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# Silicone Wristband Spray Ionization Mass Spectrometry for Combined Exposome and Metabolome Profiling

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**Abstract:** Wearing a silicone wristband exposes the internal surface of the wristband to glucose, lipids, and metabolites (metabolome) found in sweat and the external surface to occupational and environmental factors that could impact health found in the air (exposome). We use silicone wristband electrospray ionization mass spectrometry (SWE-SI-MS) to monitor these species. A 20-μL drop of a (1 : 1, *v*/*v*) water:methanol solution is sufficient to extract abundant metabolites and contacting chemicals derived from ingestion of drink, smoke, diet, drug, and air pollution exposure. A wide coverage of species is successfully detected and identified from a worn wristband including caffeine, glucose, nicotine, reserpine, lactate, phosphocreatinine, oleic acid, and urea. The signal from a triangular wristband surface triggered by applying a voltage of 5 kV to form a spray remains stable for at least 2 minutes. The response is linear from 10 pM to 100 μM. The SWESI-MS method offers the advantages of onsite sampling, no preprocessing, simple testing, and automatic high-dimensional data searching. It can be used for simultaneously monitoring hazardous chemical contamination and abnormal expression of sweat-secreted metabolites that are indicative of some physiological condition.

**Keywords:** wearable device · silicone wristband · human metabolome · exposome · electrospray ionization mass spectrometry

## 1. Introduction

Over a lifetime, human beings are exposed to a million or more commercial, environmental, and occupational chemicals.[1] Even when wearing face masks to avoid inhaling airborne pollutants, people may still be exposed to air pollutants through skin absorption, which is a complex problem.[2] Personal air pollutant sampling, including air samplers and pumps, is considered highly reliable and accurate for evaluating exposure and possible health effects.[3,4] This manner of assessment can be used for determining safe operating exposure limits and possible health risks but does not record directly an individual's exposure. Therefore, there is a need to develop wearable samplers to estimate exposure to contamination of an individual.

Silicone wristbands (SWs) have been adopted as promising wearable devices with monitoring capabilities.[5–15] Previous studies have demonstrated the relationships between phenol biomarkers found in urine and their corresponding residue on the wristband surface.[5–7] Recent studies are moving toward the use of SWs as external, inexpensive, simple, and noninvasive sampling devices for effectively recapitulating human exposures without dietary interferences.[9,10] SWs have emerged as promising external and noninvasive sampling devices in contact with the air and skin. They can passively estimate personalized exposure profiles captured in multiple microenvironments through dermal absorption or environmental pathways.[8,11–13] SWs are lightweight, convenient for human and animal participants to use, and can be mailed back and forth for analysis, admittedly with some loss of volatile species.[14,15]

Recent studies demonstrated that polymer-based spray ionization coupled with high-resolution mass spectrometry (HR-MS) provides a promising approach for molecular and metabolic profiling and quantitation of biological fluids.[16–26] Coupling of wristband technology with HR-MS can enable the evaluation of environmental contaminates, screen unexpected chemical exposures, and capture information about pesticides, flame retardants, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs).[27] We previously used polymer-based spray ionization mass spectrometry for the metabolomic and lipidomic profiling of biological fluid samples.[17,22–26] It has advantages in rapid screening and *in vitro* diagnosis of disease, identification of discriminative biomarkers and dysregulated pathways, and even illumination of gene-environment interactions, and disease-relevant genomic regions.[28]

We report here the development of *in situ* sampling coupled with an ambient ionization method, which we name silicone wristband electrospray ionization mass spectrometry (SWESI-MS), to detect some model compounds derived from drink, diet, smoke, and medicine (caffeine, acetaminophen, urea, and nicotine). SWESI-MS can simply and effectively detect these

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endogenous or exogenous analytes at an extremely low concentration from trace contaminated samples obtained from the wristband surface. We used SWESI-MS to stimulate the detection of analytes in low levels of dermal and environmental exposures in sweat and environmental analysis. Figure 1 presents the collection scheme and workflow for SWESI-MS analysis.

### 1.1 Materials and Experimental Method

#### *1.1.1 Chemicals*

Reserpine, urea, acetaminophen, and nicotine were purchased from Sigma-Aldrich (St Louis, MO). Rhodamine 590 perchlorate was purchased from Exciton (Lockbourne, OH). Caffeine (99% purity) was purchased from Alfa Aesar (Haverhill, MA). All chemicals were used without further purification. Water and methanol were purchased from Fisher Scientific (Pittsburgh, PA). Silicone wristbands were provided by 24Hour-Wristbands.com and precleaned in-house with high-temp vacuum treatment. Graphite pencil (model Mars® Lumograph® 100) was purchased from Staedtler.

#### *1.1.2 General Summary of Wristband Sample Preparation, Collection, and Measurement*

Three different sample collection methods are used:

- In the *in vitro* study, wristbands were soaked in a solution for 24 hours of various target analytes (nicotine, caffeine, reserpine, and rhodamine) at 10 μM concentration which matches closely the physiological ranges of all analytes in sweat. The wristbands were then dried. These four compounds are selected to present the typical components derived from drink, smoke, drug, and environment.
- For the *in vitro* nicotine study, silicone wristbands were cut into small triangular pieces, placed in a flask, and the outer surface was exposed to cigarette smoke, to retain nicotine over an extended exposure assessment period (24 hours).
- In the *in vivo* study, a participant wore a wristband to assess the air chemical exposure on the external surface and sweat metabolome on the internal surface. The participant wore the precleaned wristbands for two continuous days throughout all daily activities. The participant avoided coffee until the study was started. In order to detect endogenous or exogenous analytes, the participant drank coffee, took supplements (e.g., multivitamins) every day, and had exercise and physical activity in order to make the physiologically rich sweat sample accessible on SWs. The SWs were then collected, wrapped in precleaned aluminum foil, and stored at −20 °C until analysis. More details on the study can be found from a previous publication.[9]

After each sample collection method, a thin graphite layer was added with a pencil to bisect the triangular surface. The chemical species from silicone wristbands were extracted by depositing 20 μL of a (1 : 1, *v/v*) water:methanol solution onto the silicone wristbands' triangular sections. Then a home-build

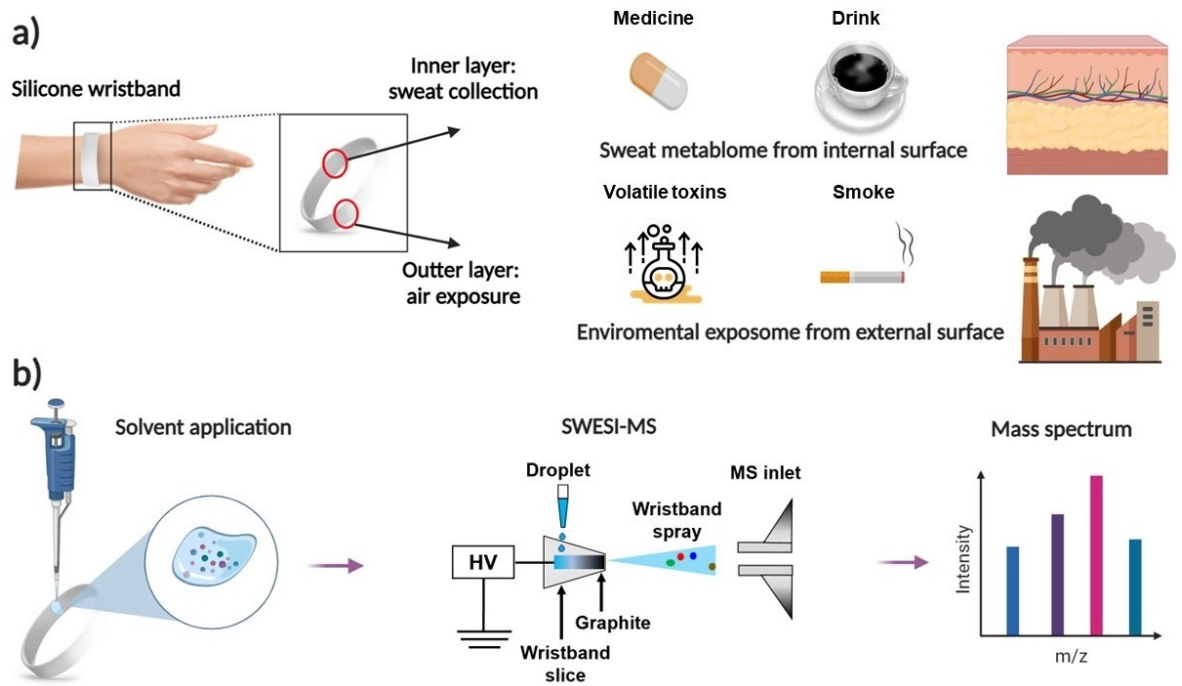


**Figure 1.** Schematic diagram of silicone wristband electrospray ionization mass spectrometry (SWESI-MS). a) Sample collection by silicon wristband. b) Workflow of SWESI-MS analysis.

high-voltage supply (+5-kV) is applied using a metallic alligator clip to the graphite line in order to electrospray the samples into the MS inlet (Figure 1). The current is less than 1 μA. We optimized the sample collection by solvent volume and extraction time to gain a simplified extraction method for reducing if not eliminating the possibility of contamination.

#### 1.1.3 Experimental Details of SWESI-MS

The silicone wristbands were cut into triangular shapes (base ~1.3 cm, each of the two sides ~1.6 cm, tip angle ~49°) using metallic scissors (Figure 2a). A conductive layer on the surface of each silicone wristband was created using a 6B graphite pencil (Figure 2b). The prepared triangles were connected to a high-voltage supply and then positioned in front of the mass spectrometer (MS) inlet with a distance at 3.0 mm. A ±5-kV voltage is then applied onto the triangular surface. 20 μL of (1 : 1, *v/v*) water:methanol solution was placed on the graphite line. This generates an electric field-induced microdroplet spray from the triangle's tip for direct MS injection (Figure 2c). Because of the hydrophobic nature of the silicone wristbands, spreading of a water:methanol solution is minimized as compared to paper, which is hydrophilic. The target analytes were detected in full scan mode at *m/z* 50–1000 under positive and negative scan modes on the LTQ Orbitrap Velos mass spectrometer (Thermo Fisher Scientific, San Jose, CA). The inlet temperature of the MS was set at 275 °C and the S-lens voltage to 55 V. The mass spectrometer was calibrated before each batch of measurements by using an ion mass calibration solution kit (Pierce positive/negative, Thermo Fisher, USA).

#### 1.1.4 Data Extraction, Processing, and Postprocessing (Preprocessing) Method Development

Data analysis of the mass spectrum data was done in MATLAB. Peaks were found using the find peaks method in MATLAB's Signal Processing Toolbox, with a minimum peak height set to an absolute abundance of 10,000. A processed sample spectrum was created by removing peaks of matching *m/z* that were present in both the raw sample spectrum and the raw silicon wristband control spectrum. Peaks from different spectra were considered matching if their maxima were within a tolerance of 0.005 *m/z* and both peaks had values exceeding an absolute abundance of 10,000. This method was used as opposed to a more standard background subtraction procedure to avoid issues with changes in absolute abundance values between samples caused by sample misalignment to the inlet of the MS. All codes of data extraction and analysis are presented in Supporting Information (see Supplementary 1). Researchers were able to reproduce/improve the cleaning process.[29] The improved protocol utilizes the Vacucell Evo oven and is programmed through 14 steps (see Table S1 in Supplementary 2).

## 2. Results and Discussion

### 2.1 Signal Intensity and Stability of Caffeine on SWs

In order to improve molecular profiling methods, it is essential to evaluate the stability and reproducibility of signals using ESI-based methods. Recent studies showed that some flat polymers could not produce an ion signal.[19] To show that wristbands do produce a stable ion signal, we monitored the ion signal over time. Figure 3a shows the total ion current (TIC) of

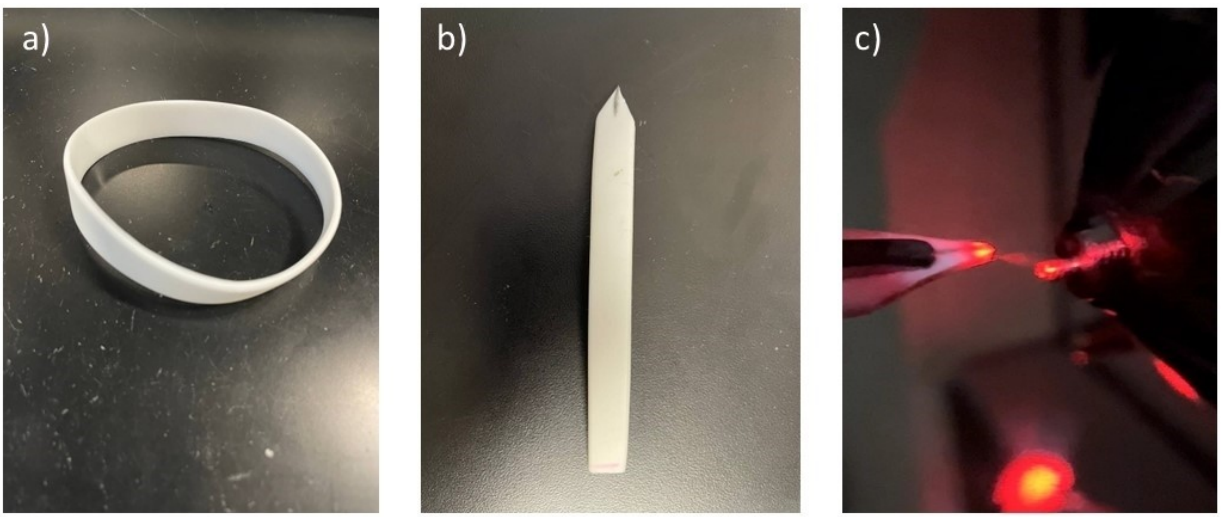


**Figure 2.** Photographs: a) a silicone wristband; b) a graphite line on a wristband triangle from a pencil; and c) 200-μL droplet of a (1 : 1, *v/v*) water:methanol solution on a silicone wristband with a flat alligator clip attached to the graphite line.

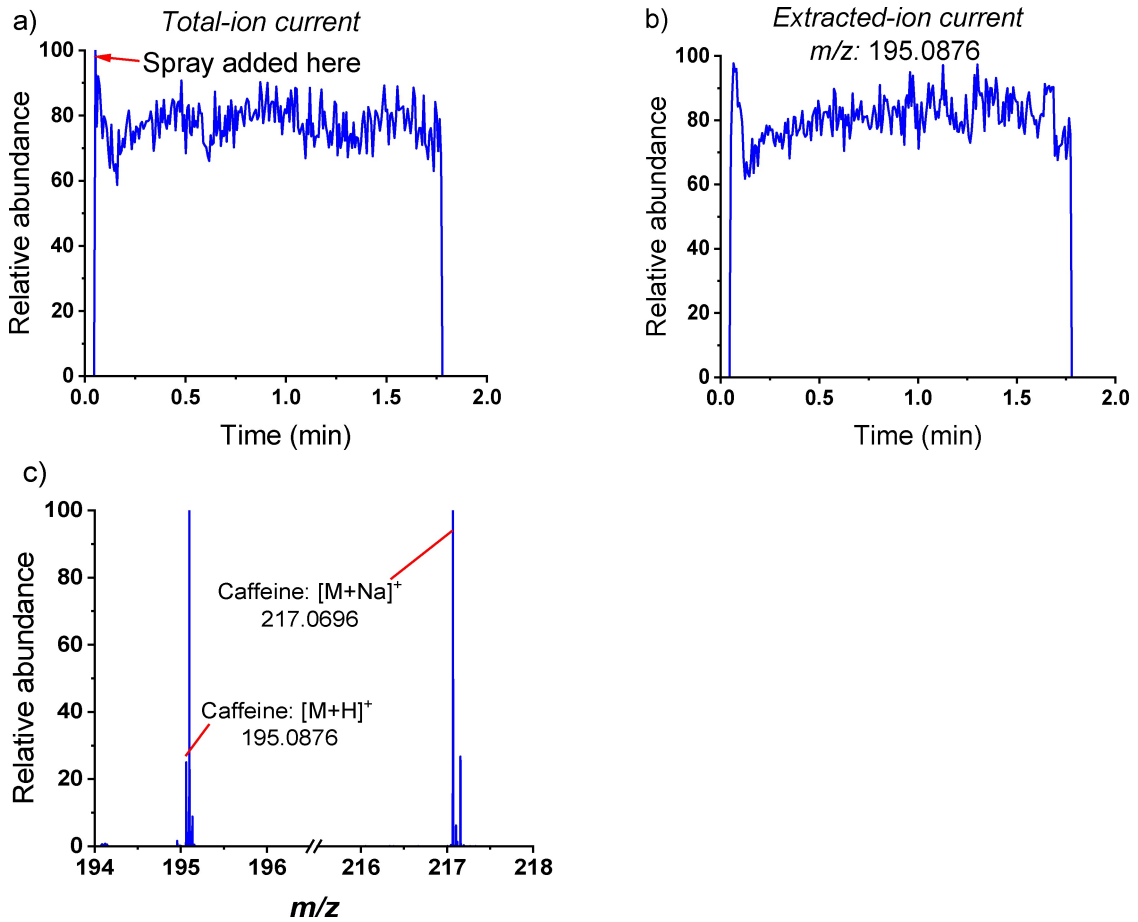


**Figure 3.** Caffeine signal stability: a) TIC of silicone wristbands over time, relative to highest detected value in the time period; b) EIC of caffeine peak ($[M+H]^+$, *m/z* 195.0876) relative to highest detected signal for the peak in the time period; and c) mass spectrum of caffeine (100 nM) in a (1 : 1, *v/v*) water:methanol solution deposited on silicone wristbands. Shown are SWESI-MS results from 100 nM concentration of caffeine via our *in vitro* method.

the detected signal for a silicone wristband in a (1 : 1, *v/v*) water: methanol solution as a function of time, which demonstrates the general stability of the signal intensity. Figure 3b demonstrates the extracted ion current (EIC) of 100 nM caffeine ($[M+H]^+$, *m/z* 195.0876; and $[M+Na]^+$, *m/z* 217.0696) as a function of time. These identifications were confirmed by tandem MS. The typical spray time for our standard 20 μL sample is ~12 seconds. To demonstrate the stability of the spray over time, we increased the deposited liquid volume to 200 μL of water: methanol mixture deposited gradually over the sample time-frame. This gives about 2.0 min duration over which to demonstrate the signal stability (Figure 3).

### 2.2 Calibration Curves and Limit of Detection (LOD)

Recent advancements in ambient ionization mass spectrometry technology have enabled direct analysis of target compounds from the biological specimen without the need of prior sample preprocessing and chromatographic separation. Major concern for its application in biological analytes is the lower limit of detection (LOD) for quantitative analysis. Figure 4 shows the zoomed-in mass spectra from 100 nM concentration of four different species deposited on the silicone wristband. Each compound can be specifically monitored by our high-resolution MS without interference from the other signals.

In this study, four different compounds from varied sources (drink, smoke, drug, and environment) and different physico-chemical properties were analyzed by SWESI-MS. Their identities are confirmed using tandem mass spectrometry (see Figure S1 in supporting information supplementary 3). Figure 5 shows the calibration curves in the lower concentration range. The results in Figure 5 show that SWESI-MS can achieve good linearities ($r \geq 0.98$) within a range of 100 folds at least (0.2–20 μM). These results demonstrate that SWESI-MS is qualified for trace-level compound detection and quantitation. Although no efforts were made in this study to perform quantitative measurements, such measurements are easily done by establishing a calibration curve, as shown in Figure 5 and comparing the signal size against the calibration curve to estimate the absolute

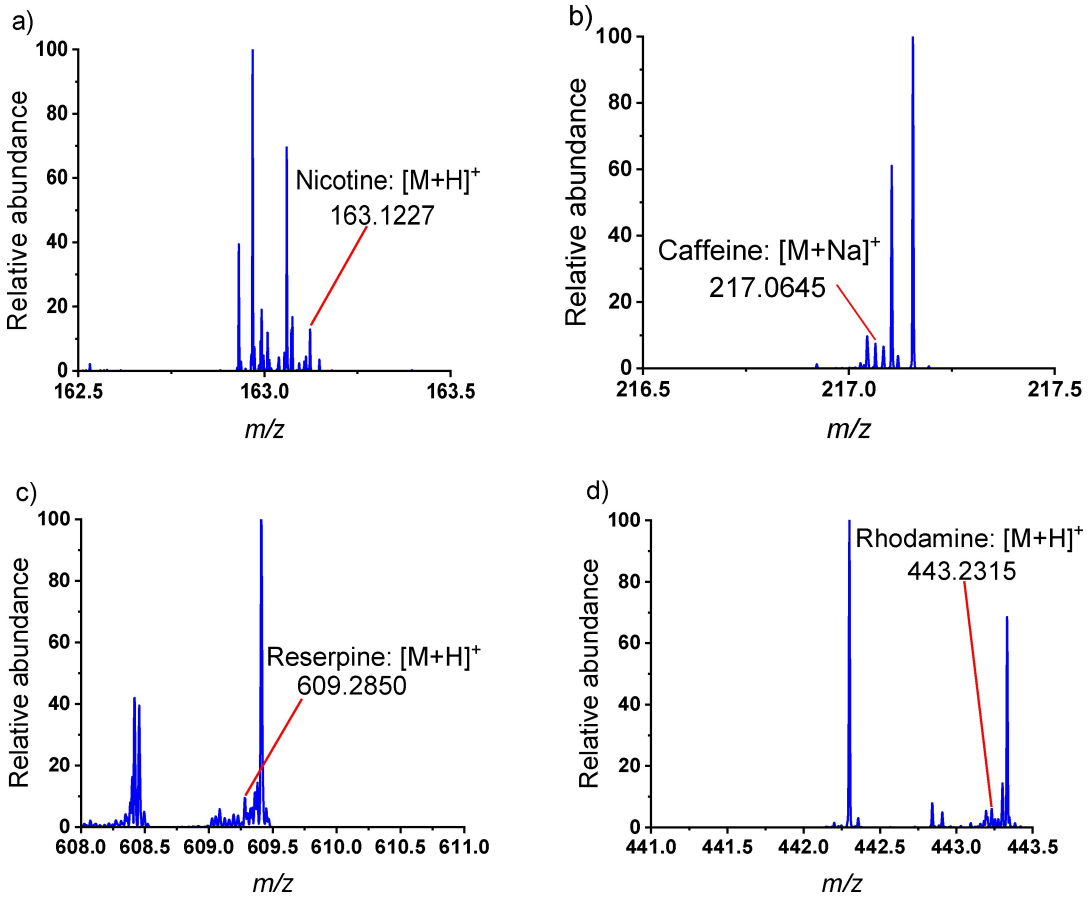


**Figure 4.** Mass spectra obtained from SWESI-MS: a) nicotine, b) caffeine, c) reserpine, and d) rhodamine. Each concentration is 100 nM.

amount of the analyte in question. Previous studies have shown that spraying from a nonporous hydrophobic surface is distinctly superior to paper spray.[19,20]

### 2.3 *In Vitro* Identification of Sweat-Based Metabolites by SWESI-MS

Therapeutic concentrations of each analyte in the aqueous mixtures range from 5–5000 ng/mL to match the physiological ranges of all analytes in sweat. In addition to the compounds recovered from the wristband, the initial set of experiments for quantitative study of biologically relevant sweat-based *in vitro* analytes are correlated with urinary or serum concentrations which include urea, acetaminophen, and caffeine. Therapeutic concentrations of caffeine and acetaminophen in sweat vary widely from 5 to 25 μM and from 72.7 to 145.4 μM.[30] Average urea level in the sweat lies between ~5 to ~40 mM for healthy subjects which is too high for evaluation and 3.6 times that in serum.[31,32] These analytes were at 10 μM concentrations in order to match the physiological ranges of all analytes in sweat. Figure 6 showed the mass spectra of sweat-based analytes in silicone wristbands with high S/N ratios over 10-fold, which is usually the default definition of lowest limit of quantification. These results support the potential of SWESI-MS for detecting and quantitating drug and metabolites in sweat.

### 2.4 Silicone Wristband as an *In Situ* Collection tool for VOC Detection

In addition to identification of sweat-based, in vitro analytes, the fresh air wristband was tested to collect nicotine and 2,4,6-trimethylpyridine (Figure 7), a type of frequently seen volatile organic compound (VOC). The silicone wristbands were placed and exposed to cigarette smoke at an isolated chamber for a 24-hour sampling period. In order to detect environmental exposures, we coupled a corona discharge setup with the SWESI-MS. When we moved the wristband near the mass spectrometer interface, the peak of *m/z* 122.0959 ($[M+H]^+$) can be clearly observed. To our knowledge, this is the first investigation to detect 2,4,6-trimethylpyridine in silicone wristbands. These study cases for the collection of environmental chemicals demonstrated the feasibility of SWESI-MS for analysis for the air pollution harvested from a worn silicone wristband. Exposure assessment plays a vital role in evaluating

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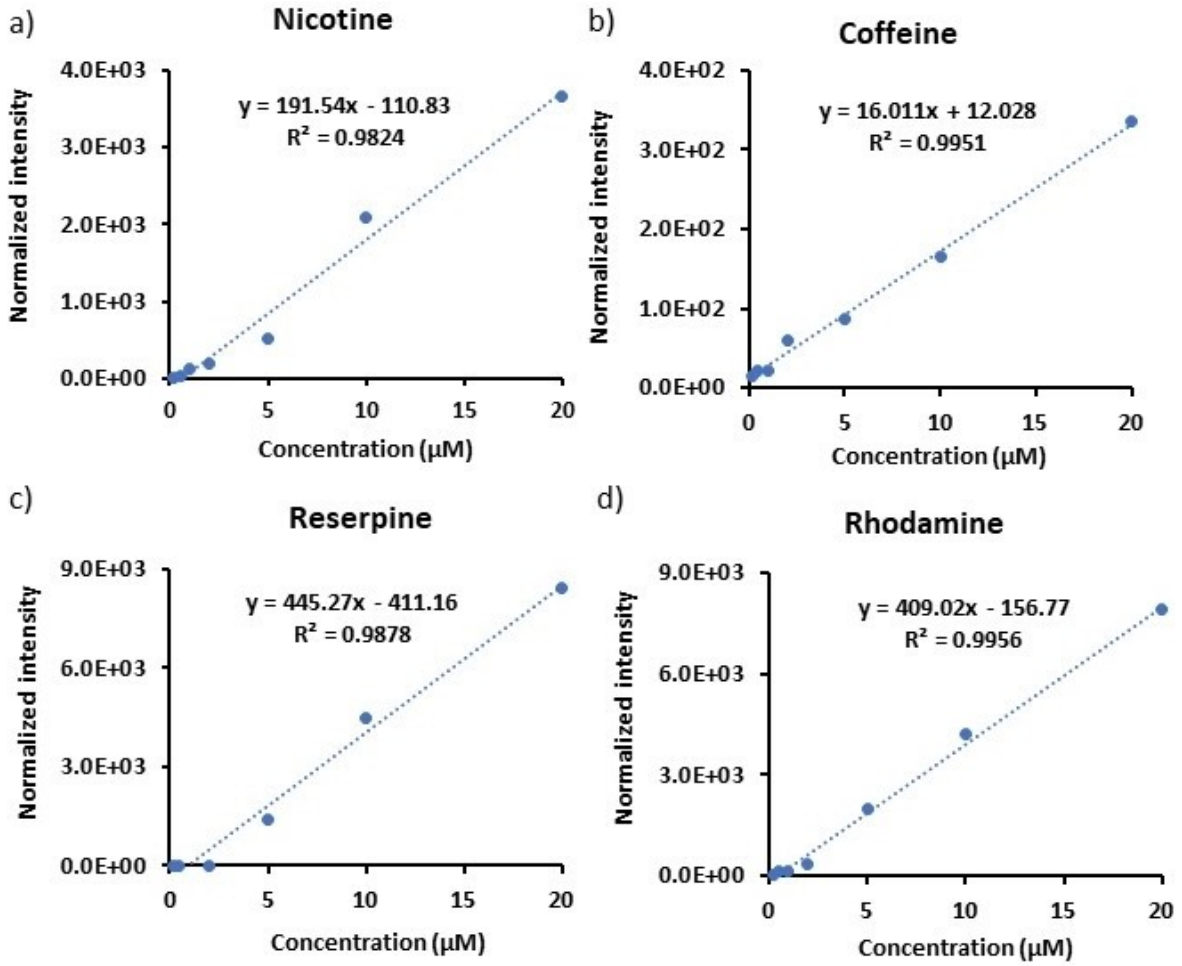


**Figure 5.** Calibration curves of silicone wristbands at the lower end of the concentration ranges: a) nicotine, b) caffeine, c) reserpine, and d) rhodamine in water:methanol analyzed by SWESI-MS.

intervention and environmental epidemiology studies as well as changes in exposure over time.[14]

### 2.5 Profiling of the Exposome Collected from the Wristband's External Surface

The wristband is a cost-effective wearable device for collecting chemical information derived from both the external environment and the body environment. First, it keeps close contact with the skin so the secreted sweat can leave a chemical trace on its internal surface. Additionally, the wristband is made of hydrophobic silicone polymer, and its external surface can also serve as a chemical collector, particularly for those nonpolar or weakly polar species derived from environmental exposure. We investigated the chemical profiles that the solvent extracted from the internal and external wristband surfaces, which represents the sweat metabolome and external exposome, respectively. As results, there were 9418 and 6602 positive ions collected from the external and internal surfaces. In addition, we also collected 18376 and 4090 negative ions from the internal and external surfaces. The identities of major peaks were confirmed by first searching its exact *m/z* value in the human metabolome database (HMDB, https://hmdb.ca) and then elucidating fragmentation patterns by MS/MS experiments. From the external surface, the top 12 compounds were successfully identified. Most of them are hydrophobic species such as ether, ester, thiol, and acyl amine, all of which carry medium or long carbon chains that are commonly used as nonionic surfactants in industrial formulations (Figure 8a, and 8b). Later, it was confirmed that the volunteer who wore the wristband indeed had a history of contacting these chemicals in the laboratory. It was worth noting that cyanamide was also identified from the external surface. It has modest toxicity to human beings. Workplace exposure to hydrogen cyanamide sprays may cause respiratory irritation, contact dermatitis, nausea, and vomiting.[33] This is a typical case that illustrates the promising usage of this wearable wristband as the collector of hazardous chemicals from the air.

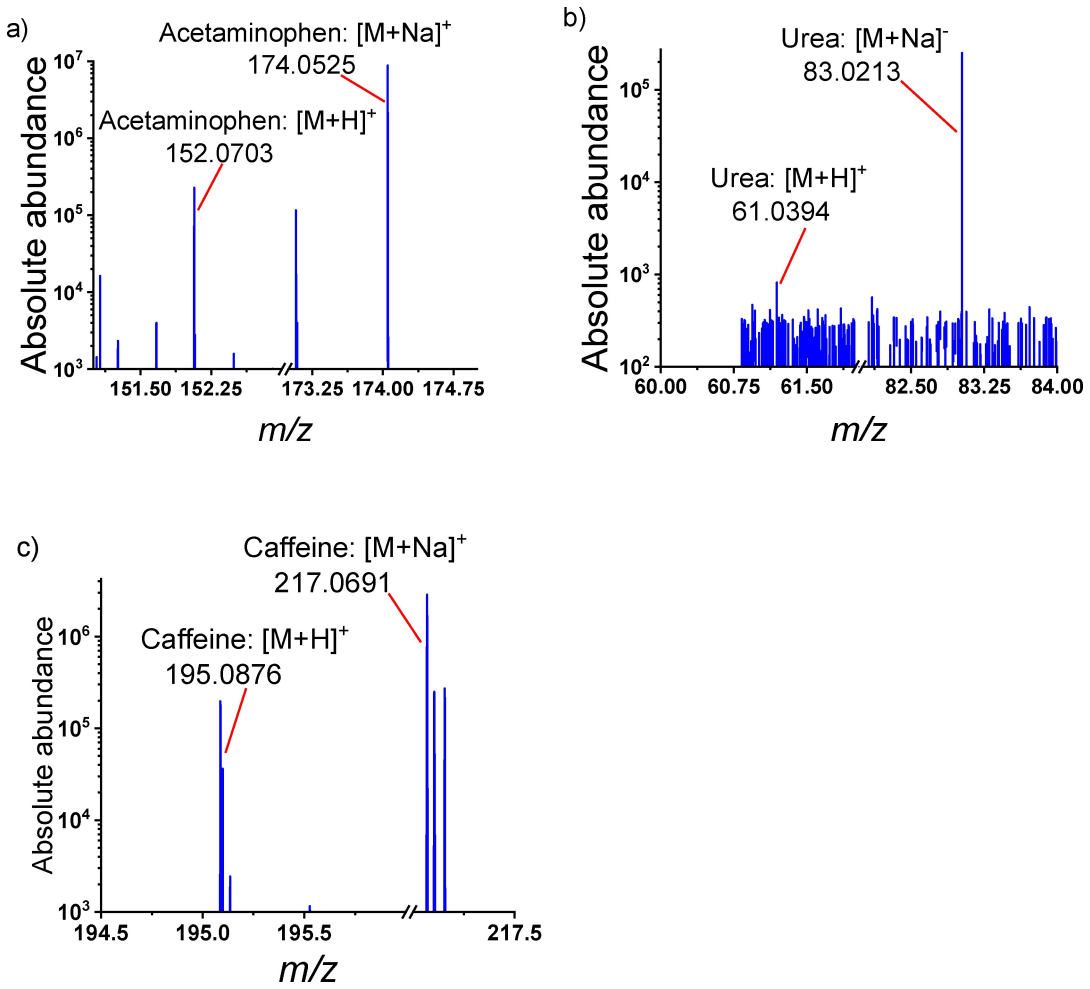


**Figure 6.** Mass spectra: a) urea, b) acetaminophen, and c) caffeine recovered by processing in10 μM solutions analyzed with SWESI-MS at +5.0 kV. All the spectra are collected in the positive-ion mode, and analyte ion peaks are labeled accordingly.

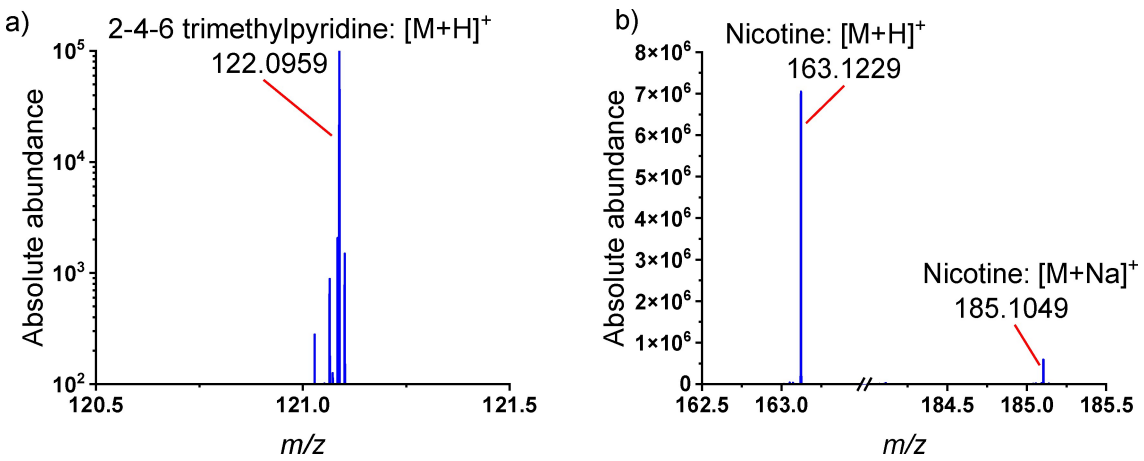


**Figure 7.** Mass spectra: a) 2,4,6-trimethylpyridine, and b) nicotine analyzed with SWESI-MS at +5.0-kV. All the spectra are collected in the positive-ion mode, and analyte ion peaks are labeled accordingly.

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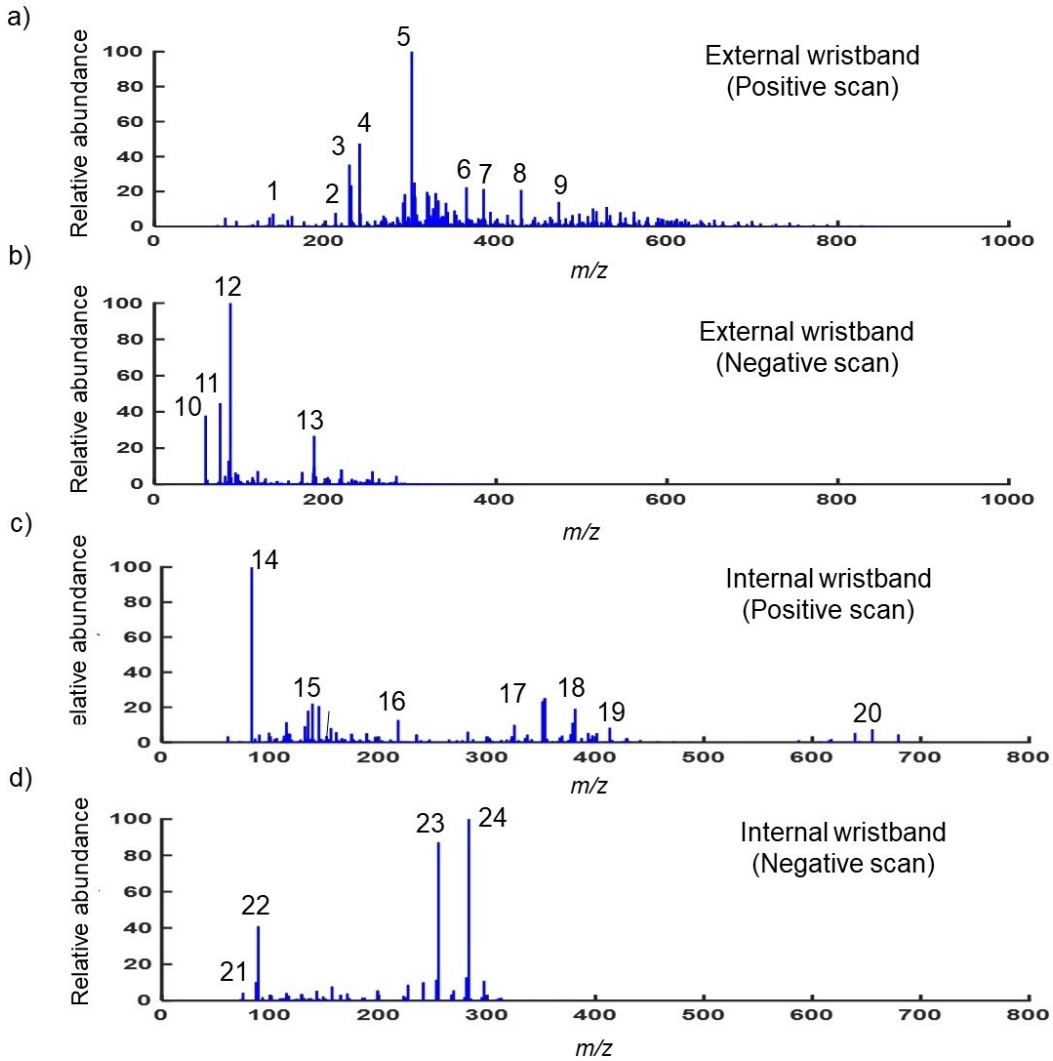


**Figure 8.** Exogenous exposome profile collected (a, b) from the external surface and endogenous metabolomic profile collected (c, d) from internal surface. Exposome and metabolome compounds: 1. 3-aminopicolinic acid ($[M+Na]^+$, *m/z* 161.031492), 2. glucose ($[M+Na]^+$, m/z 203.0510), 3. pentadecylamine ($[M+H]^+$, *m/z* 228.267054), 4. 1-hexadecanethiol ($[M+H\text{-}H_2O]^+$, *m/z* 241.234295), 5. 1-octadecanethiol ($[M+NH_4]^+$, *m/z* 304.298456), 6. tetraethylene glycol monododecyl ether, ($[M+Na]^+$, *m/z* 385.290503), 7. bis(2-ethylhexyl) terephthalate ($[M+Na]^+$, *m/z* 413.263396), 8. stearolac ($[M+H]^+$, *m/z* 429.316246), 9. octaethyleneglycol monododecyl ether ($[M+Na]^+$, *m/z* 577.368864), 10. cyanamide ($[M+Cl]^-$, *m/z* 76.988255), 11. ethylene carbonate ($[M-H]^-$, *m/z* 87.009004), 12. benzoic acid ($[M-H]^-$, *m/z* 121.029827), 13. 2-(3-mercaptopropyl) pentanedioic acid ($[M-H20\text{-}H]^-$, *m/z* 187.042535), 14. urea ($[M+Na]^-$, *m/z* 83.02094), 15. phosphocreatinine ($[M+H\text{-}2H_2O]^-$, *m/z* 158.011454), 16. glucosamine ($[M+K]^-$, *m/z* 218.043769), 17. palmitoylcarnitine ($[M+H]^+$, *m/z* 341.264091), 18. stearoyllactic acid ($[M+Na]^+$, *m/z* 379.280724), 19. vitamin D3 ($[M+2Na-H]^+$, *m/z* 429.31605), 20. PA(20:5-OH/14:0) ($[M+H\text{-}H_2O]^+$, *m/z* 665.420386), 21. pyruvic acid ($[M-H]^+$, *m/z* 87.00866), 22. lactic acid ($[M-H]^+$, *m/z* 89.024254), 23. palmitoleic acid ($[M-H]^+$, *m/z* 253.216111), and 24. oleic acid ($[M-H]^-$, *m/z* 281.247943).

### 2.6 Profiling of the Sweat Metabolome Collected from the Wristband Internal Surface

In terms of the sweat metabolome, there were at least around 400 metabolites that can be putatively assigned with certain identity by searching exact *m/z* values in the HMDB (mass tolerance at 0.005 amu). The metabolite species widely covered carboxylic acids, amino acids, fatty acids, carbohydrates, amines, purines, and pyrimidines. Among them, urea, phosphocreatine, lactic acid, pyruvic acid, oleic acid, and palmitoleic acid were the predominant sweat metabolites (Figure 8c and 8d). Urea is mainly involved in the arginine biosynthesis and catabolism process. The sweat urine was reported to be a potential marker for uraemia.[34] Lactic acid, pyruvic acid, and phosphocreatine are all important metabolites involving in the anaerobic and aerobic metabolism for energy supply. Their concentration changes in sweat can be very important metrics to evaluate the physiological status after intense physical

exercise.[35] Unlike small lipophilic (hydrophobic) molecules such as cortisol, sweat glucose exhibits only ~1% of the glucose concentration in the surrounding interstitial fluid (ISF).[36] Due to low concentration (~100 times dilution) of glucose in sweat, glucose monitoring requires highly sensitive systems.[37] Oleic acid is one of the most abundant fatty acids and building block of lipids. Previous studies have revealed that the oleic acid level is dysregulated in skin cancer cells.[38] Therefore, the monitoring of oleic acid and glucose by the wristband may also be useful for a noninvasive diagnosis of skin cancer.

Apart from the endogenous metabolites, these functional small molecules ingested from the diet and drink can also be successfully detected from the worn, internal wristband surface. As was shown in Figure 9, glucose, caffeine and taurine ions can be observed from the wristband spray. The former one is confirmed to stem from coffee and the latter one was found to derive from a functional drink. Besides, the niacin (nicotinic acid) ion was also successfully monitored after smoking by the volunteer. More surprisingly, the downstream metabolic products of niacin (nicotinamide, nicotinamide N-oxide, and N-methyl nicotinamide, Figure 9a) can also be positively detected. This result provided the possibility that the wristband can even be used to trace a whole metabolic pathway.

Vitamins are types of essential micronutrients serving critical functions in body. Only a small quantity is sufficient for proper functioning. Most vitamins cannot be synthesized in the body and only a small quantity is needed from the dietary ingestion to maintain proper organism function. Therefore, they usually are present in a low concentration in the body. Even under this situation, the wristband can still successfully capture the trace amount of several nutrition components after a complex vitamin tablet has been ingested. These include niacin, ascorbate, biotin, thiamine, tetrahydrofolate, and glycerate (Figure 9b). This result further revealed the sensitivity of SWESI-MS and the wide coverage of the sweat metabolome that the silicone wristband can collect.

## 3. Strengths and Limitations of SWESI-MS

This study explores a simple collection and detection method coupling with SWESI-MS using SWs. SWs are noninvasive, personalized sampling devices to collect extensive data about biochemical markers and outdoor air quality. Wristbands have the potential to provide insight into an individual's unique exposure profiles in contact with the air and skin. Therefore, the measured personal exposure is promising for assessing human health risks from ambient air and dermal sources. On the other hand, SWESI-MS provides fast screening/identification features associated with health outcomes for metabolites, lipids, and human exposome applications. It would also offer a practical

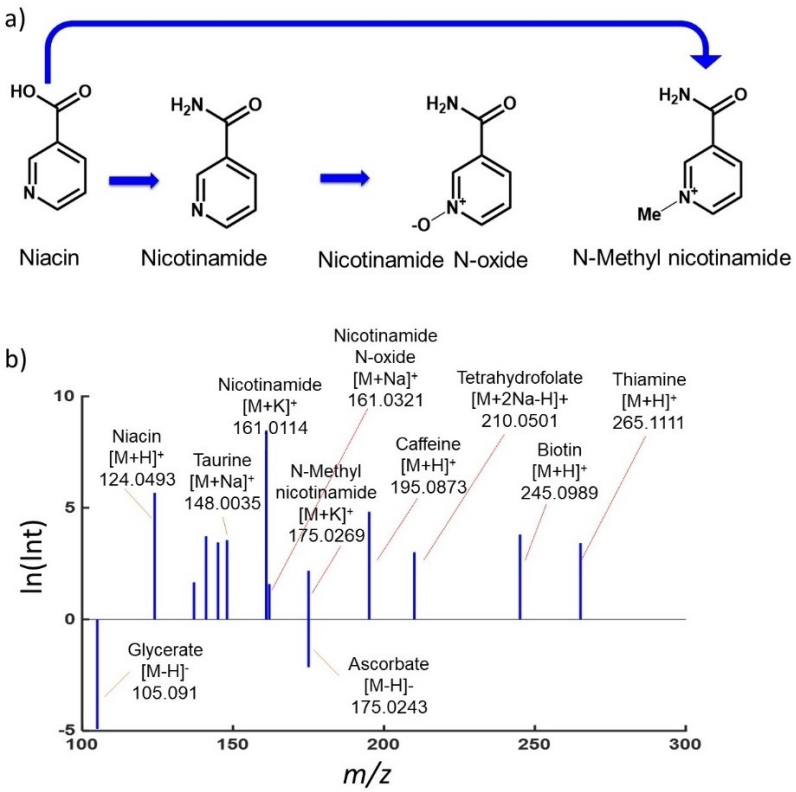


**Figure 9.** a) Diagram of the niacin metabolism pathway that the SWESI can trace and b) the mass spectrum of sweat components detected from a vitamin tablet. The intensity is logarithmically transferred. The negative ion is displayed with the negative value.

approach to advance chemical identification of human exposome research with limited sample volume in the μL range.

Limitations include that the SWs had to be cleaned to ensure the removal of any contaminants and unreacted monomers that may interfere with detecting the compounds of interest. Due to the differences in the temperature and humidity of different environments, the sampling rates of the chemicals onto the wristbands may be affected. This may need validation of chemical concentrations by regions and other factors. This method can only be used with difficulty for quantitation by separation methods like liquid chromatography. In addition, packing and transportation of the SWs may cause cross-contamination and evaporation of some volatile species. Therefore, there is a need to provide practical guidelines for preparation, application, transport, recovery, and storage of worn wristbands.

## 4. Conclusion

Silicone wristband is demonstrated to be a cost-effective, in situ sample collector for both the sweat and air pollutants. As presented in this study, SWESI-MS enables direct sample analysis from silicone wristband at a small volume of biofluids without dilution of sweat samples, in which it enhances the quality of the analytical signals. SWESI-MS addresses a critical need for lifelong complementing of the human exposome by dermal and environmental exposures. This method identifies the chemical features of analytes and silicon wristband background. The developed post processing method used to identify the analytes peaks without pre-cleaning extraction techniques of fresh silicone wristbands. Our results demonstrated that the developed method establishes the quantification of sweat-based and environmental chemicals at low levels of analytes. This method also offers high sensitivity and selectivity, high resolution, and a long-time window for the simultaneous detection of ambient air and dermal sources. The ability to record mass spectra in both positive and negative modes adds to the ability to identify compounds. Quantitation is possible but requires the construction of a calibration curve. The simplicity of the method should enable human exposome research for diverse chemical exposures in tens of thousands of individuals with limited sample volume.

## Acknowledgements

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## Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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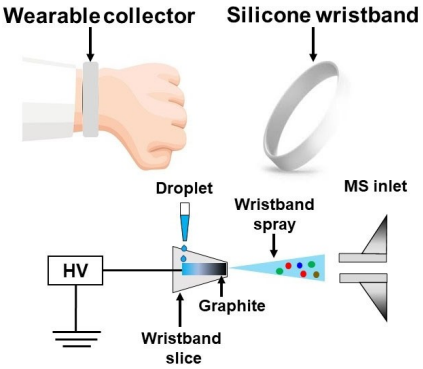


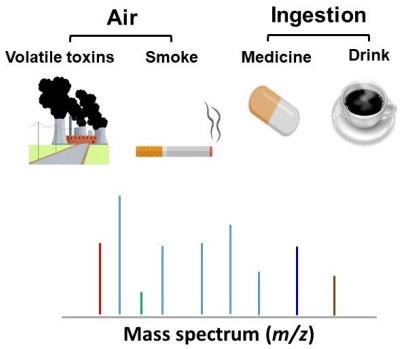


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**Silicone Wristband Spray Ionization Mass Spectrometry for Combined Exposome and Metabolome Profiling**