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Biomarkers of end of shift exposure to disinfection byproducts in nurses

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ABSTRACT

Increased disinfectant use commonly takes place in hospitals and other health care settings. A cross-sectional study among active nurses in two Cypriot public hospitals (n = 179) was conducted to examine the prevalence of exposure to disinfection byproducts (DBPs), such as trihalomethanes (THMs) using both self-reported information and biomarker measurements. The objectives of this study were to: i) quantify the magnitude and variability of occupational exposure to disinfectants/DBPs in nurses, ii) generate job exposure matrices (JEM) and job task exposure matrices (JTEM) for disinfectants, and iii) assess the major determinants of urinary THMs in nurses. End of shift urinary total THM values showed high variability among the nurses, but did not differ between hospitals. The disinfectant group of alcohols/phenols was used by >98% of nurses, followed by octenidine (82%), iodine and chlorine (39%, each), chlorhexidine (25%), formaldehyde (12%), hydrogen peroxide (11%), and peracetic acid/ammonia/quaternary ammonium compounds (QACs), all being <8% each. Chlorine use during the past 24 hr was associated with significantly ($p < 0.05$) lower brominated THMs (BrTHMs) after adjusting for age, gender and BMI, while a positive association was shown for TCM and the sum of all THMs (TTHMs), albeit not significant. Nurses were exposed to nearly double the levels of TTHMs and BrTHMs (median and IQR, 1027 [560, 2475] ng/g and 323 [212, 497] ng/g, respectively) when compared to those of the general population (552 [309,989] ng/g and 152 [87,261] ng/g, respectively). This was the first occupational health dataset reporting measurements of biomarkers of end of shift exposures to disinfectants/DBPs.

Introduction

Disinfectants are widely used in hospitals and general healthcare facilities against microorganisms on surfaces or other inanimate objects (Larson, 1997; Rutala, 1996). The use of disinfectants is essential to ensure elimination of pathogens (Rivera-Núñez et al., 2012) and other disease-causing microorganisms responsible for diseases, such as typhoid, hepatitis, Giardia, and cholera (Aylward et al., 2008). At the same time, the reaction of disinfectants with naturally-occurring organic matter commonly found in water, surfaces, dust and particulate matter could result in the production of disinfection byproducts (DBPs) (Richardson et al., 2007; Rivera-Núñez et al., 2012). The most abundant class of DBPs includes the trihalomethanes (THMs) that are comprised of chloroform (TCM), bromodichloromethane (BDCM), dibromochloromethane (DBCM) and bromoform (TBM). The THMs are ubiquitous in drinking water and they may be used as surrogate markers of exposures to DBPs (Charisiadis et al., 2014; Rivera-Núñez et al., 2012). Numerous epidemiologic

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studies for the general population have shown adverse health effects of THMs, some of them being bladder cancer, congenital abnormalities and birth defects (Nieuwenhuijsen et al., 2009; Villanueva et al., 2004; Wright et al., 2016).

The THMs may be also released into the indoor environment of the work place, when disinfectants (*e.g.*, chlorine-based) may be used for both bleaching processes or for disinfecting occupational areas/surfaces/instruments (International Program on Chemical, 2004). Occupational exposure to DBPs has been demonstrated in hospitals, water treatment plants, and paper manufacturing (International Program on Chemical, 2004). Healthcare workers had a higher risk for developing work-related asthma [OR of 2.38 (95% CI: 1.06 to 5.33)] when exposed to disinfectants/cleaning products during work, such as bleach, quaternary ammonium compounds (QACs), and chlorhexidine (Dumas et al., 2012).

The frequency of disinfection tasks in hospitals is increasing during the last years to protect patients against hospital-associated infections (Quinn et al., 2015). Nurses represent a large occupational group within the healthcare sector that is systematically exposed to disinfectants and other cleaning chemicals, including numerous volatile organic compounds (VOCs) (LeBouf et al., 2014). Using personal air measurements, nurses had the highest exposure to (semi)VOCs, such as chloroform (one of the disinfection byproducts, THMs) than to hospital cleaners or floor strippers/waxers among fourteen different occupations typically encountered in healthcare facilities (LeBouf et al., 2014).

To the best of our knowledge, no studies are currently available that deal with biomarkers of exposure to disinfectants/disinfection byproducts in occupational settings, including hospitals. We hypothesized that daily and chronic use of commercial cleaning/disinfection products in healthcare facilities that include active halogenated disinfectant ingredients, could also result in high exposures to disinfection byproducts, such as THMs. A cross-sectional study among active nurses in two Cypriot public hospitals was conducted to examine the prevalence of exposure to THMs and their major determinants using both self-reported information and measurements of end-of-shift urinary biomarkers of THM exposure. The objectives of this study were: i) to quantify the magnitude and variability of occupational exposure to disinfectants/disinfection byproducts in nurses, ii) to generate detailed job exposure matrices (JEM) and job task exposure matrices (JTEM) for disinfectants, and iii) to determine the major predictors of the urinary THMs measurements in nurses.

1. Materials and methods

1.1. Study design

This project study design and reporting conformed to guidelines of the STROBE statement (von Elm et al., 2014). A standard operations procedure protocol detailed the procedures and steps required to execute and harmonize data collection from active nurses in Cypriot hospitals. The recruitment took place during spring and summer 2016 in two major public hospitals of Cyprus. The research team distributed the study flyers to encourage nurses' participation in all departments/units of each hospital.

Sample and data collection took place always towards the end of the nurses' shift that could be either 6 am, 12 pm or 6 pm. Study participants were male and female Cypriot nurses, residing in Cyprus and working in hospitals for at least the last five years. Study participants were recruited from the general public hospitals in Limassol and Larnaca (major cities in Cyprus). Participants that were cancer patients or pregnant women were excluded. This study was approved by the Cyprus National Bioethics Committee (Prot. #ΕΕΒΚ/ΕΠ/2015/28 15/10/2015), the Office of the Commissioner for Personal Data Protection (Prot. #3.28.375 22/10/2015) and the Ministry of Health (Prot. #0332/2015 22/12/2015). Written informed consent was obtained from all volunteers.

Anthropometrics, such as waist and hip circumference, height and weight were also obtained following standardized protocols. End-of-shift urine samples were collected by all participants in polypropylene vials with no preservatives added. The formation of THMs upon usage of disinfectant chlorine was confirmed with lab experiments mixing regular tap water with commercial disinfectant chlorine solution following product mixing instructions for cleaning surfaces and areas (200 mL/5 kg water) to simulate real-life conditions; aliquots were taken at regular time intervals and analyzed for THM, pH and residual chlorine with in-house protocols; free chlorine was measured with a portable photometer (MaxiDirect, Lovibond), and pH values with a portable pH meter (Seven Duo pro™, Mettler Toledo).

Eligible participants who volunteered to participate in the study were requested to complete two questionnaires. The questionnaires included questions about frequency of use of various disinfectants in specific tasks for all departments/units of the hospitals. The validated questionnaire was adapted by a previously used questionnaire in the "Occupational Survey for Nurses' Health Study" in the U.S. (obtained approval for use by Prof. C. Camargo, Harvard Medical School). The software EpiData was used for the digitization of the questionnaires. A digitization protocol ensured consistent and universal data entry for each questionnaire and each volunteer. All the questions and the relevant variables that used in the subsequent analysis were included in two separate files that allowed for efficient data sharing. Extra variables needed for the measurements during the statistical analysis were added in the process of digitization and data processing.

1.2. Urine analyses

A liquid–liquid extraction protocol was used for the measurement of THM in urine, following the protocol by Charisiadis and Makris (2014). Three milliliters of urine (spiked with surrogate solution, 9 μL of 10 mg/L in *n*-propanol, at a final concentration of 30 μg/L) were mixed with 150 μL of *n*-propanol and 1 mL of pentane (extraction solvent), followed by the addition of 1.2 g of sodium sulfate, shaking for 10 min at 100 r/min and centrifuged for 1 min at 2500 r/min. 4-Bromofluorobenzene (internal standard) was purchased from Supelco (Belle-fonte, USA), while decafluorobiphenyl (surrogate standard) was purchased from Sigma-Aldrich. Half a milliliter of the organic phase was transferred into a gas chromatograph (GC) screw top glass vial with blue PTFE/butyl rubber septa (Restek, USA), containing the

internal standard solution, 10 μL of 10 mg/L in acetone, at final concentration of 200 μg/L. Finally, a 2 μL portion of sample was the injected volume. Gas chromatography mass spectrometry (GC–MS) spectra were recorded on an Agilent 7890A GC equipped with an Agilent 7000B triple quadrupole mass spectrometry (MS) detector.

The THMs compounds were separated on an Rxi-5ms (5% diphenyl/95% dimethylpolysiloxane) column from Restek (30 m × 250 μm × 0.25 μm) and helium carrier gas (99.999%) flow was maintained at 1.0 mL/min. The inlet temperature was set at 140 °C for 0.1 min then ramped to 300 °C at a rate 300 °C/min where it was maintained. The oven was set to 30 °C for 5 min, ramped to 100 °C at a rate 50 °C/min where it was maintained for 2.4 min, then ramped to 260 °C at a rate 120 °C/min where it was maintained for 1.6 min followed by a post-run period at 260 °C for 1 min. The total run time was 11.5 min. The injection volume was 2 μL, and the injection syringe was washed 3 times with acetone before and after sample injection. Mass selective detector (MSD) transfer line and MS source temperatures were held at 250 °C, while quadrupoles were held at 150 °C. Mass spectra were obtained using electron ionization (70 eV) in the multiple reaction monitoring (MRM) mode in 3 per second scanning cycles, with a solvent delay of 4.0 min (details in Appendix A Table SI 1). The system was controlled by the software Mass Hunter Workstation (Agilent, rev. B.05.00). Urinary creatinine was determined by the picric acid based spectrophotometric method (Jaffe method) (Angerer and Hartwig, 2010).

1.3. Development of the job-exposure (JEM) and the job-task-exposure (JTEM) matrices

Summary estimates of the exposures per chemical using job-exposure (JEM) and job-task exposure (JTEM) matrices were created following the methodology by Quinot et al. (2017). We used current job type (department/unit) and frequency of use of disinfectants to develop JEM and JTEM using two methods, based on weekly use of disinfectants (yes/no) and exposure frequency (days/week). For the development of JEM, the question of exposure to disinfectants (exposed if >1 day/week) was categorized for each department. For JTEM, two questions on disinfection tasks (disinfecting hospital equipment/operating room/sanitation of hygiene facilities, and preparation/mixing of disinfectants) were used to create a categorical variable, including i) both disinfecting materials/places and preparation/mixing of disinfectants (All), ii) either of the tasks (disinfecting only materials/places (MatPlace), or only preparation/mixing/filling disinfectants (Prep)) and iii) none of the above tasks (None).

Ten different departments/units, where participating nurses were currently employed to, namely, cardiology, emergency room (ER), gynecology, intensive care unit (ICU), nephrology, operation room (OR), orthopedic, pathology, pediatric and other, were considered. The category "Other" included all departments/units with <10 study participants. For both JEM and JTEM, a total of 6 unique disinfectants were considered including chlorhexidine, chlorine, peracetic acid, hydrogen peroxide, iodine, and QACs. The other categories investigated such as alcohols or formaldehyde were not considered due to either ubiquitous exposures (>80%) or very low prevalence of exposures (<10%) and, thus, were excluded from the development of the exposure matrices.

The development of Method 1 for JEM and JTEM was based on the % participants reporting any exposure to use of disinfectants in the department/unit they were working on and stratified by each department and department and task, respectively. The second method (Method 2) was based on a weighted score according to the frequency of exposure to the specific chemicals using the percentage of self-reported exposure weighted by a factor of either 2 for those reporting 1–3 days/week use or a factor of 5 (4–7 day/week) (Quinot et al., 2017).

The median of the exposure prevalence was used as the cut-off to define exposure to each disinfectant for Method 1, or the median of the scores for Method 2. The same cut-offs were used for both JEM and JTEM matrices. When the median of the exposure prevalence was zero, then, the cut-off used was 10% prevalence of exposure, or the score of 40, for Method 1 and Method 2 respectively. Then, each participant was assigned the category of exposure (0 or 1) for the specific job and job-task.

1.4. Statistical analysis

Total THMs (TTHMs) was defined as the sum of the four THMs that we analyzed and brominated THMs (BrTHM) as the total of BDCM, DBCM and TBM. Urinary concentrations below the method limit of detection (LOD) were assigned to half the LOD and concentrations above the LOD and below the method limit of quantification (LOQ) were assigned half the LOQ. Urinary creatinine values < 0.1 g/L were not included in the analysis, as unacceptably low values for healthy population (Barr et al., 2005). After descriptive plots (histograms, Q-Q plots) and descriptive tests (skewness and kurtosis), distributions of all THMs showed significant deviations from a normal distribution (skewed to the right and the Q-Q plots did not support the normality criterion), hence data on THMs was transformed using the natural logarithm (ln).

Associations between the urinary THM levels and the exposures were evaluated using the last 24-hour exposure metrics to any disinfectant, chlorine or chlorhexidine and the exposure categories as derived from the JEM and JTEM matrices; Spearman correlation coefficients were calculated for the former, and univariate and multivariate regression analysis for the latter. The multivariate regression models were adjusted for age, body mass index (BMI), and time of sampling. All statistical analyses were performed using R (version 3.4.0) and RStudio (version 1.0.143) and its packages: tableone, knitr, readr, readxl, plyr (R Core Team, 2015; RStudio Team, 2015). Tests were two-tailed. The level of nominal significance was set at $p < 0.05$.

2. Results

This study's population of nurses was recruited from two hospitals (67% from hospital 1) with hospital 1 being overall larger in size than hospital 2 (Table 1). Out of 720 registered nurses in both hospitals, a total of 179 nurses (25%) completed the study. Most nurses were females (62%) with a mean age of 36 years and a mean body mass index of 26.3 kg/m^2, being mostly university graduates and non-smokers (62%) with about

5 years of work experience in a hospital. Mean night shift frequency was 4.5 shifts per month. In total, 70 end of shift urine samples were collected after the morning shift (42%), 59 after the afternoon shift (35%) and 39 after the night shift (23%). With regards to time of sampling, a higher number of participants were recruited after the night shift from hospital 1 compared to hospital 2. With the exception of age being significantly ($p < 0.05$) larger for those nurses working in hospital 2, rest of descriptive covariates did not differ in magnitude for nurses among the two participating hospitals (Table 1).

End of shift urinary total THM values (ng/L) were quite high [median (interquartile range (IQR)) of 1040 (582, 1564)], showing high variability among nurses (Table 2), but did not differ among hospitals. Median total THM levels (1003 ng/g) were lower in hospital 1, but not significantly different ($p > 0.05$) than those for hospital 2 (1127 ng/g) both for raw concentrations (ng/L) and those adjusted for creatinine; raw (ng/L) concentrations of the sum of the brominated THM (BrTHM) species was higher in hospital 1, however, this difference did not hold after adjustment for creatinine (data not shown). Overall, TCM was the predominant THM compound, being always higher in magnitude than the brominated THM (BrTHM) compounds in nurses (median of 673 *vs.* 323 ng/g).

The disinfectant group of alcohols/phenols was used by >98% of nurses, followed next by octenidine (82%). The next most frequently used disinfectants in all departments using self-reported exposure metrics were iodine and chlorine (39%, each) followed by chlorhexidine (25%), formaldehyde (12%), hydrogen peroxide (11%), peracetic acid/ammonia and QAC, all being <8% each (Table 3). Overall, a larger percentage of nurses were classified as exposed to a disinfectant when the self-reported percentage of exposure to a disinfectant was relatively low (<25%), while the reverse, a smaller number of nurses were classified as exposed *via* the JEM/JTEM approaches when the self-reported percentage of exposure was >80% (Table 3). Different disinfection tasks were conducted by hospital departments showing large heterogeneity in exposure to the suite of the studied disinfectants. In Table S2 and Table S3, the complete JEM and JTEM tables with the exposure categories per job and job-task can be found.

In linear regression analysis, various exposure metrics were used to regress the biomarkers of exposure to DBPs on the nurses data, such as the self-reported frequency of any disinfectant use, the JEM and JTEM metrics using two different exposure classification methods along with the past 24-hour reported usage of disinfectant at work (Table 4, Table S5). Chlorine use during the past 24 hr was associated with significantly ($p < 0.05$) lower BrTHM levels after adjusting for age, gender and BMI, while a positive association was shown for TCM and TTHM, albeit not significant. Depending on the external environmental conditions present in the workplace and the type of disinfectant used, the concomitant THMs formation will either mostly take the form of TCM or that of BrTHMs, but not both. This was confirmed by our lab experiments mixing disinfectant chlorine solution with tap water generating TCM to the expense of BrTHM that remained unchanged (Table S6). JTEM-based, but not JEM-based, exposure to chlorine disinfectant was negatively associated with urinary BrTHM levels, similar to what was shown with the past 24-h exposure to chlorine.

3. Discussion

This is the first report on the ubiquitous presence (detection rate, >95%) of disinfection byproducts among nurses in public hospitals using end of shift biomarkers of exposure to trihalomethanes (major class of disinfection byproducts). This study also evaluated the influence of self-reported and

Table 1 – Study population characteristics, overall and by hospital.

	Overall	Hospital 1	Hospital 2	*p*
N	173	116	57	
Gender				0.455
Male, n (%)	66 (38.2)	47 (40.5)	19 (33.3)	
Female, n (%)	107 (61.8)	69 (59.5)	38 (66.7)	
Age (years, mean (sd))	36.11 (8.49)	34.85 (7.79)	38.68 (9.34)	0.005
BMI (kg/m^2, mean (sd))	26.29 (5.25)	26.26 (5.25)	26.36 (5.29)	0.909
Education level				0.186
Non-university degree, n (%)	4 (2.3)	3 (2.6)	1 (1.8)	
University degree, n (%)	126 (73.3)	80 (69.0)	46 (82.1)	
Postgraduate degree, n (%)	42 (24.4)	33 (28.4)	9 (16.1)	
Smoking status				0.652
Non-smoker, n (%)	105 (61.8)	69 (60.0)	36 (65.5)	
Former smoker, n (%)	17 (10.0)	11 (9.6)	6 (10.9)	
Smoker, n (%)	48 (28.2)	35 (30.4)	13 (23.6)	
Years working in hospital (mean (sd))	4.92 (5.02)	4.82 (5.12)	5.12 (4.86)	0.732
Night shifts per month (mean (sd))	4.47 (1.83)	4.41 (1.95)	4.62 (1.48)	0.533
Shift				<0.001
Morning, n (%)	70 (41.7)	49 (44.1)	21 (36.8)	
Afternoon, n (%)	59 (35.1)	26 (23.4)	33 (57.9)	
Night, n (%)	39 (23.2)	36 (32.4)	3 (5.3)	

BMI: body mass index; sd: standard deviation.

Table 2 – Percentiles of urinary THM concentrations for the whole study population.

	Mean	SD	Min	5th	25th	50th	75th	90th	95th	Max
DBPs (ng/L)										
TCM	1210	1668	15*	15*	220	747	1238	2686	5083	8362
BDCM	152	48	26*	60	163	163	163	187	215	406
DBCM	66	31	11*	11*	32*	72	82	100	108	159
TBM	106	64	8*	37	70	92	119	182	226	553
BrTHM	323	81	95	210	292	322	343	411	438	832
TTHM	1534	1682	225	313	582	1042	1564	2990	5379	8668
DBPs ng/g creatinine										
TCM	1743	3053	8	11	214	673	1832	5309	6394	21,957
BDCM	229	250	15	53	94	143	230	538	766	1460
DBCM	100	123	5	11	36	58	109	211	372	835
TBM	152	149	5	29	54	101	185	376	467	790
BrTHM	481	476	69	130	212	323	497	992	1603	2988
TTHM	2223	3243	145	251	560	1027	2475	5843	7962	22,745

Values marked with an asterisk are imputations derived from LOD/2 and LOQ/2. The explicit values of LOD and LOQ for each DBP are: TCM: LOD = 30, LOQ = 91; BDCM: LOD = 17, LOQ = 52; DBCM: LOD = 21, LOQ = 64; TBM: LOD = 15, LOQ = 45. All concentrations are in ng/L. THM: trihalomethane; SD: standard deviation; DBP: disinfection byproduct; TCM: trichloromethane; BDCM: bromodichloromethane; DBCM: dibromochloromethane; TBM: tribromomethane; BrTHM: brominated THM; TTHM: total THM; LOD: limit of detection; LOQ: limit of quantification.

less prone to bias exposure classification methods (JEM and JTEM) on the measured urinary THM levels. The generated JEM and JTEM estimates of disinfectant use with the aid of an occupational questionnaire related well to those of 9073 U.S. female registered nurses who frequently reported disinfection and cleaning tasks at work, varying though in magnitude by job type and task (Quinot et al., 2017).

This study's results indicated that nurses in Cyprus were exposed to nearly double levels of total THM and BrTHM (median[IQR] of 1027 [560, 2475] ng/g and 323 [212, 497] ng/g, respectively) when compared to those of a subsample ($n = 380$) of the general population (552 [309,989] ng/g and 152 [87,261] ng/g, respectively) residing in the capital of Cyprus, Nicosia (Charisiadis et al., 2014). A unified drinking-water treatment protocol is established for all major cities in Cyprus by the governmental authorities using both desalination/conventional water treatment technologies; hence, we did not anticipate major differences in tap water THM levels from district to district. This is the first occupational dataset reporting measurements for biomarkers of internal exposure to disinfection by products as surrogate measurements of

Table 3 – Two-level (no and yes, 0 and 1) percentages of exposure (n, %) to each disinfectant for all participating departments/units for both hospitals as assessed with three different approaches (self-reported, JEM and JTEM) and two methods of classification (M1 and M2).

	Level	Self-reported	JEM-M1	JTEM-M1	JEM-M2	JTEM-M2
Alcohol/Phenol	0	3 (1.7)	74 (42.8)	37 (21.4)	146 (84.4)	110 (63.6)
	1	170 (98.3)	99 (57.2)	136 (78.6)	27 (15.6)	63 (36.4)
QACs	0	164 (94.8)	115 (66.5)	141 (81.5)	134 (77.5)	150 (86.7)
	1	9 (5.2)	58 (33.5)	32 (18.5)	39 (22.5)	23 (13.3)
Octenidine	0	32 (18.5)	99 (57.2)	99 (57.2)	99 (57.2)	99 (57.2)
	1	141 (81.5)	74 (42.8)	74 (42.8)	74 (42.8)	74 (42.8)
Iodine	0	106 (61.3)	86 (49.7)	100 (57.8)	99 (57.2)	99 (57.2)
	1	67 (38.7)	87 (50.3)	73 (42.2)	74 (42.8)	74 (42.8)
Hydrogen peroxide	0	154 (89.0)	135 (78.0)	104 (60.1)	127 (73.4)	115 (66.5)
	1	19 (11.0)	38 (22.0)	69 (39.9)	46 (26.6)	58 (33.5)
Chlorine	0	107 (61.8)	130 (75.1)	111 (64.2)	50 (28.9)	95 (54.9)
	1	66 (38.2)	43 (24.9)	62 (35.8)	123 (71.1)	78 (45.1)
Peracetic acid	0	161 (93.1)	80 (46.2)	111 (64.2)	119 (68.8)	98 (56.6)
	1	12 (6.9)	93 (53.8)	62 (35.8)	54 (31.2)	75 (43.4)
Chlorhexidine	0	130 (75.1)	124 (71.7)	90 (52.0)	109 (63.0)	133 (76.9)
	1	43 (24.9)	49 (28.3)	83 (48.0)	64 (37.0)	40 (23.1)
Ammonia	0	163 (94.2)	115 (66.5)	140 (80.9)	163 (94.2)	149 (86.1)
	1	10 (5.8)	58 (33.5)	33 (19.1)	10 (5.8)	24 (13.9)
Formaldehyde	0	153 (88.4)	74 (42.8)	106 (61.3)	115 (66.5)	106 (61.3)
	1	20 (11.6)	99 (57.2)	67 (38.7)	58 (33.5)	67 (38.7)

JEM: job exposure matrices; JTEM: job task exposure matrices; QACs: quaternary ammonium compounds.

Table 4 – Multivariate (adjusted for age and BMI) linear regression analysis for the determinants of end of shift urinary THM levels in the study population (both hospitals).

	TCM			BrTHMs			TTHM		
	β	CI	*p*	β	CI	*p*	β	CI	*p*
Chlorine use (days per week)									
<1	0.25	−1.00–1.49	0.69	−0.04	−0.21–0.14	0.68	0.03	−0.54–0.61	0.91
1–3	0.46	−0.35–1.27	0.27	−0.1	−0.22–0.01	0.08	0.27	−0.11–0.64	0.16
4–7	0.15	−0.54–0.84	0.67	−0.18	−0.28–−0.08	<0.001*	0.03	−0.29–0.35	0.86
Chlorine exposure – JTEM M1	−0.09	−0.67–0.49	0.77	−0.1	−0.18–−0.02	0.02*	−0.13	−0.40–0.14	0.34
Chlorine exposure – JEM M1	0.14	−0.53–0.80	0.69	−0.02	−0.11–0.08	0.73	0.01	−0.30–0.32	0.97
Chlorine exposure – JTEM M2	−0.51	−1.06–0.04	0.07	−0.07	−0.15–0.01	0.08	−0.28	−0.54–−0.03	0.03*
Chlorine exposure – JEM M2	0.26	−0.34–0.86	0.4	−0.01	−0.10–0.08	0.85	0.14	−0.13–0.42	0.31
Chlorine use in past 24 hr	0.05	−0.58–0.69	0.87	−0.12	−0.21–−0.03	0.01*	0.08	−0.22–0.38	0.6

Chlorine use was estimated using self-reported exposure measured in days per week.
* Indicates statistically significant *p*-values, $p < 0.05$.

disinfectant use in healthcare facilities (hospitals). External exposure measurements for disinfectants (alcohols) and disinfection by-products (chloroform, TCM) have been already performed in indoor air of healthcare facilities (LeBouf et al., 2014). Personal air measurements by health professionals from fourteen different occupational types in five hospitals showed that various disinfectants and VOCs (ethanol, propanol, *etc.*), including TCM or BTEX (benzene, toluene, ethylbenzene and xylene), were present in indoor air; in effect, highest VOC exposures, including TCM levels in personal air were measured for nurses (GM 0.7–0.9 $\mu g/m^3$) among all 14 different healthcare occupations (LeBouf et al., 2014). Airborne VOC (ammonia, 2-butoxyethanol and QACs) exposures were reported during execution of short-term (10 min) cleaning tasks in controlled environment, remaining indoors even after the task stopped (Bello et al., 2010).

The use of JTEM was superior to that of JEM in reducing bias in exposure estimates associated with heterogeneous tasks and job types as shown in this study. The use of JEM and JTEM has been already advocated and used by various groups working in the field of disinfectant exposures and occupational health outcomes (Quinot et al., 2017). Self-reporting of disinfection/cleaning-related exposures is commonly used in occupational health studies. However, information bias and large heterogeneity among different job tasks and job types within a single occupation (*e.g.*, nurses) could drive the extent and direction of association between exposures and relevant outcomes at the workplace. As such, exposure assessment protocols of greater detail about job tasks and types are warranted to reduce bias-prone exposure estimates that could lead to improved understanding of occupational health outcomes for healthcare workers, including nurses.

A few limitations were observed in this study; one of them was that JTEM and JEM assessment methods for a few disinfectants such as phthalaldehydes were not available due to low exposure prevalence (<10%) in all types of jobs and tasks (Kauppinen et al., 1992). Current JTEM and JEM exposure assessment has been only conducted for the U.S. nurses' population where different patterns of products, active disinfectants, and occupational practices prevail, limiting the extent of comparability between our studies. It is warranted that other European studies should further test and evaluate the performance of these methods (Donnay et al., 2011; Quinot et al., 2017; Saito et al., 2015; Teschke et al., 2002). Also, heavy work load resulted in low participation in some departments of the two hospitals. The fact that end of shift information and sampling was required did not help in reducing attrition. Despite that both verbal and visual (pictures of common products containing the disinfectants) materials were used during the administration of the questionnaires, most nurses were not aware of the type of disinfectants that they are using. It was possible that information bias was present during data acquisition, but not more than what typically occupational studies with disinfectants face.

4. Conclusions

Here we showed for the first time the widespread exposures to THM in nurses, using a suite of questionnaire-based exposure metrics and coupled with measurements of urinary biomarkers of disinfection byproducts (THMs) used as surrogate markers of exposure to disinfectants. Exposure assessment for occupational exposures to disinfectants taking the form of JEM and JTEM matrices refined the classification of nurses to exposed and unexposed groups. The disinfectant group of alcohols/phenols was used by >98% of nurses, next followed by octenidine (82%). The next most frequently used disinfectants in all departments using self-reported exposure metrics were iodine and chlorine (39%, each) > chlorexidine (25%) > formaldehyde (12%) > hydrogen peroxide (11%) > peracetic acid/ammonia and QAC, all being <8% each. This is the first occupational health dataset in Europe describing exposures to disinfectants for nurses using biomarker data. Further data is warranted to improve our understanding of occupational exposures to disinfectants in healthcare facilities in light of increased risk for pathogens and antimicrobial-resistant microorganisms in hospitals.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jes.2017.06.031.

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