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Alkylphenolic compounds and risk of breast and prostate cancer in the MCC-Spain study

Paula Peremiquel-Trillas[a,b], Yolanda Benavente[b,c], Mayte Martín-Bustamante[d], Delphine Casabonne[b,c], Beatriz Pérez-Gómez[c,e,f], Inés Gómez-Acebo[c,g], Anna Oliete-Canela[d], Marta Diéguez-Rodríguez[d], Ignasi Tusquets[h,i], Pilar Amiano[c,j], Lourdes Mengual[k], Eva Ardanaz[c,l], Rocío Capelo[m], Antonio J. Molina de la Torre[n], Dolores Salas Trejo[c,o,p], Guillermo Fernández-Tardón[c,q], Virginia Lope[c,e], José J. Jimenez-Moleon[c,r,s], Rafael Marcos-Gragera[c,t,u], Trinidad Dierssen-Sotos[c,g], Mikel Azpiri[j], Montse Muñoz[v], Marcela Guevara[c,l], Tania Fernández-Villa[n], Ana Molina-Barceló[o], Nuria Aragonés[c,w], Marina Pollán[c,e], Gemma Castaño-Vinyals[x,y,z], Juan Alguacil[m], Manolis Kogevinas[x,y,z,aa], Silvia de Sanjosé[ab], Laura Costas[b,*]

[a] Preventive Medicine and Epidemiology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain
[b] Unit of Molecular Epidemiology and Genetics in Infections and Cancer, IDIBELL, Catalan Institute of Oncology, L'Hospitalet de Llobregat, Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública – CIBERESP, Madrid, Spain
[d] Institut Català de Seguretat i Salut Laboral, Departament de Treball, Afers Socials i Famílies, Generalitat de Catalunya, Barcelona, Spain
[e] Cancer Epidemiology Unit, National Center for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain
[f] Cardiovascular & Metabolic Diseases Unit, National Centre for Epidemiology, Instituto de Salud Carlos III, Madrid, Spain
[g] Universidad de Cantabria – IDIVAL, Santander, Spain
[h] Universitat Autònoma de Barcelona, Parc de Salut Mar Hospital del Mar, Barcelona, Spain
[i] Medical Oncology Department, Parc de Salut Mar Hospital del Mar, Barcelona, Spain
[j] Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain
[k] Department and Laboratory of Urology, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain
[l] Instituto de Salud Pública de Navarra – IdiSNA, Pamplona, Spain
[m] Centro de Investigación en Recursos Naturales, Salud y Medio Ambiente, Universidad de Huelva, Huelva, Spain
[n] Grupo de Investigación en Interacciones Gen-Ambiente y Salud (GIIGAS), Instituto de Biomedicina (IBIOMED), Universidad de León, León, Spain
[o] Cancer and Public Health Area, FISABIO – Public Health, Valencia, Spain
[p] General Directorate Public Health, Valencian Community, Valencia, Spain
[q] Instituto de Oncología de Asturias (IUOPA), Área de Medicina Preventiva, Universidad de Oviedo, Oviedo, Spain
[r] Department of Preventive Medicine and Public Health, Faculty of Medicine, University of Granada, Granada, Spain
[s] Instituto de Investigación Biosanitaria ibs.GRANADA, Hospitales Universitarios de Granada, University of Granada, Granada, Spain
[t] Epidemiology Unit and Girona Cancer Registry (UERCG), Oncology Coordination Plan, Department of Health, Autonomous Government of Catalonia, Catalan Institute of Oncology (ICO), Girona, Spain
[u] Girona Biomedical Research Institute (IDIBGI), University of Girona, Girona, Spain
[v] Translational Genomics and Targeted Therapeutics in Solid Tumors, Hospital Clínic de Barcelona, Barcelona, Spain
[w] Epidemiology Section, Public Health Division, Department of Health of Madrid, Madrid, Spain
[x] ISGlobal, Barcelona, Spain
[y] Hospital del Mar Medical Research Institute – IMIM, Barcelona, Spain
[z] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[aa] National School of Public Health, Athens, Greece
[ab] PATH, Seattle, USA

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ABSTRACT

Background: Alkylphenolic compounds are chemicals with endocrine disrupting properties that have been widely used in industry with important changes in their usage over time. Few epidemiologic studies have

* Corresponding author at: Unit of Molecular Epidemiology and Genetics in Infections and Cancer, Cancer Epidemiology Research Programme, Institut Català d'Oncologia, Av. Gran Via de l'Hospitalet 199-203, 08908 L'Hospitalet de Llobregat, Spain.
E-mail address: lcostas@iconcologia.net (L. Costas).

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Alkylphenolic compounds
Job-exposure matrix
Breast cancer
Prostate cancer
Occupational exposure

evaluated the effect of alkylphenolic compounds on human health.
Objectives: We investigated whether occupational exposure to alkylphenolic compounds is associated with breast and prostate cancer.
Methods: We carried out a population-based case–control study including 1513 incident cases of breast cancer, 1095 of prostate cancer, and 3055 controls, frequency matched by sex, age and region. Occupational exposure to alkylphenolic compounds was estimated using a recently developed job-exposure matrix, which considered different scenarios of exposure and different subtypes of alkylphenolic compounds.
Results: History of occupational exposure to alkylphenolic compounds was modestly associated with breast cancer (OR = 1.23; 95% CI = 1.01–1.48). Within the different scenarios, the occupational use of domestic tensioactives was positively associated with breast cancer (OR = 1.28; 95% CI = 1.02–1.60), while occupational exposure in other scenarios showed mostly a suggestion of a similar positive associations. Exposure to nonylphenol ethoxylates was positively associated with breast cancer (OR = 1.21; 95% CI = 1.00–1.47), while exposure to other compounds was uncommon. In general, we did not observe associations between alkylphenolic compounds and prostate cancer, except for a positive association among men occupationally exposed to cosmetic, hair and personal hygiene products.
Conclusions: Our findings suggest a modest association between breast cancer risk and occupational exposure to alkylphenolic compounds, and no associations between these compounds and prostate cancer risk. These findings warrant further corroboration in other studies.

1. Introduction

Alkylphenolic compounds are organic chemicals generally produced for the manufacture of alkylphenolic ethoxylates (APE), which are mainly used as non-ionic surfactants, but also in a wide range of applications. Nonylphenol (NP), octylphenol (OP) and their ethoxylates (NPE and OPE, respectively) are the most commonly used alkylphenolic compounds (Lassen et al., 2013). Exposure to these chemicals can occur occupationally during their production or with exposure to domestic and industrial detergents, specialty paints, pesticides, cosmetics and hair dyes, among others (Lassen et al., 2013), but also as a consequence of non-occupational exposures, such as diet and water intake, use of personal care and household cleaning products. Due to the toxicity and bioaccumulation of alkylphenolic compounds in marine organisms (Hansen et al., 2002), in 2003 the European Union limited the commercialization of products containing NP and NPE in concentrations over 0.1% (European Union, 2003). Alkylphenols and short-chain alkylphenolic ethoxylates are considered endocrine disruptors, mainly because of their effects mediated by estrogen receptors (Isidori et al., 2010; Olsen et al., 2005; Sun et al., 2008; White et al., 1994). NP has shown estrogenic effects in a number of in vitro (yeast, ZR-75 and MCF-7 human breast cancer cell lines) and in vivo assays (among rats and mice), although the potency of this activity was moderately lower than that of estradiol (in vitro assays showed an activity between 3 and 6 orders of lesser magnitude) (Bontje et al., 2004; Rotroff et al., 2014). Sex hormones play critical roles in the development of breast and prostate cancers (Acevedo et al., 2005; Gray et al., 2017; Hess-Wilson and Knudsen, 2006; Risbridger et al., 2010; Villeneuve et al., 2010a) and therefore we hypothesized that alkylphenolic compounds could have an influence on the development of these neoplasms. Over the last decades, there is growing interest in this field and a consequent increased knowledge of the potential impact of these chemicals on the environment and on human health (Bergman et al., 2013; Casals-Casas and Desvergne, 2011; Damstra et al., 2002).

Alkylphenolic compounds are ubiquitous, and they have been detected in rivers and bottled water (Amiridou and Voutsa, 2011; Bergé et al., 2012; Brix et al., 2010; Navarro et al., 2010), as well as in human fluids or tissues, such as urine (Calafat et al., 2005), blood (Gyllenhammar et al., 2012), placenta (Huang et al., 2014), breast milk (Ademollo et al., 2008; Chen et al., 2010; Sise and Uguz, 2017), adipose tissue (Ferrara et al., 2011; Geens et al., 2012; Lopez-Espinosa et al., 2009) and hair biospecimens (Nehring et al., 2017). There is considerable uncertainty in the estimated human daily intake figures. The daily intake has been estimated to be between in the range of 7.5–30 μg/day (0.1–0.4 μg/kg bw/day) from food, and 2.3×10^4 mg/kg bw/day from water (Guart et al., 2014; Guenther et al., 2002; Lu et al., 2007). The highest estimated exposure would occur with the application of specialty paints (2 mg/kg/day), use pesticides (0.35 μg/kg/day), cosmetics (0.1 μg/kg/day) and exposure via food packaging materials (0.2 μg/kg/day) and in a textile factory (4.42 mg/kg/day) (Bontje et al., 2004).

There are few epidemiologic studies assessing the effect of alkylphenolic compounds on human health. Regarding cancer, occupational exposure to alkylphenolic compounds has been associated with a higher risk of male and female breast cancer, and lymphoma (Aschengrau et al., 1998a; Costas et al., 2015; Villeneuve et al., 2010b). Also, higher NP and OP levels in urine among patients with uterine leiomyoma relative to controls were observed in two case-control studies in China (Shen et al., 2013; Zhou et al., 2013). A study assessed the association of circulating serum levels of NP, OP and other xenoestrogens with mammographic breast density, which is a marker of breast cancer risk, with negative results for alkylphenolic compounds (Sprague et al., 2013). However, the conclusions of this study were hampered by the high probability of external contamination, as well as to the suspected short half-lives of these compounds, which thus reflect only recent exposures (Calafat et al., 2013). Current methods to detect alkylphenolic compounds in biospecimens commonly used in epidemiologic studies, such as blood serum or plasma, are not sensitive enough and they are susceptible to contamination. Although not exempt of limitations, assessment of occupational exposures may overcome these flaws, and it can be used to assess lifetime rather than recent exposures of these compounds, which is relevant when evaluating diseases with long latency periods, such as cancer (Martín-Bustamante et al., 2017). The purpose of the present analysis is to explore whether occupational exposure to alkylphenolic compounds influences the risk of breast and prostate cancer.

2. Methods

2.1. Study design

Cases were recruited within the MCC-Spain study, a Spanish population-based multi-case–control study in which population controls were enrolled as well as five types of common cancers (breast, prostate, colorectal, stomach and chronic lymphocytic leukaemia). The recruitment started in 2008 and finished in 2013. In this analysis, we included incident patients diagnosed of breast (C50, D05.1, D05.7) or prostate cancer (C61, D07.5) admitted to 21 hospitals in 11 Spanish regions (Asturias, Barcelona, Cantabria, Gipuzkoa, Girona, Granada, Huelva, León, Madrid, Navarra and Valencia). Controls were frequency-matched to cases by sex, age, and region of recruitment and were randomly selected from the rosters of General Practitioners at the Primary Health

Centers participating in the study, which cover part of the population living in the corresponding area, and provides a representative sampling frame given the almost universal public coverage of the national health system in Spain. We excluded those subjects with communication difficulties (mental or speaking problems) or physical ability impairment. Response rates among the eligible subjects were 71% for breast cancer cases, 72% for prostate cancer cases and 53% for controls. Further details can be found elsewhere (Castaño-Vinyals et al., 2015). We excluded non-Caucasian participants (N = 118), subjects with missing information on occupation (N = 62), and homemakers (N = 410). A total of 1513 incident breast cancer cases, 1095 incident prostate cancer cases and 3055 controls (1575 females and 1480 males) were included in these analyses.

2.2. Data collection and exposure assessment

Data were collected through direct interviews conducted by trained personnel. The questionnaire included basic epidemiologic information such as age, educational level, family history of cancer, body mass index (BMI) one year before recruitment, tobacco and alcohol consumption one year before recruitment (Castaño-Vinyals et al., 2015; Spanish questionnaire available at www.mccspain.org). Lifetime occupational history was assessed for all jobs held for 1 year or more. For each job reported, information was collected on job title, main activity or task performed, age at start and end, and shift (day, night or rotating), among others. Each occupation was independently coded by two industrial hygienists following the national codes of occupation CNO-94, the Spanish adaptation to the International Standard Classification of Occupations (ISCO-88). When discrepancies occurred between the hygienists (20% of job titles), agreement was reached by consensus.

We applied a job-exposure matrix (JEM), originally developed to apply it to the MCC-Spain study, to assess exposure to alkylphenolic compounds which takes into account the changes over time of the alkylphenolic compounds used in Spain (Martín-Bustamante et al., 2017). The JEM considers the use of these compounds between 1931 and 2014 in Spain, given that the participants in the MCC-Spain study reported occupations between this range of years. In summary, three hygienists coded frequency (minority or majority of workers involved) and intensity of exposure (including dispersive processes, with shaking or aerosol generation, or otherwise) to alkylphenolic compounds for all the job titles by period of time. Intensity and frequency of exposure were combined in a single score as follows: unlikely = 0, occasional + low intensity = 1, occasional + high intensity = 2, frequent + low intensity = 2 and frequent + high intensity = 3. Exposure assignment was blind to the case-control status and dichotomized into exposed and unexposed. This JEM grouped the different job titles potentially exposed to alkylphenolic compounds into 6 different scenarios of exposure: a) manufacture and use of plastic and rubber products, b) manufacture and use of paints and lubricants, c) use of industrial tensioactives, d) use of domestic tensioactives, e) use of cosmetic and hair products and personal hygiene products and f) use of pesticides. This JEM also assessed common types of alkylphenolic compounds: NPE, OP/NP, APE and others. APE category includes exposure to a mixture of ethoxylated compounds, and the category 'others' includes job titles which involved a mixture of alkylphenols and alkylphenolic ethoxylates. Occupational exposure to solvents and to pesticides was assigned using a JEM designed for Spanish working conditions (MatEmESp) (García et al., 2013).

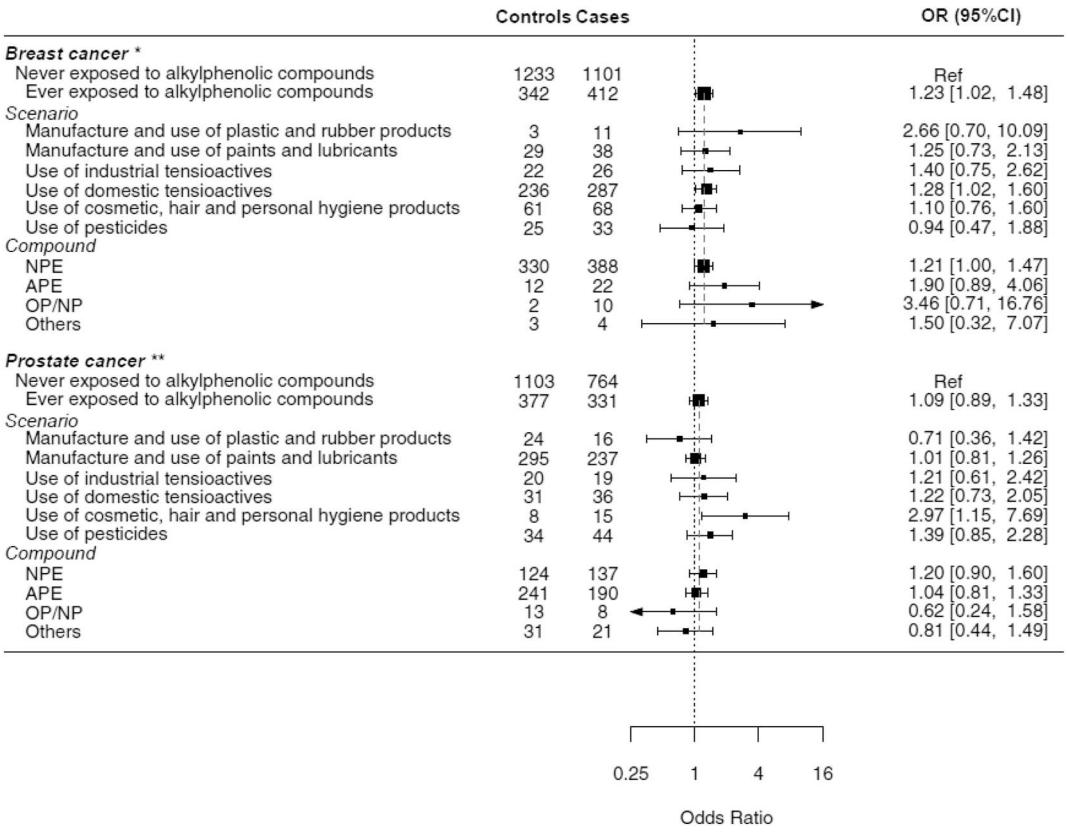

Fig. 1. Forest plot of associations on alkylphenolic compounds by scenario and type of compound.
*Ajusted for age, region, education level, BMI, smoking, alcohol consumption, occupational shift, exposure to pesticides, exposure to solvents, hormonal contraception, postmenopausal hormone therapy, menopausal status and parity.
**Ajusted for age, region, education level, BMI, smoking, alcohol consumption, occupational shift, exposure to pesticides and exposure to solvents.

2.3. Statistical analyses

The distribution of potential risk factors between cases and controls was compared using the Pearson's chi-squared test. Duration, age at first exposure, time since first exposure and time since last exposure to alkylphenolic compounds were calculated based on the years at start and stop reported for each job and the date of interview. These variables were categorized in three groups using tertiles based on the distribution among exposed controls. Multivariate unconditional logistic regression models were used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the association between occupational exposures and cancer. The variables considered for inclusion in the multivariable models are shown in the Directed Acyclic Graphs (Supplemental Fig. 1). Basic adjusted models included age at interview (< 60, 60–69, ≥70), region of recruitment and educational level (primary or less, secondary, higher). Final models, in addition to the basic adjustment, included BMI (< 18.5, 18.5–24.9, 25–29.9 or ≥30), smoking status (never, current, former), alcohol consumption (never, current, past), occupational shift (day, permanent night, rotating night, other rotating shifts), ever previous occupational exposure to solvents and/or to pesticides, and family history of cancer (breast or prostate, accordingly). For breast cancer, multivariate models were further adjusted for hormonal contraceptives use (ever, never), parity (nulliparous, 1 child, 2 children, ≥3 children), menopause status (premenopause, postmenopause) and postmenopausal hormone therapy use (ever, never), given that these variables are clearly related with breast cancer risk (Risbridger et al., 2010). For all variables, missing data was ≤10% of subjects, except for alcohol consumption which was 15%. Missing values were introduced in models as independent categories. To test for linear trend, ordinal variables were treated as continuous using midpoints in the categories as category values. Multiplicative interactions were tested by means of likelihood ratio tests comparing models with and without interactions. Several sensitivity analyses were performed. Given that exposure to solvents has been previously associated to these cancers and solvents and alkylphenolic compounds may be correlated, we excluded participants who reported occupational exposure to solvent compounds to ensure that occupational exposure to these chemicals was not driving associations between exposure to alkylphenols and cancer risk. Also, we classified those who reported occasional and low occupational exposure to alkylphenolic compounds as non-exposed, and thus we considered only frequent and high exposures, as a measure of high probability of exposure. We performed analyses on sub-phenotypes of breast and prostate cancer (hormone receptors status and Gleason score, respectively). Finally, we further explored adjusting our models for other measures of socioeconomic status (SES) than educational level, such as self-reported maternal and paternal SES. All analyses were conducted using Stata version 14.0 and the forest plot (Fig. 1) was graphed with R 3.4.1.

2.4. Ethics

The MCC-Spain Study followed the national and international directives on ethics and data protection (declaration of Helsinki and Spanish law on confidentiality of data, Organic Law on Data Protection 15/1999-LOPD). All eligible subjects signed an informed consent form for participation. Study protocol was approved by the Ethical and Research Committees of each participating center.

3. Results

3.1. Demographic features of participants

Baseline characteristics of participants are described in Table 1. Compared to female controls, female cases were more likely to be younger, to have a higher BMI, to be non-smokers and never drinkers, to have been occupationally exposed to solvents, as well as to have a family history of breast cancer, and have menarche at a younger age. Male cases were more likely to have a lower educational level, to have been occupational exposed to pesticides and to report a family history of prostate cancer, than male controls (Table 1).

Female controls exposed to alkylphenols were more likely to be older than the unexposed, to live in the Barcelona region, to have a lower educational level, to have a higher BMI, to be non-smoker and never drinkers, to have been occupationally exposed to solvents or pesticides, to be parous, to have never used hormonal contraceptives, to be younger at first delivery and to be postmenopausal at the moment of the interview. Compared to the unexposed, exposed male controls were more likely to be younger, to have a higher educational level, to live in the Barcelona region, to report occupational exposure to solvents and/or to pesticides and to have worked in permanent night shifts (Table 2).

3.2. Associations between breast and prostate cancer and alkylphenolic compounds

Occupational exposure to alkylphenolic compounds was observed among 412 breast cancer cases (27.2%) and 342 female controls (21.7%). Patterns of estimates were in general similar between basic and fully adjusted models; ORs for fully-adjusted models are reported in the text unless otherwise specified. Subjects occupationally exposed to alkylphenolic compounds had a modestly higher risk of breast cancer (OR = 1.23; 95% CI = 1.01–1.48), compared to the unexposed. Associations were significant among those who ever worked frequently exposed and with high intensity of exposure (OR = 1.25; 95% CI = 1.01–1.55). A short duration (< 6 years) was positively associated with breast cancer ($OR_{\text{tertile 1 vs. never}}$ = 1.34; 95% CI = 1.01–1.77), although no linear trend was observed with duration of exposure (p-trend = 0.30). Those starting exposure at an older age (≥29) and those who started < 30 years since the interview showed positive associations with breast cancer ($OR_{\text{tertile 3 vs. never}}$ = 1.35; 95% CI = 1.04–1.84 and $OR_{\text{tertile 3 vs. never}}$ = 1.50; 95% CI = 1.14–1.98, respectively). Estimates were higher among those whose last exposure occurred later in the calendar ($OR_{1984–2000\text{ vs. never}}$ = 1.32; 95% CI = 0.99–1.76; $OR_{\geq 2001}$ = 1.30; 95% CI = 0.98–1.72; Table 3, p-trend = 0.035). Among those exposed < 30 years ago for the first time, associations were observed regardless of the duration of exposure ($OR_{\text{duration} < 6}$ = 1.53, 95% CI = 1.04–2.27, and $OR_{\text{duration} \geq 6}$ = 1.43, 95% CI = 1.04–2.27; data not shown). Similarly, associations were stronger among those who were exposed for the first time during the last 30 years and their last use was on 2001 or onwards (OR = 1.56, 95% CI = 1.12–2.17, compared with never exposed; data not shown).

A total of 331 prostate cancer cases (30.2%) and 377 male controls (25.5%) were occupationally exposed to alkylphenolic compounds, but no significant association was observed (OR = 1.15; 95% CI = 0.96–1.39). Associations were not significant in relation to the frequency and intensity of the exposure (OR = 1.18; 95% CI = 0.88–1.59 among those frequently exposed and with high intensity of exposure compared with never exposed). Duration of exposure, age at first exposure, time since first exposure were not clearly associated with prostate cancer. A shorter time since last occupational exposure (< 13 years) to alkylphenolic compounds was associated with prostate cancer ($OR_{\text{tertile 1 vs. never}}$ = 1.36; 95% CI = 1.02–1.81), but no linear trend was observed (p-trend = 0.709, Table 3). Similarly, associations were significant for those whom last exposure occurred on 1997 or onwards ($OR_{\geq 1997\text{ vs. never}}$ = 1.33; 95% CI = 1.01–1.77; p-trend = 0.396).

3.3. Associations by scenarios and type of compound

Occupational use of domestic tensioactives, the most common scenario of alkylphenolic compounds use among women, was positively associated with breast cancer (OR = 1.28; 95% CI = 1.02–1.60). Women exposed to NPE, the most frequently used compound, had 21%

Table 1
Descriptive characteristics of controls and cases.

	Breast cancer			Prostate cancer		
	Controls No. (%)[a]	Cases No. (%)[a]	p-Value[b]	Controls No. (%)[a]	Cases No. (%)[a]	p-Value[b]
Overall[c]	1575 (51.0)	1513 (49.0)		1480 (57.5)	1095 (42.5)	
Age			< 0.001			0.003
< 60	844 (53.6)	974 (64.4)		273 (18.4)	187 (17.1)	
60–69	375 (23.8)	344 (22.7)		636 (43.0)	544 (49.7)	
≥70	356 (22.6)	195 (12.9)		571 (38.6)	364 (33.2)	
Region			0.016			0.004
Barcelona	342 (21.7)	272 (18.0)		591 (39.9)	399 (36.4)	
Madrid	325 (20.6)	301 (19.9)		332 (22.4)	308 (28.1)	
Others	908 (57.7)	940 (62.1)		557 (37.6)	388 (35.4)	
Educational level			0.085			< 0.001
Primary	686 (43.6)	672 (44.4)		767 (51.8)	695 (63.5)	
Secondary	516 (32.8)	531 (35.1)		401 (27.1)	234 (21.4)	
Higher	373 (23.7)	310 (20.5)		312 (21.1)	166 (15.2)	
BMI[d]			0.029			0.575
Underweight < 18.5	34 (2.2)	25 (1.7)		6 (0.4)	2 (0.2)	
Normal 18.5–24.99	748 (47.5)	669 (44.2)		359 (24.3)	267 (24.4)	
Overweight 25–29.99	451 (28.6)	492 (32.5)		759 (51.3)	584 (53.3)	
Obesity > 30	230 (14.6)	258 (17.1)		322 (21.8)	224 (20.5)	
Diabetes			0.524			< 0.001
No	1447 (91.9)	1398 (92.4)		1158 (78.2)	921 (84.1)	
Yes	122 (7.7)	108 (7.1)		320 (21.6)	170 (15.5)	
Alcohol consumption			0.011			0.445
Never	371 (23.6)	321 (21.2)		75 (5.1)	50 (4.6)	
Ever - current	884 (56.1)	824 (54.5)		1077 (72.8)	793 (72.4)	
Ever - past	97 (6.2)	130 (8.6)		102 (6.9)	89 (8.1)	
Smoking			0.002			0.166
Never smoker	878 (55.7)	781 (51.6)		390 (26.4)	323 (29.5)	
Current smoker	328 (20.8)	298 (19.7)		296 (20.0)	199 (18.2)	
Former smoker	367 (23.3)	430 (28.4)		793 (53.6)	571 (52.1)	
Occupational exposure to solvents			0.011			0.358
Never	1419 (90.1)	1319 (87.2)		988 (66.8)	712 (65.0)	
Ever	156 (9.9)	194 (12.8)		492 (33.2)	383 (35.0)	
Occupational exposure to pesticides			0.055			< 0.001
Never	1426 (90.5)	1337 (88.4)		1171 (79.1)	791 (72.2)	
Ever	148 (9.4)	174 (11.5)		308 (20.8)	304 (27.8)	
Occupational shifts			0.440			0.171
Day shifts	1183 (75.1)	1175 (77.7)		933 (63.0)	704 (64.3)	
Ever permanent night shifts	84 (5.3)	96 (6.3)		161 (10.9)	150 (13.7)	
Ever rotating night shifts[e]	115 (7.3)	122 (8.1)		188 (12.7)	171 (15.6)	
Other rotating schedules[e]	128 (8.1)	108 (7.1)		95 (6.4)	69 (6.3)	
Cancer family history[f]			< 0.001			< 0.001
No	1239 (78.7)	988 (65.3)		1257 (84.9)	828 (75.6)	
Yes	274 (17.4)	481 (31.8)		112 (7.6)	226 (20.6)	
Age at menarche			0.041			
≤13	1002 (63.6)	1038 (68.6)			Not applicable	
> 13	513 (32.6)	453 (29.9)				
Hormonal contraceptives			0.176			
Never	744 (47.2)	750 (49.6)			Not applicable	
Ever	829 (52.6)	758 (50.1)				
Parity (number of children)			0.113			
Nulliparous	274 (17.4)	291 (19.2)			Not applicable	
1	239 (15.2)	283 (18.7)				
2	571 (36.3)	590 (39.0)				
≥3	350 (22.2)	313 (20.7)				
Age at first delivery[g]			0.694			
≤26	584 (50.3)	586 (49.4)			Not applicable	
> 26	573 (49.4)	594 (50.1)				
Menopause status			0.519			
Postmenopause	1119 (71.0)	1075 (71.1)			Not applicable	
Premenopause	433 (27.5)	438 (28.9)				
Postmenopausal hormone therapy[h]			0.426			
Never	948 (84.7)	942 (87.6)			Not applicable	
Ever	114 (10.2)	101 (9.4)				

No. = number, % = percentage.
[a] Percentages do not sum to the total due to missing values.
[b] Chi squared, calculated without missing values.
[c] Row percentage, the rest of percentages in the table are column percentages.
[d] Expressed as weight (kg)/height^2 (m^2).
[e] Never permanent night shifts.
[f] Family history of breast/prostate cancer.
[g] Among parous women.
[h] Among postmenopausal women.

Table 2
Descriptive characteristics among controls by occupational exposure to alkylphenolic compounds.

	Breast cancer			Prostate cancer		
	Never exposed No. (%)[a]	Ever exposed No. (%)[a]	p-Value[b]	Never exposed No. (%)[a]	Ever exposed No. (%)[a]	p-Value[b]
Overall[c]	1233 (78.3)	342 (21.7)		1103 (74.5)	377 (25.5)	0.008[d]
Age			0.001			0.031
< 60	692 (56.1)	152 (44.4)		220 (19.9)	53 (14.1)	
60–69	277 (22.5)	98 (28.7)		460 (41.7)	176 (46.7)	
≥70	264 (21.4)	92 (26.9)		423 (38.3)	148 (39.3)	
Region			0.069			0.001
Barcelona	254 (20.6)	88 (25.7)		409 (37.1)	182 (48.3)	
Madrid	265 (21.5)	60 (17.5)		263 (23.8)	69 (18.3)	
Others	714 (57.9)	194 (56.7)		431 (39.1)	126 (33.4)	
Educational level			< 0.001			< 0.001
Primary	427 (34.6)	259 (75.7)		515 (46.7)	252 (66.8)	
Secondary	449 (36.4)	67 (19.6)		296 (26.8)	105 (27.9)	
Higher	357 (29.0)	16 (4.7)		292 (26.5)	20 (5.3)	
BMI[e]			< 0.001			0.954
Underweight < 18.5	30 (2.4)	4 (1.2)		5 (0.5)	1 (0.3)	
Normal 18.5–24.99	624 (50.6)	124 (36.3)		268 (24.3)	91 (24.1)	
Overweight 25–29.99	348 (28.2)	103 (30.1)		566 (51.3)	193 (51.2)	
Obesity > 30	155 (12.6)	75 (21.9)		243 (22.0)	79 (21.0)	
Diabetes			0.133			0.817
No	1140 (92.5)	307 (89.8)		865 (78.4)	293 (77.7)	
Yes	89 (7.2)	33 (9.6)		237 (21.5)	83 (22.0)	
Alcohol consumption			0.019			0.145
Never	278 (22.5)	93 (27.2)		60 (5.4)	15 (4.0)	
Ever - current	719 (58.3)	165 (48.2)		808 (73.3)	269 (71.4)	
Ever - past	72 (5.8)	25 (7.3)		69 (6.3)	33 (8.8)	
Smoking			0.002			0.234
Never smoker	664 (53.9)	214 (62.6)		292 (26.5)	98 (26.0)	
Current smoker	256 (20.8)	72 (21.1)		231 (20.9)	65 (17.2)	
Former smoker	311 (25.2)	56 (16.4)		579 (52.5)	214 (56.8)	
Occupational exposure to solvents			0.002			< 0.001
Never	1126 (91.3)	293 (85.7)		858 (77.8)	130 (34.5)	
Ever	107 (8.7)	49 (14.3)		245 (22.2)	247 (65.5)	
Occupational exposure to pesticides			< 0.001			< 0.001
Never	1161 (94.2)	265 (77.5)		897 (81.3)	274 (72.7)	
Ever	71 (5.8)	77 (22.5)		206 (18.7)	102 (27.1)	
Occupational shifts			0.082			< 0.001
Day shifts	933 (75.7)	250 (73.1)		728 (66.0)	205 (54.4)	
Ever permanent night shifts	57 (4.6)	27 (7.9)		95 (8.6)	66 (17.5)	
Ever rotating night shifts[f]	93 (7.5)	22 (6.4)		127 (11.5)	61 (16.2)	
Other rotating schedules[f]	104 (8.4)	24 (7.0)		74 (7.2)	21 (5.6)	
Cancer family history[g]			0.912			0.392
No	973 (78.9)	266 (77.8)		930 (84.3)	327 (86.7)	
Yes	216 (17.5)	58 (17.0)		87 (7.9)	25 (6.6)	
Age at menarche			0.275			
≤13	794 (64.4)	208 (60.8)			Not applicable	
> 13	394 (32.0)	119 (34.8)				
Hormonal contraceptives			0.022			
Never	564 (45.7)	180 (52.6)			Not applicable	
Ever	668 (54.2)	161 (47.1)				
Parity (number of children)[h]			< 0.001			
Nulliparous	238 (19.3)	36 (10.5)			Not applicable	
1	189 (15.3)	50 (14.6)				
2	447 (36.3)	124 (36.3)				
≥3	255 (20.7)	95 (27.8)				
Age at first delivery[g]			< 0.001			
≤26	418 (46.9)	166 (61.7)			Not applicable	
> 26	470 (52.7)	103 (38.3)				
Menopause status			< 0.001			
Postmenopause	849 (68.9)	270 (78.9)			Not applicable	
Premenopause	370 (30.0)	63 (18.4)				
Postmenopausal hormone therapy[i]			0.204			
Never	714 (84.1)	234 (86.7)			Not applicable	
Ever	92 (10.8)	22 (8.1)				

No. = number, % = percentage.
[a] Percentages do not sum to the total due to missing values.
[b] Chi squared, calculated without missing values.
[c] Row percentage, the rest of percentages in the table are column percentages.
[d] Chi-squared test of difference of exposure by sex.
[e] Expressed as weight (kg)/height^2 (m^2).
[f] Never permanent night shifts.
[g] Family history of breast/prostate cancer.
[h] Among parous women.
[i] Among postmenopausal women.

increased probability of cancer that the unexposed (OR = 1.21; 95% CI = 1.00–1.47). Occupational exposure in other scenarios or to other compounds showed mostly similar non-statistically significant associations (Fig. 1).

In general, we did not observe associations between the different scenarios and specific types of alkylphenolic compounds and prostate cancer (Fig. 1). An exception was the occupational use of cosmetic, hair and personal hygiene products, which was associated with nearly threefold risk compared to the unexposed (OR = 2.97; 95% CI = 1.15–7.69), although sample size was small (8 controls and 15 cases).

3.4. Sensitivity analyses

Among those unexposed to solvents, estimates were usually above the unity, and the ORs for the association between ever exposure to alkylphenolic compounds and breast cancer (OR = 1.19; 95% CI = 0.97–1.47) was similar to the overall ORs for whole population (Table 3) although it was no longer statistically significant (Supplemental Table 1). When we considered only those exposures that were frequent and/or of high intensity, conclusions were mostly similar (Supplemental Table 2). Adjusting models for maternal or paternal SES yielded similar conclusions. No significant interactions were detected between BMI, menopausal status or education and ever exposure to alkylphenolic compounds (data not shown). Analyses excluding 138 in situ breast tumors yielded similar results ($OR_{ever\ vs.\ never}$ = 1.25; 95% CI = 1.03–1.51). Analyses by tumor receptors revealed significant associations with ever exposure for triple negative cancers (OR = 1.83; 95% CI = 1.17–2.87), but not for HER-2 positive or hormonal receptors positive cancers (OR = 0.91; 95% CI = 0.62–1.35; and OR = 1.18; 95% CI = 0.95–1.47, respectively; Supplemental Table 3). Analyses by prostate cancer aggressiveness revealed no significant associations when comparing Gleason scores ≤ 7 and > 7 versus controls (OR = 1.17; 95% CI = 0.95–1.45; and OR = 0.75; 95% CI = 0.50–1.13, respectively; Supplemental Table 4).

4. Discussion

Using data from a large epidemiologic case-control study, we observed a moderate positive association between occupational exposure to alkylphenolic compounds and breast cancer, and in general, no associations with prostate cancer. In support of the hypothesis of an association between breast cancer and these chemicals, estimates were stronger among those who ever worked frequently exposed and with high intensity of exposure, compared with those exposed to alkylphenolic compounds but never with a frequent and high intensity. Within the different scenarios of exposure, the occupational use of domestic tensioactives was positively associated with breast cancer, while other scenarios showed similar, but not statistically significant associations. The type of compound most frequently used among exposed women was nonylphenol ethoxylates, which were positively associated with breast cancer. Overall, no associations were observed for prostate cancer and occupational use of alkylphenolic compounds. However, exposures occurred on 1997 or onwards revealed significant associations, as well as occupational use of cosmetic, hair and personal hygiene products, although based on a small sample size.

Despite the growing interest in the potential impact of these chemicals on the environment and on health, data among humans are still scarce, especially for specific EDC (Bergman et al., 2013; Casals-Casas and Desvergne, 2011; Damstra et al., 2002). Alkylphenolic compounds are considered EDC because of their estrogenic and weak anti-androgenic activities (Bontje et al., 2004). Recent in vitro and in vivo data suggested that low-dose alkylphenol exposure promotes mammary alterations, and stated that exposure to alkylphenols could be considered as a tumor promoting environment, while the effect as tumor initiators was not evident (Chamard-Jovenin et al., 2017). Although with certain inconsistencies, risks were increased with recent exposures, which could suggest that the hormone-dependent responses of alkylphenolic compounds might produce the potential effects in a relatively short period of time. However, we observed increased risks among women with triple negative cancer rather than with hormonal receptors positive cancer, which is not in line with our a priori hypothesis of alkylphenols promoting mammary cell proliferation by binding to estrogen receptors. Our findings are in accordance with the scarce published literature on the subject (Aschengrau et al., 1998b; Gray et al., 2017; Villeneuve et al., 2010a). Occupational exposure to 4-octylphenol and a higher risk of breast cancer in females has been previously reported in one study performed in Massachusetts using data from the NIOSH National Occupational Exposure Survey. However, these findings need to be interpreted cautiously as the exposed number of subjects was very small (6 cases and 5 controls) (Aschengrau et al., 1998b). A European case-control study reported an increased risk between occupational exposure to alkylphenolic compounds and breast cancer among males, although with certain inconsistencies, suggesting that alkylphenolic compounds could also play a role in the development of this cancer in men (Villeneuve et al., 2010a).

In accordance with previous literature, breast cancer was associated in our sample with BMI, tobacco, alcohol consumption, age at menarche, and family history of breast cancer (Sun et al., 2017; Winters et al., 2017). Other exposures related to estrogens trough lifetime (parity, age at menopause, use of hormonal contraceptives or postmenopausal hormonal therapy) are also relevant predictors of breast cancer (Sun et al., 2017; Winters et al., 2017). Although these variables were not statistically significantly associated with breast cancer in our bivariate analyses, they were introduced in the fully adjusted model, similarly to educational level, in order to potentially control for confounding and selection bias for these factors. Given that participation rates were lower in controls than cases, selection bias could have occurred as controls have a higher SES than cases. We therefore controlled all analyses for educational level, and explored other different measures of SES, obtaining similar results, which suggests that our results are not strongly influenced by this potential bias. Sensitivity analyses restricting analyses to the unexposed to solvents, as well as reclassifying those with occasional and low intensity as unexposed, yielded similar conclusions. Similarly, associations were not restricted to a particular scenario, such as the occupational use of pesticides. This suggests that our results are not driven by confounding for pesticides or organic solvents, which were previously associated with breast cancer, although with inconsistences (Engel, 2005; Peplonska et al., 2010). None of the previous studies examining associations between alkylphenolic compounds and cancer took into account relevant exposure changes over time. Given the short half-live of these chemicals (Müller et al., 1998) and the long latency of diseases such as cancer, it is important to use a method that allows estimating lifetime exposure and that considers the relevant changes in their use over the years. The use of these compounds has experienced relevant changes throughout last decades worldwide. For instance, in the United Kingdom, the first use of these compounds was detected in 1944, while in Spain they were introduced in 1959 with the opening to international markets. In the 70s, the first concerns about the toxicity of these compounds and their potential to bioaccumulate in marine organisms and in the environment appeared, and voluntary agreements were undertaken to reduce or eliminate the use and manufacture of these compounds. In 2002–2003 the European Union established regulations to limit the use of NP and NPE (Bontje et al., 2004; European Union, 2003; Martín-Bustamante et al., 2017). This is relevant because 92% of the exposed women and 88% of exposed males in our study had an exposure between 1965 and 2002, i.e. before regulations took place to reduce these exposures. We found significant positive associations between breast cancer and both NPE exposure and use of domestic tensioactives. This is probably due to the correlation between these two variables, as NPE is the most frequent compound within the domestic tensioactives scenario (Martín-Bustamante et al., 2017).

Table 3
Associations between breast and prostate cancer and occupational exposure to alkylphenolic compounds.

	Breast cancer				Prostate cancer			
	Controls (n = 1575)	Cases (n = 1513)	OR[a] (95% CI)	OR[b] (95% CI)	Controls (n = 1480)	Cases (n = 1095)	OR[a] (95% CI)	OR[c] (95% CI)
Never exposed to alkylphenolic compounds	1233	1101	Ref	Ref	1103	764	Ref	Ref
Ever exposed to alkylphenolic compounds	342	412	1.28 (1.07–1.54)	1.23 (1.01–1.48)	377	331	1.09 (0.89–1.33)	1.15 (0.96–1.39)
Intensity and frequency of exposure								
Occasional and/or low intensity (scores 1 and 2[d])	93	115	1.21 (0.90–1.63)	1.17 (0.86–1.60)	261	209	1.08 (0.87–1.34)	1.04 (0.83–1.31)
Frequent and high intensity (score 3)	249	297	1.31 (1.07–1.61)	1.25 (1.01–1.55)	116	122	1.32 (0.99–1.75)	1.18 (0.88–1.59)
			0.007	*0.035*			*0.061*	*0.284*
Duration (years)[e]								
Tertile 1	109	148	1.45 (1.11–1.90)	1.34 (1.01–1.77)	113	104	1.24 (0.92–1.66)	1.07 (0.79–1.44)
Tertile 2	115	135	1.17 (0.89–1.54)	1.18 (0.88–1.58)	130	95	0.98 (0.73–1.31)	0.91 (0.67–1.25)
Tertile 3	118	129	1.23 (0.93–1.62)	1.15 (0.86–1.55)	134	132	1.25 (0.96–1.64)	1.28 (0.96–1.71)
P_{trend}			*0.134*	*0.296*			*0.168*	*0.141*
Age at first exposure[f]								
Tertile 1	111	150	1.28 (0.97–1.68)	1.16 (0.87–1.54)	102	84	1.02 (0.74–1.41)	0.94 (0.67–1.32)
Tertile 2	113	119	1.17 (0.88–1.55)	1.14 (0.85–1.54)	143	135	1.27 (0.98–1.66)	1.18 (0.90–1.56)
Tertile 3	118	143	1.40 (1.07–1.83)	1.35 (1.04–1.84)	131	112	1.13 (0.85–1.50)	1.10 (0.82–1.49)
P_{trend}			*0.007*	*0.020*			*0.131*	*0.337*
Time since first exposure (years)[g]								
Tertile 1	113	182	1.47 (1.13–1.91)	1.50 (1.14–1.98)	100	95	1.26 (0.93–1.72)	1.22 (0.88–1.68)
Tertile 2	111	136	1.20 (0.91–1.59)	1.09 (0.81–1.47)	139	113	1.02 (0.78–1.35)	1.00 (0.75–1.35)
Tertile 3	118	94	1.13 (0.83–1.54)	1.05 (0.76–1.44)	138	123	1.21 (0.92–1.60)	1.08 (0.81–1.44)
P_{trend}			*0.061*	*0.265*			*0.157*	*0.502*
Time since last exposure (years)[h]								
Tertile 1	114	161	1.33 (1.01–1.73)	1.25 (0.95–1.66)	120	132	1.38 (1.05–1.82)	1.36 (1.02–1.81)
Tertile 2	114	149	1.39 (1.07–1.83)	1.39 (1.05–1.85)	130	89	0.97 (0.72–1.31)	0.93 (0.68–1.28)
Tertile 3	114	102	1.10 (0.82–1.48)	1.02 (0.75–1.39)	127	110	1.11 (0.84–1.48)	0.98 (0.73–1.32)
P_{trend}			*0.219*	*0.493*			*0.583*	*0.709*
Year of last exposure[i]								
Tertile 1	113	102	1.12 (0.83–1.51)	1.05 (0.77–1.42)	122	108	1.16 (0.87–1.54)	1.02 (0.76–1.38)
Tertile 2	112	142	1.35 (1.03–1.78)	1.32 (0.99–1.76)	126	82	0.91 (0.67–1.24)	0.88 (0.64–1.22)
Tertile 3	117	168	1.35 (1.04–1.76)	1.30 (0.98–1.72)	129	141	1.38 (1.05–1.80)	1.33 (1.01–1.77)
P_{trend}			*0.007*	*0.035*			*0.125*	*0.396*

OR = odds ratio, CI = confidence interval. Numbers do not add up to the totals due to missing values.

[a] Adjusted for region, age and educational level.

[b] Adjusted for age, region, educational level, BMI, smoking, alcohol consumption, occupational shift, exposure to pesticides, exposure to solvents, hormonal contraception, postmenopausal hormone therapy, menopausal status and parity.

[c] Adjusted for age, region, educational level, BMI, smoking, alcohol consumption, occupational shift, exposure to pesticides and exposure to solvents.

[d] Never score 3.

[e] Tertiles for breast cancer: < 6, 6–14.99, ≥15, for prostate cancer: < 6, 6–24.99, ≥25.

[f] Tertiles for breast cancer: < 19, 19–28.99, ≥29, for prostate cancer: < 18, 18–25.99, ≥26.

[g] Tertiles for breast cancer: < 30, 30–43.99, ≥44, for prostate cancer: < 40, 40–48.99, ≥49.

[h] Tertiles for breast cancer: < 9.5, 9.5–26.49, ≥26.5, for prostate cancer: < 13, 13–34.99, ≥35.

[i] Tertiles for breast cancer: < 1984, 1984–2000, ≥2001, for prostate cancer: < 1976, 1976–1996, ≥1997.

In general, we found no associations between prostate cancer and exposure to alkylphenolic compounds. Previous studies suggested a possible relationship between exposure to endocrine disrupting compounds with estrogenic activity, other than alkylphenols, and an increased prostate cancer risk (Hess-Wilson and Knudsen, 2006). However, no epidemiologic study has ever evaluated the relationship between alkylphenolic compounds and prostate cancer. Besides their estrogenic activity, alkylphenolic compounds may also have weak anti-androgenic effects, as they can act as partial agonists of androgenic receptors thus inhibiting the effect of full agonists (Weiss et al., 2009). Androgens are necessary for cancer prostate development, and androgen receptor signaling has been well characterized in the development of prostate cancer metastasis (Zhou et al., 2014). Although they have been less studied in cancer prostate risk compared with breast cancer, there is evidence that high doses of estrogens also have direct effects on the development of the prostate gland and also indirect effects through the suppression of the hypothalamic pituitary gonadal axis (Jarred et al., 2000). Metabolism of these sex hormones is complex and correlated and conversion of androgens to estrogens is mediated by an enzyme encoded by CYP19A1 (Risbridger et al., 2010; Rothenberger et al., 2018). Given the complexity of the hormonal metabolism, and the estrogenic and anti-androgenic effects of alkylphenolic compounds, further research is needed to disentangle whether and how these compounds could influence prostate cancer risk.

JEMs for occupational exposure assessment are useful and cost-efficient tool in large scale studies (Kauppinen, 1996; Kim et al., 2011; Le Moual et al., 2000; Martín-Bustamante et al., 2017), but they can lead to substantial misclassification of exposures (Rothman et al., 2007). In the present analysis, this misclassification would be non-differential as the exposure assessment was blind to the case-control status. In case of truly positive associations, it would result in the attenuation of the estimates for binary and continuous exposures (Pearce et al., 2007; Steenland et al., 2000). The JEM used in the present analyses was developed undertaking several strategies to minimize potential sources of misclassification. Among others, it considered relevant changes over time in use and manufacture of alkylphenolic compounds in the same population that it is applied, which probably results in better estimates of the exposure. However, we could not validate the JEM using biologic measurements given the short life of these compounds, and the changes in use over time. Evaluating levels among workers may help better understanding current exposures, but the scores in our JEM reflect lifetime exposures which have greatly varied over time. We had the opportunity to adjust for many potential confounders, including well-established and other potential risk factors for breast and prostate cancer. We did not observe clear evidence of confounding by any of them, although residual confounding cannot be completely discarded in explaining some of our results. Non-occupational sources of exposure, such as diet, use of personal care and household cleaning products, could be relevant sources of alkylphenolic compounds. The JEM exposure scores reflect the probability that occupational exposure contributes significantly to an individual's body burden in comparison to other sources of exposure. Although we do not expect big differences in background levels, we were not able to assess non-occupational sources of these compounds and therefore certain misclassification of the exposure cannot be ruled out. The relatively large sample size of the study, allowed us to perform several subgroup analysis. Nevertheless, some of the analyses by scenarios and compound subtypes were based on small sample sizes. Some of the job titles involving alkylphenols actually involved a mixture of alkylphenols and alkylphenolic ethoxylates, and therefore the JEM that we used did not assign a more specific category of compound. Some of the reported associations could be spurious as multiple comparisons were performed in our analysis.

5. Conclusion

To our knowledge, this is the largest study examining the relationship between occupational exposure to alkylphenolic compounds and breast and prostate cancer. We examined these associations using a method that considered relevant changes over time in the use of these compounds, and we adjusted for multiple potential confounding variables. Our findings suggest a modest association between breast cancer risk and occupational exposure to alkylphenolic compounds, while no association with prostate cancer. The elucidation of the role of alkylphenolic compounds on breast and prostate cancers should shed a light on the etiology of those tumors and help informing future public health decisions.

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Conflicts of interest

The authors have no conflict of interests to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2018.12.007.

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