understanding on exposure to DEHP. A high concentration of the primary metabolite of DEHP, MEHP (Mono(2-ethylhexyl)phthalate), was thus identified probably because of a very recent exposure to perfusion materials at the hospital. Pharmacokinetics modelling highlighted that gathering data on the time gap between exposure and biomonitoring is an essential information requirement for reconstructing the dose of non persistent pollutants. **Information about exposure pathway is also crucial for conducting effective reverse dosimetry.**