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Phthalate Exposure in Pregnant Women: Risk Perception and Preventive Advice of Perinatal Health Professionals

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Abstract

Objectives The main objective of the PERI–HELPE study (Perception of Risk–HEaLth Professionals and Environment Study) was to describe the knowledge of perinatal health professionals about phthalates and the preventive advice they give to pregnant women about exposure to these chemicals. The secondary objective was to determine whether giving preventive advice was associated with the perception of phthalates. *Methods* A cross-sectional study was performed in 2015 in France. One hundred and eighty-nine perinatal health professionals (obstetricians, midwives and general practitioners) replied to an online self-administered questionnaire (participation rate: 11%). *Results* Only 17% of health professionals felt able to provide appropriate answers to pregnant women about phthalates. Advice was given by 23% (avoid plastic kitchen cling film) to 75% (prefer homemade dishes) about eating habits, by less than 42% for the use of cosmetics and less than 25% for that of consumer products. After adjusting for covariates, the awareness that pregnant women are daily exposed to phthalates (44% of professionals) was associated with dietary advice [avoid pre-packaged food (OR 2.2; 95% CI 1.1–4.4), prefer homemade dishes (OR 2.6; 95% CI 1.2–5.9) and avoid plastic kitchen cling film (OR 2.4; 95% CI 1.0–5.6)] but not with advice about cosmetics or consumer products. The perception of phthalate exposure as a high risk (66%) was not associated with preventive advice. *Conclusions for Practice* Our sample size was not very large but the findings nevertheless show the lack of knowledge of perinatal health professionals about phthalates. If they are to take on a preventive role, health professionals in France need to be better informed about phthalates and more fully trained in environmental health in general.

Keywords Environmental health · Phthalates · Perinatal health professionals · Preventive advice · Risk perception

Significance

What is already known. The International Federation of Gynaecology and Obstetrics (FIGO) and the American College of Obstetricians and Gynecologists (ACOG) recently recommended that perinatal health professionals should contribute to the prevention of chemical exposure of pregnant women.

What the PERI–HELPE study adds. While exposure to phthalates was mostly perceived as a high risk by perinatal health professionals, preventive advice to minimize exposure was rarely given to pregnant women. Although the sample size was not very large, this study underlines the lack of knowledge about phthalates and environmental health in France.

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Introduction

Pregnant women are exposed daily to phthalates. These chemicals are commonly used as plasticizers to soften plastics, in particular polyvinyl chloride (PVC), in food packaging, wall and floor coverings and children's toys. Phthalates are also used in many consumer products such as personal care products (PCPs) and in household, do-it-yourself (DIY) and gardening products. These molecules can enter humans by oral, dermal and inhalation routes (Bekö et al. 2013; Wormuth et al. 2006) and cross the placental barrier (Jensen et al. 2012). Some phthalates have endocrine disrupting effects and the exposure of pregnant women to these molecules has been associated with negative outcomes for the foetus (growth retardation, premature birth, impaired hormonal production and malformations of the male reproductive system) (Lyche et al. 2009; Marie et al. 2015) and for the child (impaired neural and cognitive development, allergic disorders and hormonal impairment at puberty) (Ejaredar et al. 2015; Ferguson et al. 2014; Just et al. 2012).

In a public health context, the limitation of the exposure of pregnant women to phthalates is therefore essential. Studies have shown that exposure to phthalates could be reduced by a radical different lifestyle such as in the community of Old Order Mennonites (local, home-grown food and simpler and less materialist lifestyle including limited use of PCPs and household products) (Martina et al. 2012) and by a short-term lifestyle change (adopting the daily routines of Buddhist monks and a vegetarian diet during 5 days) (Ji et al. 2010). Rudel et al. (2011) demonstrate that eating "fresh foods" (i.e., "not canned or packaged in plastic") during 3 days can decrease DEHP exposure (Rudel et al. 2011). Nonetheless, two other dietary interventions did not observed significant changes in phthalates exposure (Sathyanarayana et al. 2013; Barrett et al. 2015). Other intervention study showed significant decrease of urinary phthalates levels after using PCPs without phthalates on the ingredient list during 3 days (Harley et al. 2016). Finally a cross-sectional study showed significant associations between decreased exposure to phthalates and some lifestyle habits: eating home-grown products, organic, "ecofriendly" (defined by the authors as "not harmful to the earth and its inhabitants") or "chemical-free" food, using "ecofriendly" or "chemical-free" household products (Serrano et al. 2014).

However, women remain ill-informed about the sources of exposure to phthalates and their health effects during pregnancy (Ashley et al. 2015; Sharma et al. 2014). In order to encourage them to change their lifestyle to reduce phthalate exposure, pregnant women need to be made aware of the risks involved. Perinatal health professionals (HPs) have an essential role in the provision of appropriate information and preventive advice in critical stages of human development such as before conception and during pregnancy. This position was recently affirmed by the International Federation of Gynecology and Obstetrics (FIGO), which drew up recommendations concerning the prevention of chemical exposure of pregnant women (Di Renzo et al. 2015). In addition, other studies have shown the willingness of pregnant women to receive information and advice about chemical exposure from HPs (Ashley et al. 2015; Marie et al. 2016a).

To our knowledge, few studies have dealt with the preventive advice and attitudes of perinatal HPs regarding in utero exposure to phthalates. A Canadian qualitative study (Sharma et al. 2014) reported that perinatal HPs were reluctant to discuss phthalate exposure with pregnant women, mainly because they felt insufficiently informed. However, this analysis involved only 11 HPs and therefore is not very representative. A US study reported that 5% of obstetricians routinely discussed phthalates with pregnant women (Stotland et al. 2014). Neither of these studies described in detail the perception of the risks associated with phthalates by HPs nor the advice given to pregnant women about these contaminants.

The main objective of this study was to describe the knowledge of perinatal health professionals about phthalates and the preventive advice they give to pregnant women about phthalate exposure. The secondary objective was to determine whether giving preventive advice was associated with the perception of phthalates (i.e., perception of exposure probability and perception of exposure severity).

Methods

Study Design

The cross-sectional Perception of Risk, HEaLth Professionals & Environment Study (PERI-HELPE study) study was performed between 1 July 2015 and 31 December 2015. Before the study, the perinatal HPs were informed of the aim and the modalities of the survey (completion of an anonymous self-administered online questionnaire). An invitation to take part in the survey was then sent by e-mail to 1768 perinatal HPs by various professional organisations: the Perinatal Health Network of Auvergne (RSPA), the Regional Association of Private Practice Doctors, and the Department of General Medicine and School of Midwifery of the Université Clermont Auvergne. Three e-mail follow-ups were sent during the study period. In all, 194 perinatal HPs took part in the study. Incomplete questionnaires were excluded (n = 5). The survey participation rate was 11% (189/1768).

Subjects

The population of the PERI–HELPE study was made up of perinatal HPs comprising senior or resident gynaecologist–obstetricians, general practitioners and senior or student midwives. The study was conducted in Auvergne, a region in central France. In 2014, the region had 1,360,637 inhabitants and 13,430 births. To be eligible for inclusion, the HPs had to have pregnant women among their patients, be practising in Auvergne and to agree to answer the questionnaire.

In accordance with French human research law, this study was exempt from Institutional Review approval because our database included no nominative data and the study aim was a medical practice assessment.

Questionnaire

Data were collected by a standardized, anonymous and self-administered questionnaire (Supplementary material 2). The questionnaire consisted predominantly of closed questions with nine open questions. The questions concerned the socio-demographic and professional characteristics of the perinatal HPs, their knowledge and risk perception of phthalates and 18 other environmental contaminants including bisphenol A, parabens, pesticides, air pollutants and radon, and preventive advice given to pregnant women. Results about the risk perception of the other 18 environmental contaminants have been presented elsewhere (Marie et al. 2016b). For the present study, we focused on the perception of the risk related to the exposure of pregnant women to phthalates.

Knowledge About Phthalates of Perinatal Health Professionals

We collected data on the identification of different sources of phthalate exposure (such as food, PCPs and medical tubing) and on the knowledge of the main phthalates [di-(2-ethylhexyl)-phthalate (DEHP), diisononyl-phthalate (DiNP)] and of alternative plasticizers [acetyltri-*n*-butyl citrate (ATBC), di-isononyl-1,2-cyclohexane-dicarboxylate (DINCH), trioctyl trimellitate (TOTM) and di-(ethylhexyl)-terephthalate (DEHT)]. In addition, perinatal HPs self-assessed their ability to reply correctly to pregnant women's enquiries about phthalates with a 4-point Likert scale: "absolutely sure", "fairly sure", "fairly unsure", and "totally unsure".

Preventive Advice of Perinatal Health Professionals Regarding Phthalate Exposure

The perinatal HPs self-reported the preventive advice they gave to pregnant women about (i) eating habits (prefer homemade dishes, avoid pre-packaged products, avoid cling film for preserving food and micro-waving dishes in a plastic container) use of PCPs (decrease or stop use, choose PCPs without phthalates and fragrance compounds, or organic PCPs); and (ii) the use of different types of consumer products such as household products, including products for cleaning the floor, sanitary, windows, dishes, etc., DIY and gardening products (decrease or stop use, choose less harmful products and take personal protection measures such as wearing gloves or masks).

Perception of In Utero Exposure to Phthalates by Perinatal Health Professionals

The perception of in utero exposure to phthalates was assessed by two items.

- Perception of exposure probability: "Do you think that pregnant women are daily exposed to phthalates?" with a 5-point Likert scale ("Yes, absolutely", "Yes, rather", "Rather not", "No, not at all", "Don't know"). After a review of the distribution of data, perinatal HPs were dichotomized to those considering that the exposure of women to phthalates is daily ("Yes absolutely" or "Yes, rather") or to HPs who did not perceive the exposure to phthalates as daily (other responses).
- Perception of exposure severity: "Do you think that exposure to phthalates presents a risk for the health of pregnant women and their unborn baby?" with a 5-point Likert scale ("Very high risk", "High risk", "Rather low risk", "Very low risk" and "Don't know"). After a review of the distribution of data, perinatal HPs were dichotomized to those perceiving phthalates exposure as a high risk ("Very high risk" or "High risk") or to HPs who did not perceive the exposure to phthalates as a high risk (other responses).

Statistical Analysis

Univariate analyses were performed to compare variables according to the perception of phthalates by perinatal HPs: those believing that pregnant women were daily exposed to phthalates were compared with those who did not; and perinatal HPs perceiving in utero exposure to phthalates as a high risk were compared with those who did not. The qualitative variables were compared with Pearson's Chi square or Fisher's exact test, as appropriate.

Two sets of multivariable logistic regression models were performed. The first set examined whether the perception of daily exposure predicted preventive attitudes of HPs. The second set examined whether perceiving in utero exposure to phthalates as a high risk predicted preventive attitudes of HPs. The socio-professional factors potentially

associated with the perception of phthalates were included in multivariate models when $p < 0.20$ in univariate analyses. In addition, age and parity were forced in the models as they have been identified as potentially linked with knowledge, risk perception or preventive behaviour in environmental health (Chabert et al. 2016; Ménard et al. 2012). Covariates included in the final models were selected with a manual backward stepwise procedure.

Significance was defined as $p < 0.05$. Statistical analyses were performed with R statistical software, version 2.15.2 (R Development Core Team, Vienna, Austria, 2012).

Results

The survey participation rate was 11% (189/1768). The HPs were predominantly female (87.2%) with a median age of 35 years (from 20 to 65 years). More than half of the perinatal HPs were midwives (56.6%), 26.5% were general practitioners and 16.9% gynaecologist-obstetricians. Most of those taking part held, irrespective of occupation, a senior position (74.1%) and more than half (59.3%) worked in a public health institution. A minority of HPs (18.2%) were questioned by pregnant women about phthalates (Table 1).

Table 1 Sociodemographic and professional characteristics of perinatal health professionals (HPs) according to their perception of phthalates

	Total N = 189 (%)	HPs perceiving daily exposure to phthalates[a]		HPs perceiving phthalate exposure as a high risk[b]	
		N = 84 (44.4%)	p-Value	N = 124 (65.6%)	p-Value
Sex	n = 188	n = 84		n = 124	
Female	164 (87.2)	76 (90.5)	0.33	111 (89.5)	0.28
Age	n = 188	n = 83		n = 123	
< 45 years	135 (71.8)	66 (79.5)	0.05	92 (74.8)	0.28
Parity	n = 183	n = 81		n = 120	
≥ 1	120 (65.6)	54 (66.7)	0.90	78 (65.0)	0.95
Type of profession	n = 189	n = 84		n = 124	
Senior and resident GP	50 (26.5)	17 (20.2)	0.14	28 (22.6)	0.02
Senior and resident GO	32 (16.9)	13 (15.5)		17 (13.7)	
Senior and student MW	107 (56.6)	54 (64.3)		79 (63.7)	
Occupational status	n = 189	n = 84		n = 124	
Resident/MW student	49 (25.9)	20 (23.8)	0.67	30 (24.2)	0.56
Senior	140 (74.1)	64 (76.2)		94 (75.8)	
Length of service	n = 155	n = 70		n = 102	
≤ 10 years	80 (51.6)	37 (52.9)	0.91	54 (52.9)	0.77
Place of work[c]	n = 189	n = 84		n = 124	
Private practice	63 (33.3)	22 (26.2)	0.09	41 (33.1)	1
Private health institution	3 (1.6)	1 (1.2)	1	1 (0.8)	0.57
Public health institution	112 (59.3)	54 (64.3)	0.27	73 (58.7)	1
Contact with pregnant women	n = 183	n = 82		n = 121	
Consultation	52 (28.4)	19 (23.2)	0.24	32 (26.5)	0.49
Hospital	17 (9.3)	11 (13.4)		10 (8.3)	
Both	91 (49.7)	41 (50.0)		61 (50.4)	
Others[d]	23 (12.6)	11 (13.4)		18 (14.9)	
Enquiries by pregnant women about phthalates	n = 187	n = 82		n = 124	
Yes ("sometimes" and "often")	34 (18.2)	21 (25.6)	0.03	7 (22.1)	0.09

GO gynaecologist-obstetricians, *GP* general practitioners, *HPs* health professionals, *MW* midwives

[a]Compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates is daily

[b]Compared with perinatal HPs who did not perceive the exposure to phthalates as a high risk

[c]Several possible replies for a given health professional

[d]Preparation for childbirth (n = 19) and/or pre- and postnatal home visit (n = 19)

Knowledge About Phthalates and Preventive Advice Given by Perinatal Health Professionals

Few HPs (5.8%) had received specific training in environmental health, but many (76.3%) expressed the desire to be given the opportunity to do so. The main sources of information and difficulties in environmental health are shown in Table 2.

The sources of phthalate exposure were known by less than half of the HPs. The most often cited sources were personal care products (PCPs) (48.2%), household products (41.8%) and medical devices such as tubing (39.2%). Among the users of medical devices (n = 153), 6.5% had noticed the presence of a "phthalates" symbol on the packaging of tubing (result not shown). With the exception of DEHP, familiar to 20.6%, the other plasticizers were known by 5% or less of perinatal HPs. Only 17.1% of them felt able to provide appropriate answers to pregnant women about phthalates (Table 3).

Results about preventive advice of perinatal HPs are given in Table 4. Overall, dietary advice was given by 23.0% ("avoid plastic kitchen cling film") to 75.1% ("prefer homemade dishes") of HPs. Advice about the use of PCPs was given by less than 42% of HPs and that about consumer products by less than 25% (Table 4).

Perception of Phthalates by Perinatal HPs

Forty-four percent of perinatal HPs considered that pregnant women were exposed daily to phthalates and 65.6% perceived the risk related to in utero exposure to phthalates as high. HPs who considered that pregnant women were daily exposed to phthalates were more likely to perceive phthalate exposure as a high risk than those who did not have this perception of daily exposure ($p < 0.001$, results not shown). The sociodemographic and professional characteristics of the HPs, their training in environmental health and their sources of information according to their perception of phthalates are shown in Tables 1 and 2. The perinatal HPs who considered exposure was daily and those who perceived phthalate exposure as a high risk had statistically greater knowledge about phthalates than those who did not (Table 3).

Association Between Perception and Preventive Advice

In univariate analysis, compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates was daily, those considering daily exposure were more likely to advise the consumption of homemade dishes (68.9% vs. 82.9%, $p < 0.05$), avoidance of pre-packaged food (43.3%

Table 2 Training in environmental health (EH) and sources of information of health professionals (HPs) according to their perception of phthalates

	Total N = 189 (%)	HPs perceiving daily exposure to phthalates[a]		HPs perceiving phthalate exposure as a high risk[b]	
		N = 84 (44.4%)	p-Value	N = 124 (65.6%)	p-Value
Training in EH[c] ("Yes")	11/189 (5.8)	4/84 (4.8)	0.76	7/124 (5.7)	1
Desire training in EH ("Yes")	142/186 (76.3)	67/82 (81.7)	0.18	93/122 (76.2)	1
Sources of information about EH					
Media, Internet	154/189 (81.5)	70/84 (83.3)	0.69	101/124 (81.5)	1
Scientific article	109/189 (57.7)	52/84 (61.9)	0.37	79/124 (63.7)	0.03
Health agency or institution	40/189 (21.2)	23/84 (28.4)	0.07	28/124 (22.6)	0.64
Environmental association	37/189 (19.6)	22/84 (26.2)	0.04	23/124 (18.6)	0.76
Other HPs	28/189 (14.8)	12/84 (14.3)	1	20/124 (16.1)	0.24
Difficulties					
Lack of knowledge	110/189 (58.2)	40/84 (47.6)	0.01	69/124 (55.7)	0.41
Insufficient/contradictory scientific evidence	103/189 (54.5)	45/84 (53.6)	0.93	65/124 (52.4)	0.52
Lack of time during consultation	95/189 (50.3)	43/84 (51.2)	0.94	63/124 (50.8)	0.96
Lack of interest of women	66/189 (34.9)	28/84 (33.3)	0.80	40/124 (32.3)	0.37
Low contribution of environmental factors to disorder	48/189 (25.4)	23/84 (27.4)	0.69	30/124 (24.2)	0.73
Contact with women too late in pregnancy	38/189 (20.1)	21/84 (25.0)	0.19	28/124 (22.6)	0.33
Lack of interest	16/188 (8.5)	4/84 (4.8)	0.17	9/124 (7.3)	0.58

EH environmental health, *HPs* health professionals

[a]Compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates is daily

[b]Compared with perinatal HPs who did not perceive exposure to phthalates as a high risk

[c]Master's degree (n = 1), university diploma (n = 2), other training experience (n = 7)

Table 3 Knowledge of perinatal health professionals about phthalates and other plasticizers according to their perception of phthalates

	Total N = 189 (%)	HPs perceiving daily exposure to phthalates[a]		HPs perceiving phthalate exposure as a high risk[b]	
		N = 84 (%)	p-Value	N = 124 (%)	p-Value
Identification of sources of exposure					
Personal care products	91 (48.2)	62 (73.8)	< 0.001	76 (61.3)	< 0.001
Consumer products[c]	79 (41.8)	55 (65.5)	< 0.001	63 (50.8)	< 0.001
Medical tubing	74 (39.2)	54 (64.3)	< 0.001	61 (49.2)	< 0.001
Food	49 (25.9)	34 (40.5)	< 0.001	41 (33.1)	0.004
Drinking water	41 (21.7)	34 (40.5)	< 0.001	36 (29.0)	0.001
Dietary supplements	23 (12.2)	19 (22.6)	< 0.001	18 (14.5)	0.24
Drugs	14 (7.4)	13 (15.5)	< 0.001	12 (9.7)	0.14
"Don't know"	68 (36.0)	6 (7.1)	< 0.001	30 (24.2)	< 0.001
Knowledge about plasticizers					
DEHP	39 (20.6)	28 (33.3)	< 0.001	33 (26.6)	0.005
DEHT	10 (5.3)	7 (8.3)	0.11	7 (5.7)	1
DiNP	3 (1.6)	2 (2.4)	0.59	2 (1.6)	1
DINCH	2 (1.1)	2 (2.4)		2 (1.6)	
TOTM	1 (0.5)	1 (1.2)		1 (0.8)	
ATBC	1 (0.5)	1 (1.2)		1 (0.8)	
Ability to provide appropriate answers[d,e]					
"Sure"[f]	32 (17.1)	23 (28.1)	< 0.001	27 (22.1)	0.003
"Fairly unsure"	80 (42.8)	35 (42.7)		56 (45.9)	
"Totally unsure"	75 (40.1)	24 (29.3)		39 (32.0)	

ATBC acetyltri-*n*-butyl citrate, *DEHP* di-(2-ethylhexyl) phthalate, *DEHT* di-(ethylhexyl)-terephthalate, *DINCH* di-isononyl-1,2-cyclohexane-dicarboxylate, *DiNP* diisononyl-phthalate, *DIY* do-it-yourself, *HPs* health professionals, *PCPs* personal care products, *TOTM* trioctyl trimellitate

[a]Compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates is daily

[b]Compared with perinatal HPs who did not perceive exposure to phthalates as a high risk

[c]Household, DIY and gardening products

[d]Two missing responses (n = 187)

[e]Ability of perinatal HPs to provide appropriate answers to pregnant women about phthalates

[f]"Absolutely sure" or "Fairly sure"

vs. 60.7%, $p < 0.05$) and plastic kitchen cling film (16.4% vs. 31.3%, $p < 0.05$), the use of PCPs without phthalates (32.7% vs. 52.5%, $p = 0.01$) and the wearing of personal protection when using DIY products (14.7% vs. 27.7%, $p = 0.05$) (Table 4). After adjusting for type of occupation, age, parity and ability to provide appropriate answers about phthalates, the perception that pregnant women are daily exposed to phthalates was positively associated with three pieces of dietary advice [avoid pre-packaged food (OR 2.2; 95% CI 1.1–4.4), prefer homemade dishes (OR 2.6; 95% CI 1.2–5.9) and avoid plastic kitchen cling film (OR 2.4; 95% CI 1.0–5.6)] but not with advice about PCPs or consumer products (Table 5).

In univariate analysis, compared with perinatal HPs who did not perceive the exposure to phthalates as a high risk, those perceiving this exposure as a high risk advised more frequently the avoidance of plastic kitchen cling film (13.9% vs. 27.9%, $p < 0.05$) and of PCPs containing phthalates (29.0% vs. 47.9%, $p < 0.05$) but advised less frequently to decrease or stop the use of PCPs (27.7% vs. 13.3%, $p < 0.05$). No statistical difference were observed between the subgroups in the other preventive recommendations (Table 4). In multivariate analysis (adjustment for type of occupation, age, parity and ability to provide appropriate answers about phthalates), no preventive advice was positively associated with the perception of high risk (Table 5).

Discussion

Preventive Advice of Perinatal Health Professionals Regarding Phthalate Exposure

In this PERI–HELPE study, the two dietary recommendations specifically concerning the prevention of phthalate exposure (avoid microwaving dishes in plastic containers and avoid

Table 4 Preventive advice of perinatal health professionals (HPs) to pregnant women regarding exposure to phthalates according to their perception of phthalates

	Total N = 189 (%)	HPs perceiving daily exposure to phthalates[a] N = 84 (%)	p-Value	HPs perceiving phthalate exposure as a high risk[b] N = 124 (%)	p-Value
Dietary advice[c]					
Homemade dishes	139/185 (75.1)	68/82 (82.9)	0.04	94/121 (77.7)	0.36
Avoid pre-packaged food	96/188 (51.1)	51/84 (60.7)	0.03	65/123 (52.9)	0.60
Avoid micro-waving in plastic containers	82/188 (43.6)	43/84 (51.2)	0.08	58/123 (47.2)	0.23
Avoid plastic kitchen cling film	43/187 (23.0)	26/83 (31.3)	0.02	34/122 (27.9)	0.05
Advice about the use of personal care products (PCPs)[c]					
Increase	7/185 (3.8)	2/81 (2.5)	0.47	6/120 (5.0)	0.43
Stop or decrease	34/185 (18.4)	15/81 (18.5)	1	16/120 (13.3)	0.03
Organic PCPs	55/179 (30.7)	30/80 (37.5)	0.11	40/117 (34.2)	0.23
Without fragrance compounds	77/183 (42.1)	36/81 (44.4)	0.67	53/120 (44.2)	0.53
Without phthalates	75/181 (41.4)	42/80 (52.5)	0.01	57/119 (47.9)	0.02
Advice about the use of household products[c]					
Stop or decrease	16/186 (8.6)	9/83 (10.8)	0.47	12/122 (9.8)	0.58
"Safer" products	47/186 (25.3)	26/83 (31.3)	0.12	29/122 (23.8)	0.64
Wear protection	44/186 (23.6)	22/83 (26.5)	0.52	29/122 (23.8)	1
Advice about the use of DIY products[c]					
Stop or decrease	24/187 (13.0)	10/64 (12.1)	0.91	18/121 (14.1)	0.65
"Safer" products	35/187 (18.9)	20/64 (24.1)	0.15	23/121 (19.1)	1
Wear protection	38/187 (20.5)	23/64 (27.7)	0.05	28/121 (23.1)	0.31
Advice about the use of gardening products[c]					
Stop or decrease	22/188 (11.8)	10/64 (12.1)	1	16/122 (13.1)	0.61
"Safer" products	32/188 (17.2)	17/64 (20.5)	0.39	20/122 (16.4)	0.84
Wear protection	50/188 (26.9)	26/64 (31.3)	0.29	35/122 (28.7)	0.55

DIY do it yourself, *HPs* health professionals, *PCPs* personal care products

[a]Compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates is daily

[b]Compared with perinatal HPs who did not perceive the exposure to phthalates as a high risk

[c]"Systematically", "Often" and "Rarely" versus "Never"

plastic kitchen cling film) were made by less than 44% of the perinatal HPs. In contrast, more general advice about "healthy food" (avoid pre-packaged food and prefer homemade dishes) was given by more than half. Advice concerning the reduction or precaution in the use of PCPs and consumer products was even less frequently given (often by less than one-third of the HPs). These precautions about phthalate exposure were far less mentioned by perinatal HPs than those specifically recommended by the National Authority for Health in France such as prevention of smoking, alcohol consumption, drug use, lead poisoning, toxoplasmosis and promotion of a healthy and balanced diet (HAS 2005; Marie et al. 2016b).

Association Between Risk Perception and Preventive Advice of Perinatal Health Professionals

In this PERI–HELPE study, the preventive advice of the perinatal HPs regarding exposure of pregnant women to phthalates was generally unrelated to their perception of phthalates. After considering socio-professional factors and the self-assessed knowledge of phthalates, dietary advice (except the avoidance of microwaving in plastic containers) was positively associated with the awareness of daily exposure to phthalates but not with the perception of this exposure as a high risk. Likewise, advice about PCPs and consumer products was not associated with risk perception.

These results require some comments. First, owing to the study's limited sample size, the statistical power was probably insufficient to demonstrate a significant association with certain preventive recommendations, such as the use of PCPs without phthalates (OR 1.84, 95% IC 0.90–3.77) or the avoidance of plastic kitchen cling film (OR 2.17, 95% IC 0.90–5.68) (Table 5). Second, some recommendations assessed in our study were not specific to phthalates. For example, the avoidance of pre-packaged food or the consumption of homemade dishes probably reflected the idea of

Table 5 Odds ratios for preventive attitudes of health professionals (HPs) in relation to their consideration that pregnant women are daily exposed to phthalates and to their perception of phthalate exposure of pregnant women as a high risk

	N	HPs perceiving daily exposure to phthalates[a]		HPs perceiving phthalates exposure as a high risk[b]	
		Crude OR (95% CI)	Adjusted OR (95% CI)[c]	OR (95% CI)	Adjusted OR (95% CI)[c]
Dietary advice					
Avoid pre-packaged food	179	2.03 (1.13–3.66)	2.20 (1.13–4.36)	1.23 (0.67–2.25)	1.13 (0.59–2.20)
Homemade dishes	176	2.19 (1.09–4.57)	2.57 (1.17–5.95)	1.47 (0.73–2.91)	1.32 (0.62–2.76)
Avoid micro-waving in plastic containers	179	1.75 (0.98–3.15)	1.40 (0.70–2.81)	1.52 (0.83–2.85)	1.24 (0.62–2.51)
Avoid plastic kitchen cling film	179	2.33 (1.17–4.75)	2.37 (1.04–5.62)	2.40 (1.11–5.68)	2.17 (0.90–5.68)
Advice about PCPs					
Stop or decrease PCPs	180	0.98 (0.46–2.07)	0.77 (0.33–1.75)	0.39 (0.18–0.82)	0.27 (0.11–0.61)
Organic PCPs	171	1.78 (0.94–3.39)	1.24 (0.58–2.66)	1.63 (0.82–3.34)	1.18 (0.55–2.59)
PCPs without fragrance compounds	175	1.19 (0.66–2.15)	0.87 (0.43–1.76)	1.29 (0.69–2.42)	0.86 (0.42–1.75)
PCPs without phthalates	174	2.28 (1.25–4.20)	1.84 (0.90–3.77)	2.25 (1.18–4.41)	1.69 (0.82–3.61)
Advice about consumer products					
Stop or decrease household product use	180	1.68 (0.60–4.90)	1.34 (0.40–4.39)	1.63 (0.54–6.04)	1.33 (0.40–5.23)
Safer household products	178	1.78 (0.92–3.50)	1.55 (0.74–3.29)	0.80 (0.40–1.60)	0.62 (0.29–1.33)
Use protection to clean	178	1.33 (0.67–2.63)	1.04 (0.49–2.22)	1.02 (0.50–2.12)	0.84 (0.39–1.84)
Stop or decrease DIY product use	180	0.88 (0.36–2.08)	0.67 (0.23–1.80)	1.32 (0.53–3.57)	1.22 (0.46–3.54)
Safer DIY products	177	1.84 (0.88–3.93)	1.98 (0.85–4.71)	1.02 (0.48–2.26)	0.95 (0.40–2.29)
Use protection for DIY	177	2.22 (1.08–4.69)	1.67 (0.76–3.79)	1.63 (0.75–3.75)	1.24 (0.54–2.99)
Stop or decrease gardening product use	180	1.05 (0.42–2.56)	0.90 (0.31–12.46)	1.46 (0.57–4.24)	1.42 (0.51–4.42)
Safer gardening products	178	1.51 (0.70–3.28)	1.52 (0.64–3.65)	0.85 (0.39–1.92)	0.85 (0.36–2.07)
Use protection to garden	178	1.50 (0.78–2.89)	1.06 (0.51–2.17)	1.32 (0.53–3.57)	0.97 (0.46–2.09)

DIY do it yourself, *HPs* health professionals, *PCPs* personal care products

[a]Compared with perinatal HPs who did not consider that exposure of pregnant women to phthalates is daily

[b]Compared with perinatal HPs who did not perceive the exposure to phthalates as a high risk

[c]Each row represents a separate multivariable logistic regression model to examine if risk perception (daily exposure perception and high risk perception) predicts preventive behaviour, adjusting for: type of occupation (Gynaecologist–obstetricians; General practitioners; Midwives), age (< 45 years; ≥ 45 years), parity ≥ 1 (Yes; No) and ability to provide appropriate answers about phthalates ("Sure"; "Unsure")

having a healthy and balanced diet, which is recommended during pregnancy, rather than that of decreasing phthalate exposure via plastic food packaging. PCPs and other consumer products contain many other chemicals such as parabens, bisphenol A and triclosan that are increasingly the object of media coverage. Precautions for use may then be recommended without any knowledge of phthalates or perception of their risk. Finally, the PERI–HELPE study evidenced the considerable lack of knowledge about phthalates of the majority of the perinatal HPs since only 17% of them felt able to provide appropriate information. Some HPs did express an awareness of phthalate exposure and risk but their responses were probably more subjective than factually informed. In addition, only 6% of the HPs included in the study had received training in environmental health. This lack of knowledge of HPs about phthalates (Sharma et al. 2014; Stotland et al. 2014) and of training in environmental health in general (Ménard et al. 2012) have been reported in other studies. Thus, in our study, the interest of delivering preventive advice about phthalates may have been underestimated by the lack of knowledge and training of the perinatal HPs. In a study on French general practitioners' perception of environmental risks, the provision of preventive advice depended on whether they had received training in environmental health (Ménard et al. 2012). Psychosocial models have shown that the adoption of preventive attitudes is a complex process resulting from a combination of factors such as knowledge, risk perception and awareness of the benefits related to behaviour change (Janz and Becker 1984).

This incoherence between risk perception and preventive attitudes was previously observed in the study of Kasemsup and Neesanan (2011). Health personnel were aware of the adverse health effects of plastic containers on food and drinks but did not know how to counter or avoid them, owing to inadequate knowledge about different types of plastic containers, symbols for consumers, microwave use and so on (Kasemsup and Neesanan 2011).

Need to Enhance the Knowledge of Perinatal Health Professionals and Their Involvement in Environmental Health

The results of the PERI-HELPE study emphasize the need to lend support to perinatal HPs in their role as educators and in helping to prevent exposure of pregnant women to phthalates. This support is all the more necessary as the discourse on risk is complex. For example, PCPs are often perceived as beneficial for the body and a source of comfort, especially during pregnancy.

Appropriate advice could help to decrease the exposure of pregnant women to phthalates. Several intervention studies have reported a reduction in exposure to phthalates following changes in dietary habits such as adopting a vegetarian diet, eating fresh food, avoiding canned or plastic-packaged products (Ji et al. 2010; Rudel et al. 2011) and using PCPs without phthalates (Harley et al. 2016). In addition, cross-sectional studies have reported an association between a lower level of exposure to phthalates and some habits such as eating home-grown, organic and fresh food, avoiding canned or plastic-packaged products (Martina et al. 2012; Serrano et al. 2014) and the use of PCPs and household products without chemicals (mainly phthalates) (Buckley et al. 2012; Martina et al. 2012; Serrano et al. 2014). Conversely, authors have shown an increase in exposure to phthalates in relation to fast-food consumption (Zota et al. 2016), to the number of PCPs used (Romero-Franco et al. 2011) and to the frequency of use of cleaning products (Ait Bamai et al. 2014).

Specialized training in environmental health (declared desirable by the participants in our study) would improve the level of knowledge of HPs. The provision of information to pregnant women in the form of brochures or leaflets or posters in waiting rooms, and the posting of advice on the website of perinatal networks could also prompt conversations about phthalates and act to reinforce women's own knowledge. Some authors, particularly in the United States and Canada, provide certain tools to assist clinicians in counselling their patients on how to limit phthalate exposure such as ceasing the use of plastic cling film, of plastics with the recycling codes #3 and #7 and of PVC kitchen utensils, reducing consumption of fast foods and other processed foods, reading the label and avoiding consumer products containing phthalates (Di Renzo et al. 2015; Haruty et al. 2016). In Europe, no recommendations currently exist from health authorities to perinatal HPs regarding exposure to phthalates, and more broadly to chemicals, during pregnancy. Such recommendations could increase their awareness of the value of providing prevention advice.

Limitations

Our study has several limitations. A risk of selection bias is possible because the participants were volunteers and may therefore have been more alert to the issues involved and more aware of environmental problems. This selection bias would be limited, however, since the proportion of HPs who had received training in environmental health (5.8%) was not higher than that in a representative sample of French general practitioners (5%) (Ménard et al. 2012) or that in a US study of obstetricians (6.7%) (Stotland et al. 2014). The major limitation of the PERI-HELPE is its low participation rate (11%), which limits the extrapolation of the results observed. Thus, results should be taken with caution and further studies involving larger and more representative samples are needed to confirm our findings. Nonetheless, the overall response rate to our web-based questionnaire (11%) was similar to (Csajka et al. 2014; De Ruddere et al. 2014; Stotland et al. 2014) or slightly lower than (Berg-Beckhoff et al. 2014; Saylor et al. 2011) that of other surveys in which HPs replied to an online questionnaire. In addition, 87% of the perinatal HPs included in our study were women. This high proportion is due to the fact that most of the HPs were midwives, whose profession is predominantly female. This factor did not seem to have any influence on our results since sex was not related to the perception of risk regarding phthalates and preventive advice nor in another study involving French general practitioners (Ménard et al. 2012). Compared to national figures, the general practitioners and gynaecologist-obstetricians in our study were younger and more often women (DREES 2013). However, we also recruited residents, who are not included in national figures. The proportion of general practitioners in private practice and public health institutions was consistent (DREES 2013). In addition, the midwives, who were the predominant professional group in our study, are representative of the overall population of French midwives in terms of gender, age and location of exercise, i.e. private practice or public health institution (DREES 2012). Data about socio-economic and education level of women population that the HPs serve are important data lacking in our study. Although the varied places of work of HPs throughout the Auvergne region (private/public, academic or not) can suggest that patient were representative, we were not able to take account of the possible difference between HPs who serve women highly educated and those serving lower educated women for example.

Conclusions

Perinatal health professionals have an essential role in preventing exposure to chemicals, including phthalates, in critical stages of foetal development. To our knowledge, the

PERI–HELPE study is the first to describe the knowledge, risk perception and preventive advice of perinatal health professionals regarding in utero exposure to phthalates. While exposure to phthalates was predominantly perceived as a high risk, preventive advice to minimize phthalate exposure was rarely given to pregnant women. Although our results must be confirmed by a larger study with a bigger sample size, the PERI-HELPE study underlines the lack of knowledge of perinatal health professionals about environmental health. In France, adoption of the preventive role of health professionals advocated by the FIGO will necessarily involve the development of appropriate information programmes and improved training in environmental health.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

References

Ait Bamai, Y., Araki, A., Kawai, T., Tsuboi, T., Saito, I., Yoshioka, E., et al. (2014). Associations of phthalate concentrations in floor dust and multi-surface dust with the interior materials in Japanese dwellings. *The Science of the Total Environment, 468–469*, 147–157.

Ashley, J. M., Hodgson, A., Sharma, S., & Nisker, J. (2015). Pregnant women's navigation of information on everyday household chemicals: Phthalates as a case study. *BMC Pregnancy and Childbirth, 15*(1), 312.

Barrett, E. S., Velez, M., Qiu, X., & Chen, S. -R. (2015). Reducing prenatal phthalate exposure through maternal dietary changes: Results from a pilot study. *Maternal and Child Health Journal, 19*(9), 1936–1942.

Bekö, G., Weschler, C. J., Langer, S., Callesen, M., Toftum, J., & Clausen, G. (2013). Children's phthalate intakes and resultant cumulative exposures estimated from urine compared with estimates from dust ingestion, inhalation and dermal absorption in their homes and daycare centers. *PLoS ONE, 8*(4), e62442.

Berg-Beckhoff, G., Breckenkamp, J., Larsen, P. V., & Kowall, B. (2014). General practitioners' knowledge and concern about electromagnetic fields. *International Journal of Environmental Research and Public Health, 11*(12), 12969–12982.

Buckley, J. P., Palmieri, R. T., Matuszewski, J. M., Herring, A. H., Baird, D. D., Hartmann, K. E., & Hoppin, J. A. (2012). Consumer product exposures associated with urinary phthalate levels in pregnant women. *Journal of Exposure Science & Environmental Epidemiology, 22*(5), 468–475.

Chabert, M.-C., Perrin, J., Berbis, J., Bretelle, F., Adnot, S., & Courbiere, B. (2016). Lack of information received by a French female cohort regarding prevention against exposure to reprotoxic agents during pregnancy. *European Journal of Obstetrics, Gynecology, and Reproductive Biology, 205*, 15–20.

Csajka, C., Jaquet, A., Winterfeld, U., Meyer, Y., Einarson, A., & Panchaud, A. (2014). Risk perception by healthcare professionals related to drug use during pregnancy: A Swiss survey. *Swiss Medical Weekly, 144*, w13936.

De Ruddere, L., Goubert, L., Stevens, M. A. L., Deveugele, M., Craig, K. D., & Crombez, G. (2014). Health care professionals' reactions to patient pain: Impact of knowledge about medical evidence and psychosocial influences. *The Journal of Pain, 15*(3), 262–270.

Di Renzo, G. C., Conry, J. A., Blake, J., DeFrancesco, M. S., DeNicola, N., Martin, J. N., et al. (2015). International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *International Journal of Gynaecology and Obstetrics: The Official Organ of the International Federation of Gynaecology and Obstetrics, 131*(3), 219–225.

Direction de la Recherche, des Études, de L'évaluation et des Statistiques (DREES) (2012). La profession de sage-femme: constat démographique et Projections d'effectifs. *Etudes et résultats*. Accessed Apr 20, 2017, from http://drees.social-sante.gouv.fr/IMG/pdf/er791.pdf.

Direction de la Recherche, des Études, de L'évaluation et des Statistiques (DREES) (2013). Les médecins au 1er janvier 2013. *Série Statistiques*. Accessed Apr 20, 2017, from http://drees.social-sante.gouv.fr/etudes-et-statistiques/publications/documents-de-travail/serie-statistiques/article/les-medecins-au-1er-janvier-2013.

Ejaredar, M., Nyanza, E. C., Eycke, T. K., & Dewey, D. (2015). Phthalate exposure and childrens neurodevelopment: A systematic review. *Environmental Research, 142*, 51–60.

Ferguson, K. K., Peterson, K. E., Lee, J. M., Mercado-García, A., Blank-Goldenberg, C., Téllez-Rojo, M. M., & Meeker, J. D. (2014). Prenatal and peripubertal phthalates and bisphenol A in relation to sex hormones and puberty in boys. *Reproductive Toxicology, 47*, 70–76.

Harley, K. G., Kogut, K., Madrigal, D. S., Cardenas, M., Vera, I. A., Meza-Alfaro, G., et al. (2016). Reducing phthalate, paraben, and phenol exposure from personal care products in adolescent girls: Findings from the HERMOSA intervention study. *Environmental Health Perspectives, 124*(10), 1600–1607.

Haruty, B., Friedman, J., Hopp, S., Daniels, R., & Pregler, J. (2016). Reproductive health and the environment: Counseling patients about risks. *Cleveland Clinic Journal of Medicine, 83*(5), 367–372.

Haute Autorité de Santé (HAS). (2005). Comment mieux informer les femmes enceintes? Recommandations pour les professionnels de santé. Accessed Apr 23, 2017, from http://www.has-sante.fr/portail/upload/docs/application/pdf/infos_femmes_enceintes_rap.pdf.

Janz, N. K., & Becker, M. H. (1984). The health belief model: A decade later. *Health Education Quarterly, 11*(1), 1–47.

Jensen, M. S., Nørgaard-Pedersen, B., Toft, G., Hougaard, D. M., Bonde, J. P., Cohen, A., et al. (2012). Phthalates and perfluorooctanesulfonic acid in human amniotic fluid: Temporal trends and timing of amniocentesis in pregnancy. *Environmental Health Perspectives, 120*(6), 897–903.

Ji, K., Lim Kho, Y., Park, Y., & Choi, K. (2010). Influence of a five-day vegetarian diet on urinary levels of antibiotics and phthalate metabolites: A pilot study with 'Temple Stay' participants. *Environmental Research, 110*(4), 375–382.

Just, A. C., Whyatt, R. M., Perzanowski, M. S., Calafat, A. M., Perera, F. P., Goldstein, I. F., et al. (2012). Prenatal exposure to

butylbenzyl phthalate and early eczema in an urban cohort. *Environmental Health Perspectives, 120*(10), 1475–1480.

Kasemsup, R., & Neesanan, N. (2011). Knowledge, attitudes and practices relating to plastic containers for food and drinks. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet, 94*, S121–S125.

Lyche, J. L., Gutleb, A. C., Bergman, A., Eriksen, G. S., Murk, A. J., Ropstad, E., et al. (2009). Reproductive and developmental toxicity of phthalates. *Journal of Toxicology and Environmental Health. Part B, Critical Reviews, 12*(4), 225–249.

Marie, C., Cabut, S., Vendittelli, F., & Sauvant-Rochat, M.-P. (2016a). Changes in cosmetics use during pregnancy and risk perception by women. *International Journal of Environmental Research and Public Health, 13*(4), 383.

Marie, C., Lémery, D., Vendittelli, F., & Sauvant-Rochat, M.-P. (2016b). Perception of environmental risks and health promotion attitudes of french perinatal health professionals. *International Journal of Environmental Research and Public Health, 13*(12), 1255.

Marie, C., Vendittelli, F., & Sauvant-Rochat, M.-P. (2015). Obstetrical outcomes and biomarkers to assess exposure to phthalates: A review. *Environment International, 83*, 116–136.

Martina, C. A., Weiss, B., & Swan, S. H. (2012). Lifestyle behaviors associated with exposures to endocrine disruptors. *Neurotoxicology, 33*(6), 1427–1433.

Ménard, C., Léon, C., & Benmarhnia, T. (2012). Médecins généralistes et santé environnement. *Evolutions, Institut National de Prévention et d'Education Pour la Santé (INPES)*, 26, 1–6. Accessed Apr 23, 2017, from http://inpes.santepubliquefrance.fr/CFESBases/catalogue/detaildoc.asp?numfiche=1402.

Romero-Franco, M., Hernández-Ramírez, R. U., Calafat, A. M., Cebrián, M. E., Needham, L. L., Teitelbaum, S., et al. (2011). Personal care product use and urinary levels of phthalate metabolites in Mexican women. *Environment International, 37*(5), 867–871.

Rudel, R. A., Gray, J. M., Engel, C. L., Rawsthorne, T. W., Dodson, R. E., Ackerman, J. M., et al. (2011). Food packaging and bisphenol A and bis(2-ethyhexyl) phthalate exposure: Findings from a dietary intervention. *Environmental Health Perspectives, 119*(7), 914–920.

Sathyanarayana, S., Alcedo, G., Saelens, B. E., Zhou, C., Dills, R. L., Yu, J., & Lanphear, B. (2013). Unexpected results in a randomized dietary trial to reduce phthalate and bisphenol A exposures. *Journal of Exposure Science & Environmental Epidemiology, 23*(4), 378–384.

Saylor, A., Prokopy, L. S., & Amberg, S. (2011). What's wrong with the tap? Examining perceptions of tap water and bottled water at Purdue University. *Environmental Management, 48*(3), 588–601.

Serrano, S. E., Karr, C. J., Seixas, N. S., Nguyen, R. H. N., Barrett, E. S., Janssen, S., et al. (2014). Dietary phthalate exposure in pregnant women and the impact of consumer practices. *International Journal of Environmental Research and Public Health, 11*(6), 6193–6215.

Sharma, S., Ashley, J. M., Hodgson, A., & Nisker, J. (2014). Views of pregnant women and clinicians regarding discussion of exposure to phthalate plasticizers. *Reproductive Health, 11*, 47.

Stotland, N. E., Sutton, P., Trowbridge, J., Atchley, D. S., Conry, J., Trasande, L., et al. (2014). Counseling patients on preventing prenatal environmental exposures—A mixed-methods study of obstetricians. *PLoS ONE, 9*(6), e98771.

Wormuth, M., Scheringer, M., Vollenweider, M., & Hungerbühler, K. (2006). What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? *Risk Analysis: An Official Publication of the Society for Risk Analysis, 26*(3), 803–824.

Zota, A. R., Phillips, C. A., & Mitro, S. D. (2016). Recent fast food consumption and bisphenol A and phthalates exposures among the U.S. Population in NHANES, 2003–2010. *Environmental Health Perspectives, 124*(10), 1521–1528.