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Article

Wristband Personal Passive Samplers and Suspect Screening Methods Highlight Gender Disparities in Chemical Exposures

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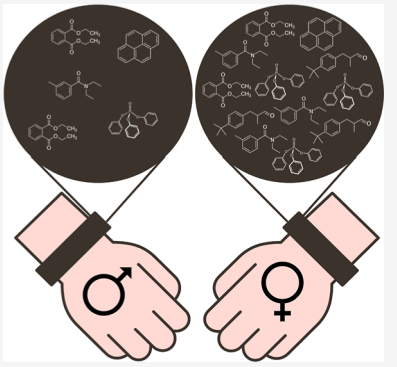
ABSTRACT: Wristband personal samplers enable human exposure assessments for a diverse range of chemical contaminants and exposure settings with a previously unattainable scale and cost-effectiveness. Paired with nontargeted analyses, wristbands can provide important exposure monitoring data to expand our understanding of the environmental exposome. Here, a custom scripted suspect screening workflow was developed in the R programming language for feature selection and chemical annotations using gas chromatography−high-resolution mass spectrometry data acquired from the analysis of wristband samples collected from five different cohorts. The workflow includes blank subtraction, internal standard normalization, prediction of chemical uses in products, and feature annotation using multiple library search metrics and metadata from PubChem, among other functionalities. The workflow was developed and validated against 104 analytes identified by targeted analytical results in previously published reports of wristbands. A true positive rate of 62 and 48% in a quality control matrix and wristband samples, respectively, was observed for our optimum set of parameters. Feature analysis identified 458 features that were significantly higher on female-worn wristbands and only 21 features that were significantly higher on male-worn wristbands across all cohorts. Tentative identifications suggest that personal care products are a primary driver of the differences observed.



KEYWORDS: *wristbands, personal samplers, exposome, suspect screening, chemical exposure*

INTRODUCTION

Personal passive samplers, including silicone wristbands brooches and the Fresh Air Band, are quickly becoming popular tools to support human exposure assessments for a wide range of chemicals.[1−8] Personal passive samplers provide integrated average measures of exposure with more precision, lower cost, and reduced invasiveness compared to traditional exposure assessments such as bulk air, dust sampling, and biofluid analysis.[9,10] Because these personal samplers are attached to the body, they sample all the varied microenvironments where an individual spends time, including home, work, while commuting, retail stores, salons, sporting events, and other activities in which an individual might participate. Current studies also suggest that these samplers integrate exposure that occur via different routes such as inhalation, dermal absorption, and hand-to-mouth contact.[3,5,11−15] Contrarily, exposure estimates for more traditional bulk sampling methods, such as dust or air samples, typically provide estimates for one primary exposure pathway or source and often only for one location.

Wristbands have been shown to measure a wide range of organic chemicals found in everyday consumer products, furnishings, and building materials.[16−18] Specifically in consumer products, wristbands are used to measure plasticizers (i.e., phthalates and organophosphate esters; OPEs)[19,20] and other personal care product (PCP) additives, such as phenols.[10,16,18,21,22] A myriad of studies have shown that wristbands can detect a wide range of pesticides; legacy contaminants (i.e., polychlorinated biphenyls; PCBs); combustion byproducts (i.e., polycyclic aromatic hydrocarbons; PAHs); and legacy and alternative brominated flame retardants (BFRs) and novel OPE flame retardants (OPFRs).[11,12,23−34]

Research also demonstrates that silicone wristband personal samplers provide meaningful measures of exposures for both compounds with short half-lives in the body (i.e., OPFRs) and long half-lives in the body (i.e., BDEs). This has been supported by studies that collected paired samples of

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Table 1. Summary of Demographic Data for the Cohorts Included in This Study

demographics		Durham Firefighter (n = 20)	Research Triangle Residents (n = 30)	Global Office Workers—USA (n = 56)	Global Office Workers—China (n = 51)	Global Office Workers—India (n = 27)
gender	male	15 (75%)	6 (20%)	21 (38%)	16 (31%)	16 (59%)
	female	5 (25%)	24 (80%)	35 (63%)	35 (69%)	11 (41%)
age (y)	19−29	4 (20%)	10 (33%)	19 (34%)	30 (59%)	11 (41%)
	30−39	10 (50%)	11 (37%)	21 (38%)	20 (39%)	10 (37%)
	40+	6 (30%)	9 (30%)	16 (29%)	1 (2%)	6 (22%)
race/ethnicity	White	18 (90%)	30 (100%)	38 (68%)	0 (0%)	0 (0%)
	Asian	0 (0%)	0 (0%)	6 (11%)	51 (100%)	26 (96%)
	Black or African American	1 (5%)	0 (0%)	2 (4%)	0 (0%)	1 (4%)
	other races	1 (5%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)
	two or more races	0 (0%)	0 (0%)	2 (4%)	0 (0%)	0 (0%)
	Hispanic, Latin, or Spanish origin of any race	0 (0%)	0 (0%)	6 (11%)	0 (0%)	0 (0%)

wristbands with either pooled urine or serum to examine correlations and understand how well wristband measurements predict the internal dose. For example, Hammel et al. (2016) observed moderate to strong positive correlations between levels of OPEs measured on wristbands with the levels of several urinary exposure biomarkers for OPFRs, which are rapidly metabolized ($t_{1/2}$ = hours to days).[11] They also found that the wristbands outperformed hand-wipe sampling in predicting urinary biomarker levels. Hammel et al. (2018) similarly observed a positive and significant correlation between serum levels and wristband levels of polybrominated diphenyl ethers (PBDEs), which have longer half-lives in the body ($t_{1/2}$ = 2−5 years).[12] Many other similar studies have also shown correlations between wristband levels and biomarker levels.[10,21,25,34−38]

Wristbands have also shown promising results as a tool to examine chemical exposures in domestic pets,[39−42] which can act as sentinel species for humans. Other studies have utilized wristbands to assess occupational exposures, such as those experienced by firefighters, agricultural workers, and e-waste workers.[19,26,43−50] The simplicity of the wristband sampler helps to isolate exposures that are experienced within a specific environment (i.e., the work environment) and helps disentangle exposures that might otherwise be tied with diet if relying upon blood or urine measurements. Furthermore, wristbands can be mailed back and forth with ease to reach larger numbers of participants and particularly more remote participants that may not otherwise be included in studies for logistical reasons.

While studies targeting a certain class of chemicals are important, they only interrogate a small portion of the total chemical exposome. The term exposome often refers to the totality of an individual's environmental exposures over the life-course and includes the corresponding biological responses.[51−56] Thus, most exposome studies rely upon blood sampling and are often used in a case-control or cross-sectional study design. However, exposures change over the life-course, and due to the rapid metabolism of some chemicals, blood sampling at one point in time may not adequately reflect average or cumulative exposures accurately. Therefore, measures of the personal exposome or, as we define it here, the cumulative and integrated measure of exposures occurring from the ambient environment are needed to support environmental health research. In addition, the increasing complexity of chemical mixtures present in our environment and everyday lives means many chemicals are not being studied or detected.[55,57,58] However, the use and evolution of suspect screening and nontargeted analysis (NTA) approaches are becoming increasingly important tools for environmental exposure monitoring.[59−62] Combining the use of personal samplers with NTA provides a more ideal opportunity to characterize the complexity of our ambient exposures over the lifetime.

This study sought to develop and apply suspect screening methods to examine gender disparities in complex exposure patterns using personal samplers, specifically silicone wristbands. Given the existing difficulties of accurately annotating every unknown feature via gas chromatography (GC) suspect screening work, which relies heavily on mass spectral libraries and matching, it is important that we also develop approaches that investigate and describe patterns of exposures. The objectives of this research were (1) to develop a custom R-based workflow with quality control (QC) validations to identify chemical features, (2) to apply the suspect screening workflow to wristband data collected from several independent cohorts to test robustness of the method and estimate true positive identifications based on previously acquired targeted data, and (3) to examine gender disparities observed in exposure patterns using the silicone wristband personal samplers.

MATERIALS AND METHODS

Study Populations. Wristbands examined in this study were collected across three different independent cohorts. Table 1 provides a brief overview of the four cohorts and the demographics of the participants. The first cohort consisted of participants employed as firefighters working in fire stations in Durham, North Carolina (NC) in 2019. Full population details have been discussed previously.[45] Briefly, 43 firefighters (38 male, 13 female, and 2 not reported) were recruited to wear wristbands both on-duty and off-duty between August 2019 and February 2020. In this study, we specifically examined 20 wristbands collected off-duty (i.e., representing nonoccupational exposures). Wristbands in this study were worn for 6 continuous days.

The second cohort consisted of 251 office workers from 36 urban office buildings in the United States, United Kingdom, India, and China from the preexisting Global Office Workers Study cohort. Full population details have been discussed previously.[18] In this study specifically, we will examine a subset of wristbands from 56 participants in the United States (21 male and 35 female), 51 participants in China (16 male and 35

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female), and 51 participants in India (16 male and 11 female) collected in 2019. These subsets were selected based on sample size, availability of demographic data, and analysis batch consistencies. Wristbands in this study were worn for 4 consecutive workdays for a median worn time of 33 h.

The third and final cohort examined in this study, consisted of participants living in the greater Durham-Raleigh area in NC and samples were collected in 2022. This cohort includes 30 silicone wristbands samples collected from 6 male and 24 females and were extracted and analyzed using our previous protocols.[63] Wristbands in this study were worn for 5 continuous days.

Laboratory Methods. Wristband samples were analyzed by the following methods, which were adapted from previously published methods.[11,12]

Briefly, wristbands (24hourwristbands.com, Houston, TX) were solvent-cleaned via Soxhlet extraction prior to deployment to study participants. Samples are disseminated to participants wrapped in combusted aluminum foil placed in a ziplock bag. After the sampling period, participants remove wristbands from wrist, wrap them in a clean piece of aluminum foil, and place them back in a ziplock bag, which is subsequently stored in a freezer. Field blanks are wristbands that were cleaned, transported, and handled similar to wristband samples but were not worn by participants. They were treated the same way, except they remained stored in foil at room temperature during the sampling period. Upon return to the laboratory, all wristband samples and field blanks were stored at −20 °C until extraction.

Approximately 1 g of the wristband was cut from the whole wristband and placed in a 50 mL glass centrifuge tube. Both the 1 g sample and the weight of the whole wristband were precisely measured. Lab processing blanks consisting of solvent (hexane) and field blanks (unworn wristbands) were analyzed in tandem with the samples during laboratory processing. Samples and blanks were processed in random order in laboratory batches of 12−18 samples per batch, ensuring that at least one lab or field blank was present in every batch. A suite of isotopically labeled surrogate standards were spiked to each sample prior to extraction. A full list of the standards added can be found in the Supporting Information (Table S1). Samples were extracted using a 15 min sonication extraction with 10 mL of a 50:50 (v/v) mixture of hexane/dichloromethane, for 3 cycles, equating to a total sample volume of 30 mLs. Samples were then evaporated to ∼1 mL under a vacuum with a Savant SPD121P SpeedVac Concentrator (Thermo Scientific).

Sample cleanup was conducted by passing samples through a large glass chromatography column loaded with 8 g of 2.5% water deactivated Florisil (Acros Organics Florisil, 100−200 mesh, FisherScientific) and ∼2 g of sodium sulfate. The column was preconditioned with 25 mL of ethyl acetate and 25 mL of a 50:50 (v/v) mixture of hexane/dichloromethane. Samples were eluted with 40 mL of hexane until dry, followed by 40 mL of ethyl acetate. Both fractions were collected in a single vessel. Samples were then evaporated to ∼1 mL using an automated nitrogen evaporation system (Turbo Vap II, Zymark Inc.) and transferred to an autosampler vial for GC−mass spectrometry (MS) analysis. Samples were solvent-exchanged to hexane by evaporating the samples to near dryness and reconstituted in hexane. Prior to instrument analysis, a suite of internal standards were added.[18,45]

Instrument Analysis. All samples were analyzed using a single Q Exactive GC hybrid quadrupole-Orbitrap GC−MS/MS system (Thermo Scientific) at Duke University. The QE−GC has a maximum scan range of 30−3000 m/z, is capable of mass resolution up to 100,000 (m/z 272), and has a mass accuracy below 1 ppm (internal calibration). The QE−GC was equipped with a Thermo Scientific TraceGOLD TG-5HT GC Column capillary column (30 m × 0.25 mm ID, 0.25 μm film thicknesses) with helium as the carrier gas flowing at 1.3 mL/min. The programmable temperature vaporizer inlet is operated in split injection mode with a 1 μL injection and a split ratio of 10. The GC oven temperature program was 80 °C for 2 min, 80−250 °C at 20 °C/min, 250−260 °C at 1.5 °C/min, 260−300 at 25 °C/min with a 12 min hold at 300 °C, 300−320 °C at 25 °C/min and final hold 15 min (total run time 46 min). The transfer line and ion source were held at 300 °C for the duration. For this analysis, the electron energy was set to 70 eV and the QE−GC was operated in full scan electron ionization (EI) mode with an automatic gain control (AGC) of 1×10^6, a maximum IT of 200 ms, and a mass resolution of 60,000 (at m/z 200). Samples were run with a scan range of 70−1050 m/z and quantified by using the Tracefinder software. For each independent study mentioned above, all samples in a given cohort were run in a single instrument without instrument randomization.

Quality Assurance and Control. Prior to analysis of samples, the QE−GC was tuned and calibrated to ensure maximum mass accuracy (<0.5 ppm). The tune was examined during and after sample runs to ensure no significant sensitivity loss had occurred. Additionally, a QC mixture was injected approximately every 15 samples to monitor sensitivity losses during the sample run across all m/z values of interest. The QC mixture consists of ∼160 analytes, including PCBs, PBDEs, PAHs, pesticides, and OPEs of which a majority are present in libraries utilized in this study. For targeted analyte analysis, lab and field blanks were analyzed in tandem with samples to assess the levels of contamination and develop a method detect limit (MDL). The MDL was calculated as the average plus three times the standard deviation. If sample values exceeded the MDL, they were then blank-subtracted with the average blank value to produce blank-subtracted values. More QA/QC information can be found in the previous publications focusing on targeted analysis and results.[18,45]

Targeted Analysis Data. Samples were analyzed for a target list of 104 GC amenable compounds, which consist primarily of BFRs, OPEs, phthalates, PCBs, and pesticides. The targeted analysis results for the Durham Firefighters and the Global Office Workers cohorts have been published previously,[18,45] and the results for the Research Triangle cohort are in review.[63] Some targeted analytes were detected in all samples across all cohorts, such as tris(2-chloroisopropyl)-phosphate (TCPP), while other analytes, such as tripropyl phosphate, were detected infrequently (<5% of samples). Other analytes, such as PCB 11, were frequently detected (>80%) on wristband samples but were present at lower overall abundances (i.e., area counts). These distinctions are important to note, as with targeted analysis, low abundance analytes (i.e., smaller peak areas) can be analyzed with ease because known ions and retention times can be monitored. Conversely for suspect screening methods, low abundance analytes may not be found and annotated because the

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deconvolution program are unable to adequately extract and align peaks that are hard to distinguish from noise.

Spectra Deconvolution. After analysis of wristband extracts on the QE−GC, data files were first processed using a deconvolution plugin in Thermo's Tracefinder. The deconvolution settings are presented in Table S2. This software plugin identifies common features across all samples, conducts retention time alignment to ensure all features are unique entries, and re-evaluates files to support gap filling (i.e., to ensure they were not missed in some sample files). Here, we define a feature as spectra for an unknown compound and the resulting data set will be an array of data with a value for base peak area response for each sample and feature. After deconvolution, retention time alignment, and gap filling, the identified features were screened against three mass spectral libraries. All libraries contain deconvoluted full-scan (e.g., MS1) EI spectra for comparison. The first library screened was the NIST (2023) library, which consists of 347,100 low resolution EI spectra. The second library used was the Thermo Hi-Res Library, which consists of approximately 1203 high resolution EI spectra generated with an Orbitrap instrument. The third and final library was an in-house library, which consists of approximately 121 high resolution EI spectra generated in house using authentic standards (>95% purity) analyzed on the QE−QC specified above. Thermo's Deconvolution plug-in offers a variety of metrics to consider when library matching to determine the best possible match for each feature and includes both forward and reverse search scoring metrics. The different scoring metrics evaluated in this analysis are listed in Table S3.

Custom R-Based Workflow. After deconvolution, retention time alignment, gap filling, and library searching were complete, the database files generated were queried and analyzed using custom R scripts. The custom R scripts developed and utilized here were designed to support blank subtraction and aggregate various scoring metrics to rank results and produce tentative identifications (IDs).

First, the workflow conducted blank subtraction and internal standard normalization. These steps are necessary to ensure contamination present in field and lab processing blanks is accounted for and removed. The normalization step improves accuracy to support the use of the data in a semiquantitative fashion. Features were internal standard normalized by generating a response ratio for all unknown features that compared the feature abundance to the abundance of a specified internal standard. In this study 13C-PCB-52 [2,3,4,4′-Tetrachloro ($^{13}C_{12}$) biphenyl] was used as the normalization standard due to its reliability, midrange retention time in chromatographic analysis, and high recovery through laboratory processing. A standard normalized peak area is determined for each feature by dividing the peak area response of the unknown feature by the peak area response of 13C-PCB-52 in each sample, producing a response ratio. Detection limits for each individual feature were calculated by taking the average plus three times the standard deviation of the internal standard normalized peak area responses (i.e., response ratios) in blanks. If no difference is observed between laboratory processing blanks and field blanks (i.e., wristbands that were not worn), both were used; otherwise, field blanks were used. Response ratios in samples were then compared to the feature detection limit, and if values were above feature detection limits, they were then blank-subtracted with the average response ratio in blanks for each feature. If values were below the feature detection limits, they were zeroed. If all sample responses were zeroed for a given feature, that feature was then removed from the feature list as it was then deemed a nondetectable feature in all samples (i.e., likely originated from blank contamination).

After blank subtracting feature lists, tentative annotations were assigned to unknown features. A custom aggregate ranking system assigned annotations by simultaneously considering multiple scoring metrics (including forward and reverse search metrics) and metadata information. The aggregate ranking system works by scoring each individual metric (Table S2) from best to worst and assigning them a value from 1 to the maximum number of observations (i.e., matches). An aggregate rank is then determined by summing up the rank of each individual metric for a feature and ranking that sum from the lowest to highest. The suspect screening library match with an aggregate rank of 1 has the best possible rank among the considered matches.

The aggregate ranking system allowed for a wide degree of customizability and allowed additional metrics to be added into the workflow with ease. One such workflow customization was a metric that allows for the prioritization of the specific library that is matched. For example, if a feature matches our in-house library, we assign that a rank of 1, in the Thermo High-Resolution library, we assign that a rank of 2, and in the NIST low resolution library, we assign that a rank of 3. This allowed us to give more priority to high quality high-resolution mass spectra and thus improved the quality of our matching. Every instrument has spectral differences for analytes due to differences in analytical conditions; thus, spectra produced on the same instrument with the same conditions (i.e., in-house library) will have the greatest true match potential. Similarly, spectrum produced on the same type of analytical instrument (i.e., Thermo High-Resolution library) will have a greater degree of similarity in ionization patterns than spectrum produced on other types of instruments. Lastly, any library spectrum produced on a high-resolution instrument will produce a higher quality match than library spectrum produced on a low-resolution instrument (i.e., NIST library).

The workflow also included a metric for the peak area response. Blank-subtracted, standard normalized peaks are ranked from the highest abundance to lowest abundance across the sample list. This allows matches with higher abundance peaks to be prioritized more heavily. This rank metric is predicated on the idea that the sample with the highest abundance of an unknown feature in a sample list will have the most spectral components and cleanest spectrum to match against when compared to low level detections of the same unknown feature (Figure S1).

Additionally, the workflow uses the PubChemLite database[64] and incorporates basic PubChem metadata into our workflow. Specifically, this is used for the number of patents and the number of PubMed entries. Presumably compounds with higher patent counts will be higher-use compounds and be more likely to be observed in environmental data and specifically in wristbands.

Lastly, our workflow was able to predict sources for feature annotations with the use of the CPCAT database.[65] CPCat (Chemical and Product Categories) is a database containing information mapping more than 43,000 chemicals to a set of terms categorizing their usage. By mapping the CPCAT product usage to the feature annotations, we were able to predict feature usage based on the top ranked annotation for

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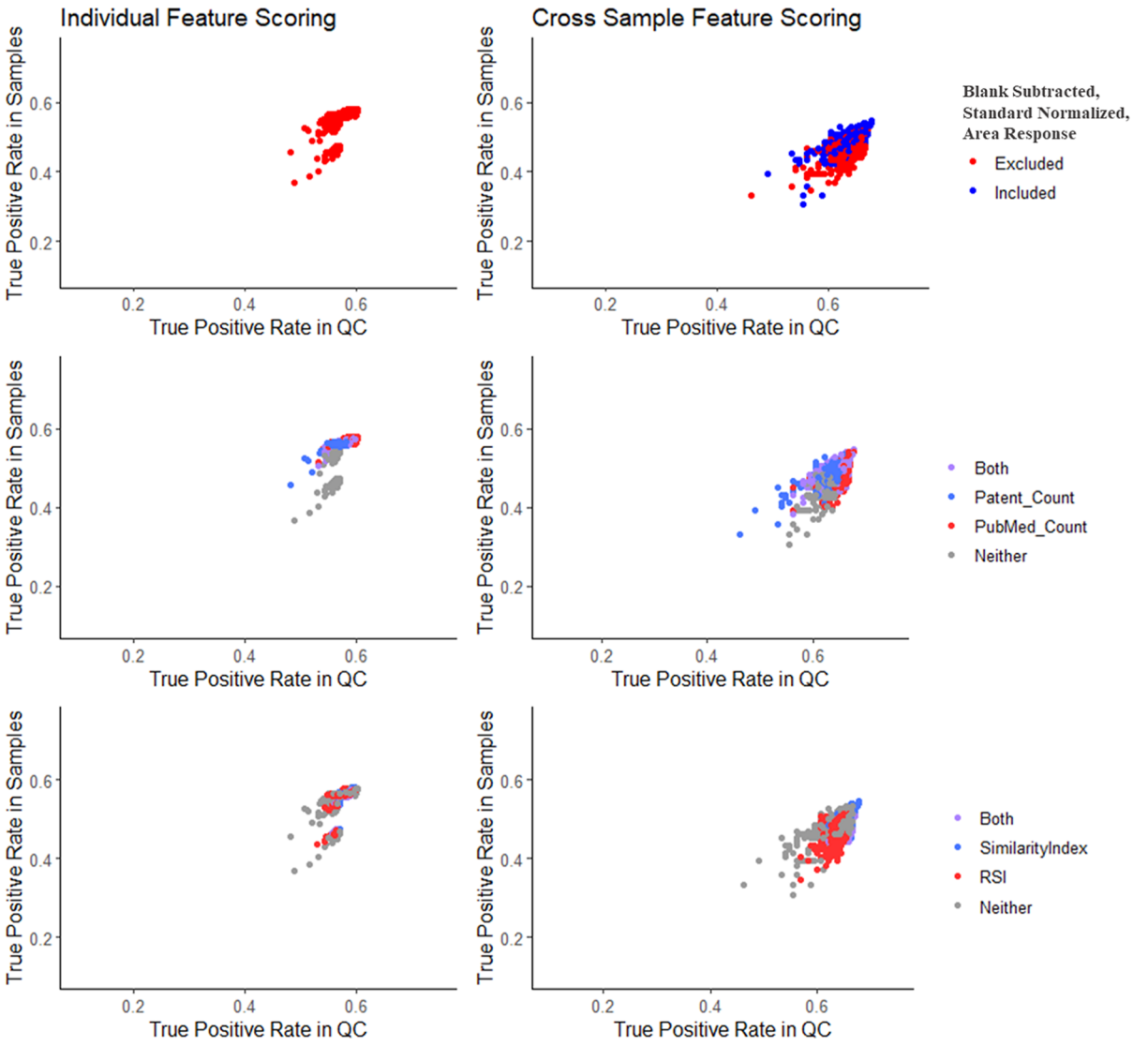

Figure 1. Comparison of the various models that predict true positive rates between the wristband sample matrix and the QC matrix as determined from the suspect screening workflow. The left-hand plots show the results of the sample independent feature scoring, while the right-hand plots show the batch specific feature scoring. Batch-specific feature scoring includes the use of the peak abundance metric in the ranking system models, while the sample independent feature scoring models exclude this metric from its models. Each side-by-side plot highlights a specific metric within the workflow to illustrate the effects of certain scoring parameters on the true positive rate.

each match. We also determined a probable usage for each unknown feature by assigning CPCAT usage predictions to all potential library matches for a given feature and determining which usage was most common among all potential matches of the feature. This probable usage assignment is based on the hypothesis that library matches for a given feature will likely be a closely related isomer or related compounds with similar usages. This allows us to observe trends in chemical exposures even if our top-rated library match was incorrect. Probable usages were aggregated only from library matches with a search index score >600 and the top 20 ranked matches to remove low quality library matches from consideration. Each feature may have more than one predicted (i.e., top match) and probable usage categorizations due to the compound itself having more than one potential use classification.

Statistical Analysis Methods. For this analysis, non-parametric univariate tests were used. Feature analysis was conducted on blank-subtracted, standard-normalized peak areas of unknown features detected in >50% of samples. Differences between male and female-worn wristbands were assessed for each feature with a Mann−Whitney *U* test. For these analyses, we considered a p-value <0.01 as statistically significant. This analysis was visualized with volcano plots, which allow us to identify features with significant differences between male and female-worn wristbands. Correlations between blank-subtracted, standard-normalized peak areas of unknown features were assessed with Spearman correlations. Spearman correlations were also estimated between unknown features and targeted analytes. As these analyses are exploratory in nature and intended to generate hypotheses, we did not adjust for multiple comparisons.[66] Similarly models were not adjusted for location, temperature, humidity, or other environmental conditions due to the exploratory nature of the analysis. In addition, it would be near impossible to approximate these values because each wristband sampler moves with the individual (i.e., it is not stationary) and samples every microenvironment the participant resides in during the sampling period. Additionally, we would not expect these

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Table 2. Summary of the Feature Detection Counts in the Independent Cohorts and the Breakdown of Feature Detections by Gender[a]

cohort	country	time wristband worn (hours)	# of features detected	# of features detected by gender (>50% detect)	feature detection frequency comparison
Durham Firefighter	U.S.A.	144	2469	female: 2151 (1886) male: 2256 (1800)	> in female: 971 = in both: 1084 > in male: 414
Research Triangle Residents	U.S.A.	120	1970	female: 1862 (1533) male: 1734 (1405)	> in female: 627 = in both: 771 > in male: 572
Global Office Workers—USA	U.S.A.	33	2041	female: 1871 (1509) male: 1792 (1333)	>in female: 1119 = in both: 541 > in male: 381
Global Office Workers—China	China	33	1724	female: 1338 (898) male: 1289 (788)	>in female: 639 = in both: 374 > in male: 711
Global Office Workers—India	India	33	2041	female: 1802 (1443) male: 1788 (1356)	>in female: 582 = in both: 207 > in male: 1252

[a]As a note, wristbands were worn for different lengths of time across these various cohorts and that may bias the observed numbers presented in the table.

variables to be a confounder between the gender and chemical exposures.

RESULTS AND DISCUSSION

Workflow Parameter Determination. To determine how different scoring metrics impacted the correct annotation of a feature, we tested every possible combination of scoring metrics (Table S3) within our workflow on all of the wristband samples in each cohort examined and on the QC mixture analyzed simultaneously on the instrument (10−20 per cohort). In total, 1023 ranking system models were evaluated. Tentative IDs from all ranking system models (n = 1023) were compared to our targeted results (i.e., produced from a calibration curve with authentic standards) to evaluate each ranking system in the form of true positive rates. From these results, we identified an optimum performing set of parameters. The best ranking system model produced an average true positive rate of 62 and 48% for the QC matrix spike and wristband samples. On average across cohorts, an additional 4% of top matches identified the correct molecular formula. The best ranking system model included the parameters, Similarity Index (forward search dot product); Total Score (combined dot product and high resolution filtering score); Number of PubMed Entries; Number of Patents; and the blank-subtracted, standard-normalized, peak abundance of the feature (Figures 1, S2 & Table S3). Lower true positive rates were observed in wristband samples compared to the QC matrix spike likely due to lower feature abundances and likely due to matrix complexities in the wristbands worn by people (e.g., with a high degree of coelution in complex matrix the AGC reduces the in-spectrum dynamic range, thus lowering the intensity of low-abundance ions). This is also exhibited by 36% of target analytes (on average across cohorts) producing a false negative result in all ranking system models, indicating that these analytes fall above the limits of detection of targeted analysis but below the detection limit of suspect screening analysis in wristband samples. When considering only a single metric, specifically the Similarity Index, the multiple metric aggregate ranking system improved the true positive rate from 59% in QC matrix spike samples to 39% in wristband samples. Based on the average true positive rates across cohorts in wristband samples, a majority of ranking system models (299 of 512) that included similarity indexes were ranked in the top half of models. Fewer (210 of 512) ranking system models ranked in the top half of models included the reverse similarity index (Figures 1 and S2). This difference was more drastic for the QC matrix for both the similarity index (366 of 512) and reverse similarity index (206 of 512). These results suggest that forward search metrics perform better than reverse search metrics in our workflow. Additionally, in the data collected from wristband samples, a majority of ranking system models that included PubMed Entries (333 of 512) and the number of patents (334 of 512) were ranked in the top half of models, demonstrating their value in aiding true positive designations. Interestingly, using the blank-subtracted, standard-normalized, peak abundance of the feature as a rank parameter in wristband samples was beneficial (384 of 512 ranked in the top half of models); however, this parameter did not assist true positive designations in the QC matrix (235 of 512 ranked in the top half of models). This suggests that this rank metric is beneficial in complex matrices and in environmental samples where compound responses and concentrations could vary by orders of magnitude.

Suspect Screening Results—Feature Detection Frequencies. Using the optimized suspect screening method outlined above, we then applied this method to data files collected from five different cohorts (Table 1) to investigate exposure differences based on gender. Within these cohorts, we detected 2469, 1970, 2041, 1724, and 2041 features in total for the Durham Firefighters, the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China,

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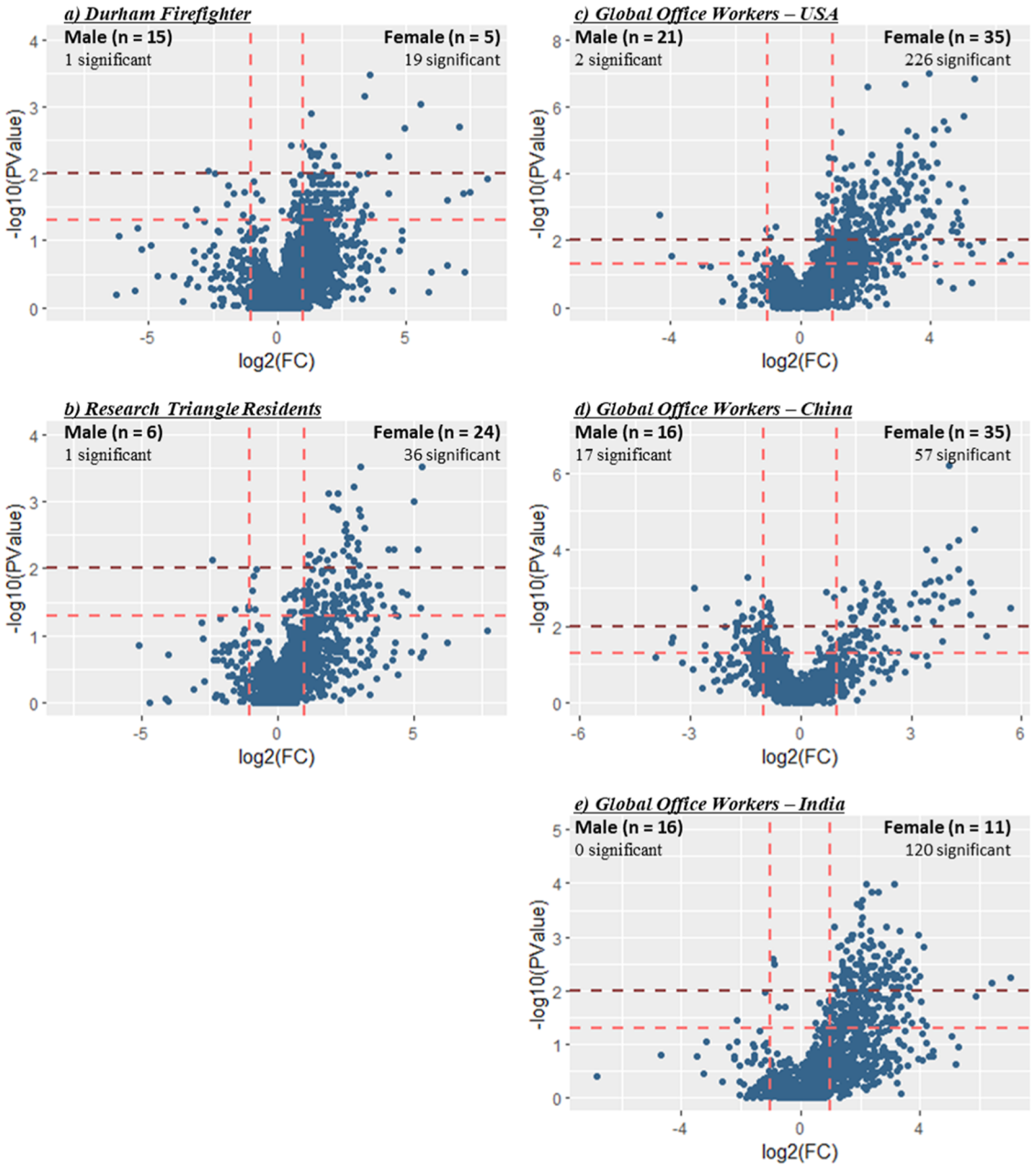

Figure 2. Volcano plots highlighting the exposure differences observed for male- and female-worn wristbands for the (A) Durham Firefighters, (B) Research Triangle, (C) Global Office Workers—USA, (D) Global Office Worker—China, and (E) Global Office Worker—India cohorts. The features represented on these plots are blank-subtracted, standard-normalized, and detected in >50% of samples. The *y*-axis represents the p-value from a nonparametric Wilcoxon rank sum test and the *x*-axis represent the log 2-fold change between the median of male-worn and female-worn bands for each individual feature. Features right of the zero line on the *x*-axis were higher in female-worn bands, and features to the left of the zero line on the *x*-axis were higher in the male-worn bands. The numbers in parentheses next to the gender represent the sample size of each gender. The number directly below that represents the number of significantly different features for each gender ($p < 0.01$).

and the Global Office Workers—India cohorts, respectively. Given the challenges associated with identifying all unknown features in all samples, we sought to use data analytic tools to reduce the priority list of features queued for annotation. First, we applied a cohort-specific detection frequency filter of 50% to remove infrequently detected analytes from further statistical analyses. As the samples from each cohort were run batchwise on the GC−HRMS, this was important in maintaining consistency before combining data from all cohorts. However, due to the gap filling step in the deconvolution process, detection frequencies are generally high for our feature list. On average the detection frequency across all unknown features was 65%, with an average of 1412, 1128, and 823 features being detected in greater than 50, 75, and 90% of samples, respectively.

When examining the total number of features detected on both male- and female-worn bands, no difference was observed between the two genders (Table 2). However, when the detection frequencies of features were examined, more features were detected at greater frequency in female-worn bands than in male-worn bands in three of our five cohorts (Table 2). For example, our Durham Firefighter cohort detected 971 features

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more frequently in female-worn bands and only 414 features more frequently in male-worn bands. This is evidence to support the claim that women are exposed to a greater number of chemicals at higher levels when compared to men of the same population. Interestingly, the Global Office Workers based in China and India are divergent to this trend, with 639 and 582 features, respectively, detected more frequently in female-worn bands and 711 and 1252 features, respectively, detected more frequently in male-worn bands. All the other cohorts examined in this study exist within the continental United States, which suggest cultural norms and practices may be contributing to chemical exposure profile differences between males and females.

Suspect Screening Results—Differential Analysis. In addition to evaluating detection frequencies between male- and female-worn wristbands, we also investigated the relative abundance of these features by gender. Interestingly, we observed that female-worn wristbands contained more features with higher abundances than male-worn wristbands for the three US-based cohorts, while the China and India cohorts showed the opposite trend. Figure 2 presents differential analysis visualized as volcano plots that highlight the differences in the abundance for the various features. The volcano plots highlight a greater number of features that are more heavily skewed to the right of the vertical line in the middle (indicating no difference between males and females). This skewness reflects the greater abundances of these features in female-worn wristbands compared to male-worn wristbands. These differences were statistically significant in some cases (note p-values on the horizontal lines) but not significant in all cases.

We further compared the median values for each feature between genders and found that all cohorts experienced enrichment in female-worn wristbands. Medians were higher in 73, 68, 72, 49, and 73% of the total features, for the Durham Firefighters, the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China, and the Global Office Workers—India cohorts, respectively. Combining the log fold 2 change and statistical significance thresholds, 20 of 1878, 37 of 1539, 228 of 1660, 74 of 1105 and 120 of 1596 were identified as features of interest, for the Durham Firefighters, the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China, and the Global Office Workers—India cohorts, respectively. Specifically for this study, "features of interest" refers to features identified in the upper right or upper left quadrants of the volcano plots [i.e., log2(Fold change) > 1 and p-value <0.01]. Most of these statistically significant features of interest were higher in female-worn wristbands compared to male-worn wristbands, specifically 19 of 20, 36 of 37, 226 of 228, 57 of 74, and 120 of 120 for the Durham Firefighters, the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China, and the Global Office Workers—India cohorts, respectively. This is particularly noteworthy for the Global Office Workers—China and the Global Office Workers—India cohort because raw feature detections suggest male-worn bands detected a greater number of features, but the volcano plots suggests female-worn bands detect significantly higher levels of exposure.

The identified features of interest are highly correlated with each other within a cohort and are moderately correlated with targeted analyte results (see Figures S3 and S4 for examples). Specifically, in the Durham Firefighters cohort (Figure S3), 81% of the correlations between features of interest were statistically significant (Spearman, p-value <0.05) with an average Spearman correlation coefficient of 0.44. Conversely, only 40% of the correlations between features of interest and targeted analytes (n = 64) were statistically significant (Spearman, p-value <0.05) with an average Spearman correlation coefficient of 0.24. This finding was similar to the Research Triangle cohort (Figure S4), with 48% of the correlations between features of interest being statistically significant (Spearman, p-value <0.05) with an average Spearman correlation coefficient of 0.42 and only 12% of the correlations between features of interest and targeted analytes being statistically significant (Spearman, p-value <0.05) with an average Spearman correlation coefficient of 0.18. This trend is likely a result of differences in exposure sources examined by targeted and suspect screening methods, respectively. There is likely a bias in the detection of features using targeted approaches versus suspect screening. Features highlighted via suspect screening methods are more likely features with higher abundances while compounds analyzed via targeted methods are often detected with lower abundances and are also identified a priori. Therefore, these two sets of analytes likely highlight different exposure patterns and sources.

The finding that chemical exposures are occurring to a greater degree in female-worn wristbands compared to that in male-worn wristbands was observed in multiple independent cohorts from different locations, professions, time periods, and even cultures. Interestingly, the three United States-based cohorts all showed stark differences between female and male exposure patterns, while the cohorts based in China and India showed a less distinct gender disparity trend. The results for both the Global office worker—China and the Global office worker—India cohorts suggest that men in these populations are exposed to a wider variety of chemicals (higher detection frequencies) than women but that women have higher intensities of exposures (more significant features) than men. The results suggest that there may be cultural and lifestyle differences significantly contributing to the gender exposure disparities observed in our cohorts.

Feature Characteristics and Annotations. When directly comparing the suspect screening results to the target data analysis results, 53, 51, 45, 42, and 45% of target analytes were detected and identified by the suspect screening workflow for the Durham Firefighters, the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China, and the Global Office Workers—India cohorts, respectively. Targeted analytical methods have much lower detection limits due to the ability to rely on a few spectral components (quantification ions and qualifier ions) as opposed to having to rely on a deconvolution program to extract a complete spectrum that is required for library matching.

Using the scoring framework described by Koelmel et al. (2022) on all features across all cohorts, 102 features (~1%) were identified with a level 1 confidence (or confirmed identification), namely, a high score library match with an in-house library, across all cohorts within this study.[67] A total of 7963 features (~78%), across all cohorts, were identified with a level 3 confidence (or tentative annotation) with a high score library match (RSI >600) in an external library. Finally, 2180 features (~21%) would be classified as a level 5 annotation, meaning that they remain unknown features. No features were classified with level 2 or 4 annotations due to the lack of retention index matching. No single feature was identified with

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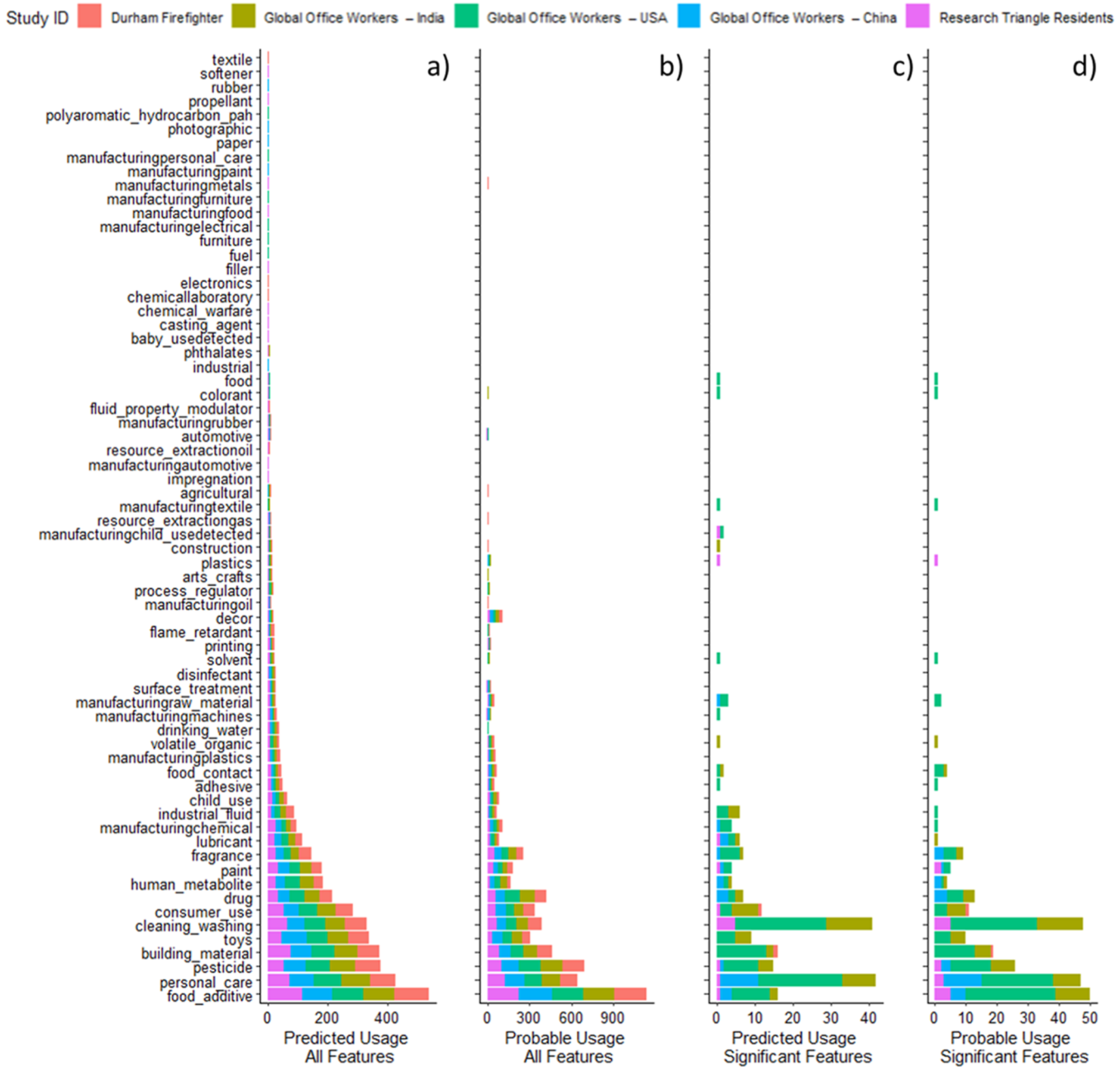

Figure 3. Distribution for CPCAT usage identifications for the feature list. Plots A and B show all features identified with plot A representing the product use of the top match and Plot B representing the probable usage aggregated from the top 20 ranked matches with a search index score >600. Plots C and D show only the features determined significantly from the differential analysis (i.e., features of interest). The individual colors represent different cohorts, and the *y* axis product usages are arranged from most to least classifications moving up.

level 1 confidence in all cohorts present in this study. If we look specifically at the features of interest, three features in the Global Office Workers—USA and two features in the Global Office Workers—India cohort were identified with a level 1 confidence. Approximately, 86% of features of interest were identified with a level 3 confidence, and the remaining 13% were identified with a level 5 confidence.

To our knowledge, the scoring framework laid out by Koelmel et al. is the most comprehensive annotation framework described for GC−MS suspect screening analysis. However, this scoring framework may not be perfectly applicable to the results described here. By collapsing several scoring metrics (i.e., similarity index and total score) and additional metadata into a single aggregate ranking metric, we divorce ourselves from the ability of any single specific scoring metric to tell us how good the match is and instead must look at the results holistically. Additionally, the scoring framework laid out by Koelmel et al. relies heavily on reverse scoring metrics; however, our workflow iterations using reverse scoring performed poorer than forward scoring metrics (Figure S2). This highlights the fact that until such a time that GC suspect screening workflows are harmonized, every sample matrix and suspect screening pipeline will have slightly different optimized parameters. In addition, GC-based suspect screening methods are dependent on matching to accurate and robust libraries since molecular ions are typically not present in an EI spectra.

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This implies that the quality of the spectra produced for the libraries has a great impact on our ability to match against them, including the type and mass accuracy of the MS instrument used, the MS parameters, and even the GC column and inlet conditions.

Ultimately, many of the features examined in this study remain as tentative annotations or unknowns despite the workflow we have developed and the adjustments we have made. Examining the distributions of the scores used in our final scoring metric combination for features of interest identified via the volcano plots provides some interesting insights (Figure S5). First, our top matches were more likely to be from the low resolution NIST spectral library with approximately 93% of these features of interest having a NIST entry as the top match. This is perhaps unsurprising given the size of the NIST spectral library compared to the size of the other spectral libraries used in this study. Second, low counts for patents and PubMed entries ultimately suggest that many of these features of interest are either not widely used or incorrectly identified. Approximately 37% of these features of interest have no patent or PubMed entries using our PubChemLite annotation approach. An examination of the patent or PubMed entries for the top ten matches for each feature of interest reveals that 36% of the features of interest still have no patent or PubMed entries. Features without patent information have a statistically significantly (Wilcoxon rank-sum test: p-value <0.0001) lower normalized peak area response than features with patent information (Figure S6). This likely indicates poor spectral quality in samples due to lower abundances, which in turn leads to poor library matches.

Tentative annotations for many of the features of interest allowed further examination of the likely uses of these compounds. Across all cohorts, compounds associated with PCPs were common features of interest (Table S4). Various siloxanes and benzoic acid derivatives common to cosmetics, lotions, and other PCPs were identified in multiple cohorts. Specific analytes such as 1-hexadecanol (CAS 36653−82−4), dibutyl phthalate (CAS 84−74−2), and octocrylene (CAS 142−91−6) were all identified as features of interest in multiple cohorts and are common PCP additives, and all were present at significantly higher levels in female-worn wristbands. For these specific compounds, 1-hexadecanol is commonly used as an emulsifier; dibutyl phthalate is commonly used as a plasticizer in cosmetics; and octocrylene is commonly used as a UV absorber in a wide range of PCPs, including sunscreen.[65] All of these tentative annotations suggest that PCP usage is a significant driver of the trends observed for gender specific exposure differences. A similar trend was also observed in a recent study investigating PFAS exposure in the general population in which 6:2 diPAP was observed at higher levels in female worn wristbands compared to male worn wristbands (Hoxie et al. 2024).[68] This PFAS was identified as a common water-repellent PFAS used in cosmetics such as foundation and mascara.[69] These combined data suggest that wristbands may be detecting exposures to facially applied PCPs, perhaps as these chemicals volatilize from the skin surface and remain in the air near an individual. Further research is needed to verify this possibility.

This trend was also observed in the predicted and probable CPCAT usage assignments (Figure 3) of the tentative feature annotations for the features of interest. Personal care, cleaning and washing, food additive, building materials, pesticide, and fragrance were the most common usage classifications. Interestingly, the cleaning and washing CPCAT classification had many inclusions for the Research Triangle, the Global Office Workers—USA, and the Global Office Workers—India cohort, indicating workplace habits of regular office space cleanings or personal product uses (i.e., hand sanitizer, hand soap, fragrances, etc.) being a contributor to gender specific exposure difference observed in that cohort. For the Global Office Workers—China cohort, the personal care CPCAT classification was the primary contributor to gender specific exposure differences observed.

When we examine all tentative feature annotations, we see trends similar to those observed for the features of interest identified via volcano plots (Figure 3). Food additive, personal care, building materials, pesticide, toys, cleaning and washing, and consumer use were the most common predicted and probable CPCAT usage classifications within our workflow. Interestingly, the Durham Firefighters had 9 annotated features that were flame retardants, while in contrast, only 3, 3, 2, and 3 features annotated as flame retardants for the Research Triangle, the Global Office Workers—USA, the Global Office Workers—China, and the Global Office Workers—India cohorts, respectively. This is likely a reflection of occupationally driven exposures compared to the general population. Given that the built environment and personal behaviors are significant drivers of our exposure to many semivolatile organic chemicals, it is unsurprising that these classifications would be most common, yet it illustrates the ability of the wristband personal sampler to capture a range of exposures from a range of sources. As a note, examining the distributions of all CPCAT categories used in this study provides insights into potential biases of CPCAT category classification due to the number of entries for each category. The most abundant CPCAT category classification for features in samples, i.e., food additive, personal care, building materials, pesticide, toys, cleaning and washing, and consumer use, represent 2.5, 5.3, 3.6, 13.1, 0.3, 3.1, and 1.5% of total CPCAT entries, respectively (Figure S7).

IMPLICATIONS

The gender-specific exposure differences are highlighted in this study, which are presumably driven by PCP usage, given that women of reproductive age report routinely using more than 10 PCPs on average;[70] however, the starkness of the exposure differences measured by WBs is surprising.

To our knowledge, wristband personal samplers have not yet been used to specifically examine gender-specific exposure differences. However, Young et al. (2023) analyzed wristband extracts for total hormonal activities toward estrogen (ER), androgen (AR), and thyroid hormone (TR) receptors in human cell assays and found that women were exposed to mixtures that were more estrogenic (180% higher), more antiandrogenic (110% higher), and more complex. Targeted and suspect chemicals with uses as plasticizers, fragrances, sunscreen, and pesticides were important codrivers of overall mixture effects in these in vitro assays, highlighting the importance of exposure from PCPs. In the Global Office Workers study, Young et al. (2021) previously found that perfume/makeup and deodorant users had higher exposures to diethyl phthalate (DEP) compared to minimal product users.[18] Though associations with gender were not explicitly investigated in this targeted analysis study, 79% of males were classified as minimal product users and only 32% of females were, suggesting that the differences in DEP exposures

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are related to gender specific PCP usage and reflecting trends observed in this suspect screening analysis.

This gender-specific exposure trend has been observed in other sample matrices in previous studies. Calafat et al. (2010) observed significantly higher urinary levels of parabens in females within the 2005−2006 NHANES cohort.[71] Silva et al. (2004) observed significantly higher urinary metabolite levels of certain phthalates in females within the 1999−2000 NHANES cohort.[72] Both parabens and phthalates are common PCP additives, and both have been detected in wristbands.[73] Similarly, Hoffman et al. (2015) showed that females exhibited higher urinary levels of diphenyl phosphate, the primary urinary metabolite of triphenyl phosphate (an organophosphate flame retardant and plasticizer).[74] This specific exposure difference can likely be attributed to the use of nail polish.[75] Several studies have shown that urine collected from children and adolescents in the German Environmental Survey of Children and Adolescents (GerES V, 2014−2017) reflected gender-specific exposure differences to phthalates, phthalate replacements, parabens, and a fragrance ingredient (Lilial CAS: 80−54−6).[76−79] Additionally, a recent study conducted suspect screening analysis on pooled serum samples and found more substances in female pools (472) than male pools (271) with 273 features being unique to female pools.[80] These findings combined suggest that gender-specific exposures differences resulting from PCP usage may be relevant throughout a majority of a person's lifespan.

Interestingly, the gender-specific exposure patterns observed in this study were observed across cultural divides, though varying in magnitude. Even within the three United States-based cohorts, differences were observed with exposure patterns. Specifically, the Global Office Workers—USA cohort had substantially more features identified as significantly higher in female-worn wristbands compared to the Durham Firefighter and Research Triangle cohorts. These results suggest that our exposures are shaped not just by the consumer choices we make and the environments where we spend our time but also by our cultures. Cultural norms promote practices and behaviors that are likely to contribute to the magnitude and patterns of chemical exposure, prompting disparities in chemical exposures based on gender and location. This is particularly important with the growing body of research showing chemicals associated with PCPs are hormonally active and that women of color report higher uses of these PCPs, such as hair relaxers, hair oils, skin lighteners, and scented products compared with white women.[70,81−84]

As suspect screening workflows improve, so will the ability to identify specific compounds and to use wristband personal samplers to further elucidate trends and patterns of exposure and identify the primary factors and variables that drive overall exposure. One of the best ways to improve suspect screening methods is to improve the quality of the mass spectral libraries that are queried for feature annotation. Better quality spectra and more spectral entries will vastly improve our ability to make true identifications. Additional workflow functions, like including in-silico fragmentation spectra to boost scores of likely candidates or using hierarchical clustering methods to classify features and examine neighbor relationships, can also be used to improve the unknown annotation potential.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.est.4c06008.

The SI contains additional information about internal standards, suspect screening parameters, additional figures characterizing scoring parameter behaviors, correlation plots for targeted results compared to suspect screening features of interest as identified by volcano plots, a table tallying the cross study counts for features of interest, and a histogram showing the distribution of top categories in the CPCAT database (PDF)

The complete R script package for running this workflow (ZIP)

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Notes

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