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Recent progress in wearable extractive sampling technology

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ABSTRACT

The inevitable incline in the daily exposure to various chemicals has raised a necessity to monitor the body's exposure and biological responses to these stimuli more comprehensively and easily; conceivably, integrating novel designs, extractive phases, and state-of-the-art instrumentation with the primary aim of taking the chemical snapshot of the system. Wearable extractive devices are promising tools that are present in the analytical toolbox and address the abovementioned needs. These devices consist of a particular class of samplers that an individual can wear without limiting her/his daily life activities. In addition to being wearable, these devices show the ability to preconcentrate the analytes in an extractive phase while integrating the sampling and sample preparation. In addition to being imperative for personal exposure investigations, applications in diagnostic and prognostic health monitoring are among their emerging applications. Besides, in vivo soft samplers based on microextraction techniques provide non-invasive to low invasive approaches for non-lethal monitoring of various biosystems. Although in these applications they are not used in an 'obvious way' as wearable devices as they are not placed directly on the subject's skin and are instead immersed under the skin, in the scope of this review they will still be considered to provide a picture for future directions of extractive wearable devices. This review aims to cover the wearable extractive devices used in exposure studies (with a special focus on the last two years), in vivo, and in situ applications (with a focus on the last five years) where reliable information about the system is under interest.

1. Introduction

Wearable extractive devices are a group of samplers that perform the sampling and preconcentration of the analytes using extractive phases in wearable configuration. Samplers that fit within the above definition can be divided into two groups, namely, active, and passive wearable samplers. Passive samplers, consisting of sorbents placed in contact or in the headspace of the investigated surface, extract the analyte via passive diffusion from the sample matrix to the sorbent. The analytes diffuse from the sampling medium to the sampler due to a chemical potential difference between the two media. The diffusion phenomenon of the analytes continues until equilibrium is established [1]. In equilibrium-based sampling, the equilibrium constant of the analyte (for sample matrix and extractive phase) and extracted amount of the analyte on the device can be used for quantitative analysis; alternatively, the device can be calibrated experimentally. The sampling can also be stopped at a pre-equilibrium state in which the calibration of the device is based on Fick's first law of diffusion, which states that the analyte extracted on the sampler is directly related to the sampling period. The pre-equilibrium sampling results in time-weighted-average (TWA) concentration determination if the sampling rate is known [1,2]. Needle trap (NT) devices, solid phase microextraction (SPME), thin film microextraction (TFME), extractive patches, wrist bands, and dog-tag type devices made of silicone or polydimethylsiloxane (PDMS) are among various passive samplers which fall into the category defined above. In the case of active samplers, the device is equipped with a tubing within which the extractive phase is placed, and it is integrated with a portable pump (usually a low volume pump). The requirements of a sampling pump to collect air, and a stable battery source for long time sampling, makes the active sampling less affordable and unpractical due to the high weight of the pump placed on the individuals. Unlike passive sampling, active sampling is an exhaustive technique requiring close control of the sample volume via controlling the air flow rate and sampling time to ensure that the breakthrough volume for targeted analytes is not reached. Therefore, in

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Abbreviations

Abbreviation	Explanation
ACGIH	American Conference of Governmental Industrial Hygienists
APPI	Atmospheric Pressure Photoionization
BaP	Benzo(a)pyrene
BTEX	Benzene-Toluene-Ethylbenzene-Xylene
CEN	European Standards Organization
CYP1A1	Cytochrome P450 Family 1 Subfamily A Member 1
DEET	N,N-diethyl-meta-toluamide
DPP	Diphenyl phosphate
DVB	Divinylbenzene
EPA	Environmental Protection Agency
FLD	Fluorescence Detector
FPSM	Fabric-Phase Sorptive Membrane
GC	Gas Chromatography
GC-MS	Gas Chromatography-Mass Spectrometry
GC-MS/MS	Gas Chromatography Tandem Mass Spectrometry
GFF	Glass Fiber Filter
GPS	Global Positioning System
HFR	Halogenated Flame Retardants
HLB	Hydrophilic—Lipophilic Balance
HPLC	High-Performance Liquid Chromatography
HRMS	High-Resolution Mass Spectrometry
IPA	Isopropyl Alcohol
ISO	International Organization for Standardization
LC	Liquid Chromatography
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
LOQ	Limit of Quantification
MD	Microdialysis
MIP	Molecularly Imprinted Polymer
MSM	Molecular Selective Membrane
MS-OECT	Molecularly Selective-Organic Electrochemical Transistor
μPC	NT Microfabricated Chip-Based Needle Trap
NIOSH	National Institute of Occupational Safety and Health
OCP	Organochlorine Pesticides
OPE	Organophosphate Ester
PAH	Polycyclic Aromatic Hydrocarbons
PBDE	Polybrominated Diphenyl Ethers
PCAP	Phosphino-Polycarboxylic-Acid Polycarboxylate
PCB	Polychlorinated Biphenyl
PDMS	Polydimethylsiloxane
PEDOT	Poly(3,4-ethylenedioxythiophene)
PEG	Polyethylene Glycol
PET	Polyethylene Terephthalate
PLV-AAS	Personal Low Volume-Active Air Sampler
PP	Polypropylene
PPG	Polypropylene Glycol
PSMS	Paper Spray Mass Spectrometry
PSS	Polystyrene Sulfonate
PTFE	Polytetrafluoroethylene
PTHF	Polytetrahydrofuran
PUF	Polyurethane Foam
SEBS	Styrene-Ethylene-Butadiene-Styrene
SPE	Solid Phase Extraction
SPME	Solid Phase Microextraction
SSRI	Selective Serotonin Reuptake Inhibitor
SVOC	Semi Volatile Organic Compound
TDE	Total Dermal Exposure
TDU	Thermal Desorption Unit
TEAM	Total Exposure Assessment Methodology
TENAX TA	Poly(2,6-diphenylphenylene oxide)
TFME	Thin Film Microextraction
TPhP	Triphenyl Phosphate
TWA	Time-Weighted Average
UE	Unit Exposure
UPLC	Ultra-Performance Liquid Chromatography
UV—Vis	UltraViolet-Visible
VOC	Volatile Organic Compound
VVOC	Very Volatile Organic Compound

quantitative analysis, the analyte concentration in the sample can be found simply from the ratio of the analyte extracted on the sampler to the sampling volume [2]. In fact, NTs described under passive samplers also act as active samplers when connected to a pump.

One of the emerging areas of the application of the above-mentioned wearable devices is exposome studies. Exposome, a term that has become frequently pronounced in recent years, can be defined as the combination of all exposures to which a person is subjected through his/her entire life span [3]. The combination of exposome studies with cutting-edge instrumentations such as mass spectrometry can become a powerful tool for personal and public exposure assessment. In addition, this combination provides a reliable analytical tool for investigating the linkage between disease risks and exposure creating additional platforms for preventive medicine and public awareness.

The primary sources of human exposure are air, water, and food consumption. Air is the most critical contributor to the human exposome as we breathe and get exposed through the skin. Because the skin, the largest organ in the human body in direct contact with the external environment, has the highest risk. Therefore, studies that search for the linkage between the exposure and extrapolation of this effect on the human body from skin metabolites are critical. Consequently, samplers capable of monitoring the exposure of individuals to chemicals present in the environment over a period of time are in high demand. For practical and reliable exposure investigation, various wearable samplers were developed, with operational principles based on passive or active sampling. Fig. 1 shows various applications of wearable extractive samplers used in exposure studies.

In addition to the external effect of the environment on the body, many metabolites excreted on the skin can be used to monitor the inner state of the individual. Moreover, many diseases which are not directly related to the skin (e.g., Parkinson's) [4,5] and diseases that are directly occurring on the skin [6] (e.g., dermal ulcer, cancer etc.) frequently alter the skin's metabolomic profile. These changes sometimes are related to dysregulations in metabolome or variation in skin microflora which directly affects the skin chemistry [4–7]. As in the case of exposome studies, such changes can be monitored with wearable extractive devices. Unlike the exposure studies, which usually aim for long-term monitoring, screening for dysregulations on skin metabolome reflecting the person's inner state can be performed with short sampling times directly from the skin surface. Therefore, wearable devices become paramount to diagnostic medicine, preventive medicine, and general health monitoring, in addition to exposure assessment.

When specific keywords are typed in Web of Science such as 'wearable devices,' 33702 publications are listed, which include

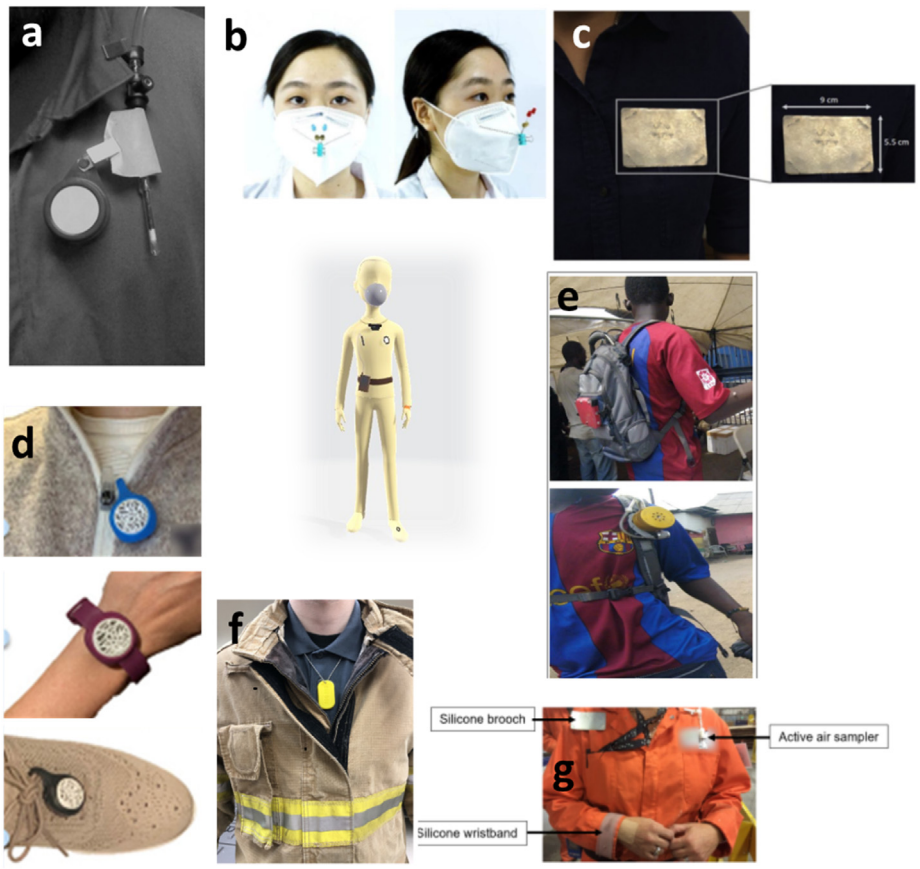

Fig. 1. Wearable extractive samplers used in exposure studies, (a) active and passive samplers attached to collar of a worker [31], (b) solid phase microextraction fiber as passive sampler on a face mask for exhaled breath aerosol analysis [57], (c) a PDMS on aluminum support broch for passive sampling of semi volatile organic compounds [19], (d) FreshAir passive samplers placed on chest, wrist and shoe [48], (e) active sampling in determination of occupational exposures to particulate matter and PAHs [30], (f) the use of dog-tag type of silicone passive sampler for investigation of firefighters chemical exposure [34], (g) using passive and active samplers for investigation of e-workers exposure to flame retardants [46].

mainly electronic devices. When the keyword is changed to 'wearable samplers' to narrow down the devices that act as samplers, 40, for 'wearable passive samplers' 12 and for 'wearable active samplers' 7 articles are listed. When the keywords are changed to 'in vivo sampling' for most of which samplers can be considered wearable, 78459, for 'exposure studies', 760332, and for 'exposomic', 54 articles are listed. The keywords of 'personal active samplers' and 'personal passive samplers' listed 153 and 509 articles, respectively. These statistics show that although the areas of 'wearable devices,' 'exposure studies,' and 'in vivo studies' are hot research topics, and the wearable samplers are commonly used in many of these studies, the terminology is not widespread yet. Moreover, it highlights that despite the tremendous benefits of the wearable extractive samplers, full advantage of this approach is still not taken. This review article compiles the current development of wearable extractive samplers at the crossroad of wearable technologies, showing the potential for new applications.

It is worth to mention that there is an incline in devices integrating electronic chip technologies and sensory detection mechanisms as intelligent wearables, most of them in proof of the concept studies [8,9]. In addition to be expensive, the most crucial disadvantage of these wearable devices is that the information gathered from such devices is restricted to a single compound or only a group of closely related compounds. However, in many cases, monitoring several compounds or the overall changes in the system are more meaningful as they provide additional information about the investigated system, especially when biomarkers discovery is in the quest. Therefore, devices that can take the chemical snapshot of the investigated system are paramount for such studies. One of the most effective ways to address the abovementioned needs is to transform and integrate the sampling and sample preparation to wearable technologies prior to more selective detection with mass spectrometry. Such a combination can provide a reliable platform for untargeted analysis with a wide range of analyte coverage, providing a more precise image for understanding the system under investigation. Table 1 shows a general comparison of the features of wearable passive and active samplers as well as shows their position compared to the wearable sensors and other samplers that do not have extractive properties. This review focuses on applications of wearable extractive devices suitable for exposure assessment and bioanalytical investigations.

2. Wearable samplers in exposure studies

One of the most concerning problems around the world is air pollution and it is caused mainly by aerosols (in the form of dust, spray, smoke), gases and vapors released from industries, vehicles, agricultural applications (e.g., pesticides), smoking, and some products used in cleaning, dry-cleaning, painting or personal care and cosmetics [10–17]. The release of these compounds into the environment eventually results in uncontrollable pollution in air, soil, or water around the world which affects human health and wildlife [18]. Therefore, monitoring the exposure is one of the crucial steps to take for both human health and the environment.

Table 1
Comparison of wearable samplers.

	Passive samplers				Active samplers		Non-extractive samplers	
	SPME	TFME	Needle trap	Wristbands, necklaces, dog-tags	Classical (tubes and filters)	Needle trap	Wearable sensors	Wipes, swaps
Cost	xx	xx	xx	x	xxx	xx	xxx	x
Pump requirement	no	no	no	no	yes	yes	no	no
Calibration difficulty	xx	xx	xx	xx	x	x	xx	xx
Instrumental coupling	x	xx	x	xxxx	xxxx	x	no	no
Commercial availability	yes	yes	yes	yes	yes	yes	no	yes
Detection on device	no	no	no	no	no	no	yes	no
Extraction of analytes	yes	yes	yes	yes	yes	yes	no	no

Cost: x cheap, xx moderate cost, xxx expensive.
Calibration difficulty: x easy, xx moderately difficult.
Instrumental coupling: x easy, xx moderately easy, xxxx not possible.

The main route of exposure to these pollutants is via air, water, soil, consumption of crops, or skin contact. However, reliable determination of exposure through determination of environmental concentration levels of pollutants is challenging due to the heterogeneity in distribution and low spot concentration in many cases. Still, researchers look for more reliable novel methods, which at the same time hold the advantage of being practical. At this point, scientists turn their steps toward the development of practical and non-labor-intensive on-site samplers which can be combined with portable instrumentation allowing to perform the full analysis on-site. Besides, on-site analysis with proper (automated) samplers (methods), provides advantages over classical laboratory analysis because it doesn't require labor-intensive and time-consuming sample preparation procedures (Fig. 2). Technologies capable of short- and long-term monitoring are especially important in exposure analyses as long-term and short-term exposure may have different effects on the biological system.

2.1. Air sampling with wearable extractive devices

Among various exposure routes, exposure to air pollution is the most common and in most of the cases, it is inevitable. According to Environmental Protection Agency (EPA), people are exposed to air pollutants mainly by breathing contaminated air, consumption of contaminated products, or direct contact with the contaminated products or surfaces. Only analysis of stationary air may not be informative for a realistic personal exposure evaluation since this sampling excludes the effect of personal activities during the exposure. One of the best approaches to determine the real exposure to any contaminants by taking into account the effect of personal activities is to use wearable samplers during the exposure studies [19]. In this part of the review, wearable devices that are used as samplers for monitoring human exposure to different pollutants or their primary metabolites indicating the exposure were summarized.

Short and long-term exposure to pollutants is linked to respiratory and cardiovascular diseases [20–23]. Among various classes of potential pollutants, volatile organic compounds (VOC) is one of the primary classes of compounds that are investigated in exposure studies. EPA defines VOCs as any compound of carbon, excluding CO, CO_2, H_2CO_3, metallic carbides, or carbonates. Therefore, VOCs consist of a large group of compounds that can be subgrouped as:

- Very volatile organic compounds (VVOCs) with boiling point range <0 to 50–100 °C (such as propane, butane, methyl chloride) [24].
- Volatile organic compounds (VOCs) with boiling point range 50–100 to 240–260 °C (such as, benzene, toluene, ethylbenzene, and xylene (BTEX), formaldehyde, acetone, ethanol, hexanal, naphthalene, para-dichlorobenzene) [12,17].
- Semi volatile organic compounds (SVOCs) with boiling point range 240–260 to 380–400 °C (such as organochlorine pesticides (OCPs), polychlorinated biphenyls, (PCBs), polycyclic aromatic hydrocarbons (PAHs) [19].

Human exposure to these chemicals might be the most critical concern due to the health effects of these pollutants in case of acute and chronic exposure. In addition to being present in free form in the air, VOCs and SVOCs can be found bound to airborne particles. These particles are categorized by the American Conference of Governmental Industrial Hygienists (ACGIH), the International Organization for Standardization (ISO), and the European Standards Organization (CEN) according to the size of the particle as inhalable particles with a particle size up to 100 μm which enter the body from nose and mouth and deposits in the respiratory tract; thoracic particles with a particle size up to 10 μm which penetrate beyond the larynx; and respirable particles with a particle size up to 4 μm which deposit in the gas exchange regions of the lungs [25]. These particulates are carried to the rest of the body via the bloodstream by entering the lungs [20,26,27]. In addition, VOCs and SVOCs are released from the particles mentioned above, even from home cleaning products, hobby paintings, or cosmetics, making the exposure inevitable [17,23,28]. For instance, Godoi et al. found that over 80% of indoor VOCs contribution is from the abovementioned sources [28]. According to EPA's Office of Research and Development's "Total Exposure Assessment Methodology (TEAM) Study" (Volumes I through IV, completed in 1985), common pollutants have between 2 and 5 times higher concentrations in the houses than outside [16,29], so indoor air analysis is also crucial as much as outdoor air analysis due to high risk of human exposure which causes irritations, organ damage, and cancers or other serious diseases.

Many studies have been conducted on occupational exposure of workers in different working areas such as waste recycling sites [30], industrial sites [31], rural and urban sites [32]. The reported values are much higher than unit exposure (UE) values. They also showed that the hands are the most contaminated anatomical region with 39% total dermal exposure (TDE). Therefore, it can be said that there is a huge demand for fast, simple, and reliable methods to monitor the exposure of workers to eliminate or at least minimize the risk of exposure. Many studies published after 2020 focused on assessing personal pesticide exposure via inhalation by using passive air samplers or silicone wristbands/dog tags (Fig. 1) [14,26,33–43].

Both active and passive samplers have been used for air sampling in wearable format [44]. In general, for personal exposure assessment, an active or passive sampler is placed at the height of

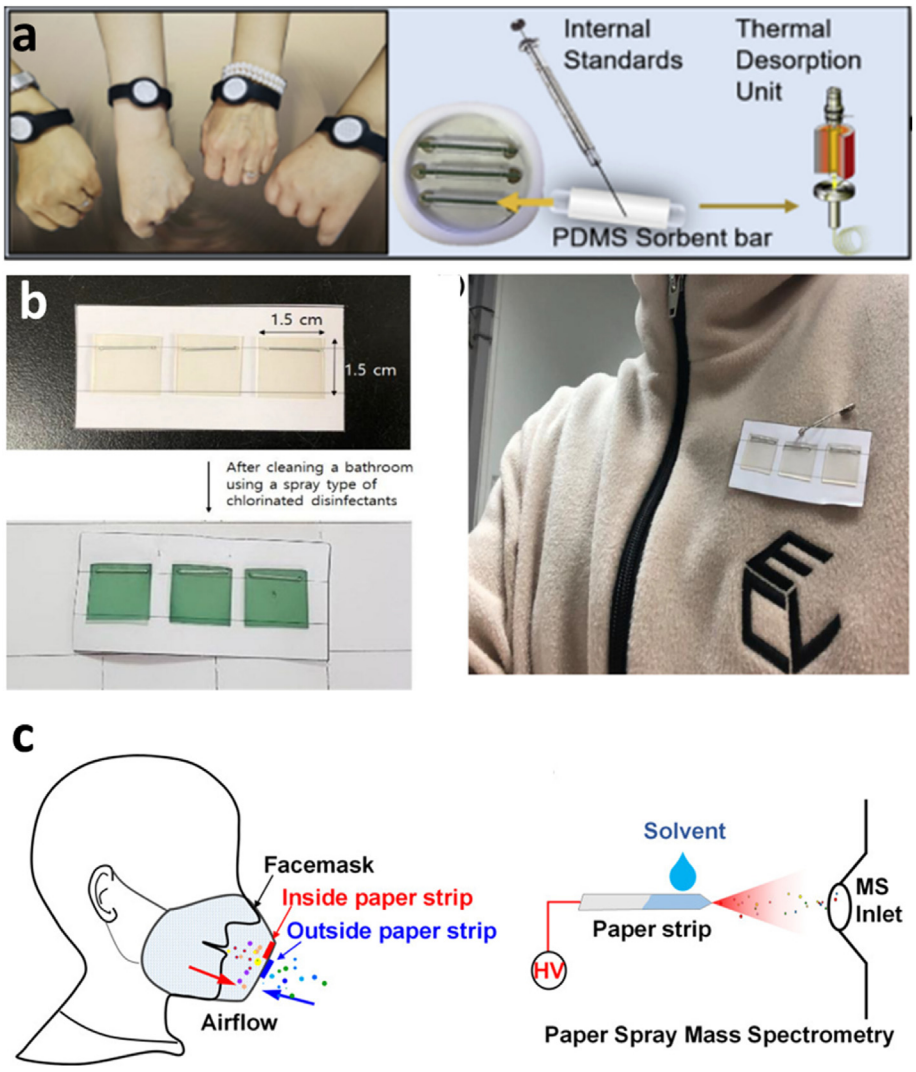

Fig. 2. Sample preparation free detection of analytes from various passive samplers, (a) coupling of thermally stable PDMS samplers to GC-MS via larger volume thermal desorber for sensitive analysis [36], (b) analyte specific coloration of chemically dopped PDMS for rapid and cheap detection of exposure to chlorinated disinfectants [47], (c) coupling of paper-based strip sampler to mass spectrometry for fast and reliable detection of ionizable analytes [56].

the person's breathing zone to represent the pollutants inhaled through the nose and mouth. In the case of active sampling, to not affect the everyday life of a person who carries a sampling pump, it is attached to the worker's belt without affecting his/her work during sampling. Due to their operational convenience the passive samplers are more attractive than conventional air samplers in exposure studies [44]. Also, such samplers allow time-averaged concentrations (TWA) determination in locations where active samplers would not be practical over long periods due to a lack of electricity supply. As a result of their simplicity and practicality, passive samplers more frequently are transformed into wearable devices such as badges, brooches, and diffusion tubes for screening ambient pollutants such as PAHs, phthalates [19,26,39,41,45], flame retardants [34,39,41,46], and pesticides [33,38]. Table 2 summarizes various applications reported in the literature after 2020 with active and passive samplers in exposure studies.

For instance, Reche et al. showed the application of wearable passive samplers to monitor athletes' exposure to air pollutants. As sampler silicone wristbands were used. Gas chromatography-mass spectrometry (GC-MS) results of the four-day sampling revealed the presence of PAHs due to the incidence of various combustion activities (e.g., traffic) in the area. Acenaphthene, fluorene, acenaphthylene, and phenanthrene were 8-fold higher in the used samplers than the blanks (unused samplers) [42].

Because of the above-demonstrated practicality of use, wristband passive samplers can be used efficiently for exposure studies involving children. An example of such a study was reported for investigation of if the children were exposed to phenols in their home environments. The sampling with wristbands over seven-day period followed by liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis revealed the presence of triclosan in the samplers. Moreover, it was found that the concentration of this compound in the sampler was significantly correlated with the urinary concentrations of triclosan collected on alternated days over the same sampling interval [37].

Among various samplers, dog-tag types of passive samplers can be considered one of the most appropriate designs for exposure analysis of workers with extreme activities, e.g., firefighters. For instance, Poutasse et al. developed silicone dog tags to investigate firefighters' exposure to air pollutants in a fire. Relatively long-term exposure study was designed in which the firefighters wore the dog tags for 30 working days and 30 off days (Fig. 1). The study results

Table 2
Application of wearable extractive samplers in exposure analysis.

Matrix	Sampling Device	Sampling Type	Sorbent	Analyte(s)	Analytical Technique	LOD or LOQ	Year	Reference
Air	Air sampler	Active	TENAX,TA	VOCs	GC-MS	Not given	2020	9
Air	Air sampler	Active	PUF	Pesticides	LC-MS/MS	LOD: 0.3 ng/mL	2021	11
Air	Air sampler	Active + Passive	Charcoal	IPA	GC/FID	Not given	2017	28
Air	Brooch	Passive	PDMS	SVOCs	GC/ENCI-MS	LOD: 0.07–12 pg/m^3	2018	16
Air	Wristband	Passive	PDMS	VOCs, PAHs, NO_2	GC/MS-TOF	Not given	2020	7
Air	Wristband	Passive	PDMS	Airborne chemicals	GC-HRMS	Not given	2020	33
Air	Wristband	Passive	PDMS	SVOCs	GC-HRMS	Not given	2021	45
Air	Air sampler	Active	XAD-2	TPhP	UPLC-APPI-MS/M	LOD: 0.10–0.16 μg/g	2020	46
EBA	Face mask	Passive	PDMS, PTHF, PEG–PPG-PEG, PCAP–PDMS-PCAP, CW20 M, mixed-mode zwitterionic sorbent	Different pollutants	LC-MS/MS	Not given	2021	52
Air	Face mask	Passive	Paper strip	Different pollutants	LC-MS/MS	Not given	2021	53
Air	Face mask	Passive	PP, PET	PAHs	HPLC-FLD	LOD: 0.06–0.8 ng/mask	2021	51
Air	Patch	Passive	PDMS	Chlorine	UV/vis spectrophotometer	Not given	2020	44
Air	Bird borne air sampler	Passive	PUF-GFF, PDMS	HFRs	GC/MS	LOD for PUF-GF: 0.01 ng/g LOD for PDMS: 0.01–0.23 ng/g	2017	15
Air	Wristband	Passive	PDMS	PAEs	GC-MS	LOD: 1.1 ng/cm^2	2021	23
Air	Wristband	Passive	Silicone	OPEs	GC-MS/MS	LOD: 0.01–27.19 ng/g	2021	47
Air	Wristband	Passive	Silicone	Phenols	LC/MS/MS	LOD: 0.7–2.7 ng/g	2021	34
Air	Wristband	Passive	Silicone	Pesticides	GC/micro ECD	LOD: 0.7–5.1 pg/μg	2021	35
Air	Dog-tag	Passive	Silicone	pEDCs	GC-MS	Not given	2021	36
Air	Wristband	Passive	Silicone	OPEs	UPLC-MS/MS	LOQ: 0.04–0.15 ng/band	2021	37
Air	Wristband	Passive	Silicone	OPEs	GC-MS-EI	LOD: 0.04–32.88 ng/g	2020	38
Air	Wristband	Passive	Silicone	PAHs	GC-MS	Not given	2020	39
Air	Wristband	Passive	Silicone	Pesticides	GC-MS/MS	1 ng/g	2021	30
Air	Dog-tag	Passive	Silicone	Different pollutants	GC-MS/MS	LOD: 0.241–2.84 pmol/g	2020	31
Air	Wristband, dog-tag	Passive	Silicone	Pesticides	GC-MS/MS	Analytical LOD: 0.03–0.6 μg/L	2021	32
Air	Wristband, brooch, armband	Passive	Silicone	FRs	GC-MS	LOD for brooch: 0.003–7.73 ng dm^{-2} h^{-1} LOD for wristband: 0.003–7.97 ng dm^{-2} h^{-1}	2020	43
Air	Wristband	Passive	Silicone	PAHs	GC-MS	LOQ: 0.03–56.85 ng/wristband	2021	12
Air	Wristband, brooch,air sampler	Active + Passive	Silicone (PUF)/XAD-2/PUF sandwich	Phthalates and OPEs	GC-MS	LOD for active air sampler: 0.0001–0.14 ng m^{-3} LOD for brooch: 0.03–33 ng dm^{-2} h^{-1} LOD for wristband: 0.03–35 ng dm^{-2} h^{-1}	2021	42

obtained after gas chromatography tandem mass spectrometry (GC-MS/MS) analyses revealed critical data showing 18 new PAHs, which were not reported in exposure studies before. Also, overall, 45 PAHs were detected during the on-duty sampling showing the potential hazard risk on firefighters [34]. In the abovementioned studies involving wristbands and dog-tag type of devices, the benefit gained by 'practicality in use' was partially offset because additional sample preparation steps were incorporated prior to analyses. These steps included desorption to solvent, evaporation, and the second extraction with solid phase extraction (SPE).

PDMS, one of the materials which have been used as (in) passive samplers, has various advantages. For instance, crosslinked PDMS has high thermal stability. When GC is equipped with a large volume thermal desorber, thermal desorption directly from the PDMS sampler to the column head is possible (Fig. 2). This combination allows for performing more sensitive analysis because it facilitates the introduction of all extracted analytes to the instrument and eliminates the solvent dilution effect seen in liquid injection. The second advantage of PDMS is its optical transparency in the visible region, which allows the combination of the PDMS film sampler with spectrophotometric detection. Ha et al. has reported one of the appealing applications of integration of spectrophotometric detection with a PDMS-based passive sampler. In this study, a personal passive air sampler made of PDMS sheets doped with o-dianisidine was used to determine chlorine species following exposure to HOCl. When the PDMS sheet loaded with o-dianisidine is exposed to oxidant gases, its color changes from colorless to brown/green due to the oxidation-reduction reaction between o-dianisidine and HOCl and Cl_2, which allows the use of a simple spectrophotometric detection (Fig. 2). As proof of the concept, the PDMS passive sampler was worn during the cleaning using bleach. The samplers were analyzed by a UV/vis spectrophotometer with a maximum absorbance of 305 nm and 429 nm for o-dianisidine and its oxidized form, respectively. Based on the results of the study it can be concluded that this design can be successfully used for the quantitative determination of Cl_2-equivalent exposure-in critical places (e.g., hospitals and schools) [47].

In addition to human-related personal exposure, many applications with passive wearable samplers were also reported for screening wildlife and other animal exposures. Sorais et al.

developed a novel passive air sampler with two different sorbents, PDMS and polyurethane foam (PUF), coupled to a glass fiber filter (GFF) for the monitoring atmospheric exposure of birds to halogenated flame retardants (HFRs) [18]. In this study, four adult ring-billed gulls were captured, and the samplers were mounted in the middle back of the birds and the sampling was carried for 1, 2, and 3 weeks. Based on the reported results, the novel air sampler could collect all major polybrominated diphenyl ethers (PBDEs). The study results can be considered a "proof of concept" for the non-dietary environmental exposure to HFRs of wild birds. Another example illustrating the potential of the passive samplers conducted by Wise et al. showed the exposure of both people and their dogs' to pesticides in the home environment by the wrist bands passive samplers [35]. Urine samples were also collected and analyzed for 15 common pesticide metabolites. Various pesticides, including permethrin, N,N-diethyl-meta-toluamide (DEET), and chlorpyrifos, were detected in the majority of the samplers. Moreover, strong correlations were observed for the concentrations of permethrin and DEET between the silicone sampler and their corresponding urinary metabolites. In addition, the results of human and animal exposure to pesticides were similar.

It is worth mentioning that although in general the wearable samplers are practical tools, it should be kept in mind that these samplers are in contact with skin; therefore, any personal care product used on the skin by individuals may affect the uptake rate and sorbent capacity by creating a thin layer on the wristband. To overcome this problem, the FreshAir wristband (see Fig. 1) as a novel passive sampler was developed by Lin et al. [10]. The device consisting of a PDMS sorbent enclosed in a polytetrafluoroethylene (PTFE) chamber, eliminating the possible interferences that might come from direct contact with the skin during sampling has been used in many studies [10,29,36,48].

In one of the applications of this sampler, Koelmel et al. showed that the position of passive samplers affects the sampling of analytes [48]. For this purpose, FreshAir wristbands containing four PDMS bar sorbents were placed on the chest, wrist, and shoe, and the sampling was performed for 24 h (Fig. 1). Since the PDMS bars are thermally stable, they were desorbed using a large-volume thermal desorption unit (TDU) directly to GC-HRMS. Such a combination provides an opportunity for more sensitive analysis as all extracted analytes on a sampler can be introduced directly to the instrument. Therefore, the dilution effect, which is mainly seen for solvent desorption followed by liquid injections to GC, was eliminated. Based on the results, PAHs were primarily found in shoe samplers. At the same time, they were present the least on the chest samplers indicating the importance of the sampling position as the chest samplers were more specific for the analysis of volatile compounds. In contrast, shoe and wrist samplers were found most sensitive as the highest SVOCs were accumulated on the shoe samplers. However, the possible difference in sorption kinetics based on the position of the sampler that might affect the sampling sensitivity, as more static conditions on the chest and more active conditions on the shoes and wrist, was not discussed.

Another approach to avoid contamination of the sampler was described by Okeme et al. [19]. In this study, the PDMS strip was pinned to aluminum supports to prevent its contamination caused by clothes (Fig. 1). Personal low volume active air sampler (PLV-AAS) that contains PUF and styrene-divinylbenzene copolymer (PUF/XAD/PUF) sandwich was used (placed in the breathing zone for 8 h with sampling flow rate of 0.4–0.5 L/min) to calibrate the PDMS brooch type of passive sampler (placed on the chest). After calibration was completed, a seven-day field experiment was conducted with the passive sampler to measure personal exposure in work offices. The study results showed diversity in concentrations obtained with PDMS brooches for phthalates and organophosphate esters (OPEs), demonstrating the effect of different activities performed by the individuals in their daily lives. Moreover, the sampling rate obtained with the brooch type of sampler was high enough to adsorb phthalates and OPEs in detectable amounts when worn for 8 h daily for several days three to four days [19].

Despite their impracticality in use, several publications have reported active samplers as wearable devices. For instance, Estill et al. evaluated the exposure of nail salon technicians to triphenyl phosphate (TPhP), which is used as a plasticizer in nail polish [49]. In this study, the wearable active air sampler containing a GFF and two XAD-2 sorbent layers operated at a flow rate of 1.0 L/min were used throughout the work shift (~8 h). After solvent desorption of the sorbents of the sampler, the analysis was conducted on ultra-performance liquid chromatography-atmospheric pressure photoionization-tandem mass spectrometry (UPLC-APPI-MS/MS). The geometrical mean concentration of TPhP for the active sampler (air sampling) was found as 7.39 ng/m^3. In addition, diphenyl phosphate (DPP), the common metabolite of TPhP, was found in urine samples collected from the volunteer further verifying the subject's exposure to the pollutant [49]. Another exemplary study investigating pesticide exposure with active samplers was reported by Venugopal et al. In this study, the effect of pesticides on agricultural workers and individuals living close to the application field was investigated [14]. The samplers were mounted at the height of the worker's breathing zone in a way not to affect their work, and then the active sampling was performed with a flow rate of 1 L/min. Also, environmental air samples were collected by a high-volume PUF sampler coupled to a GFF with a flow rate of 200 L/min. Based on the results, pesticides, thiamethoxam and chlorpyrifos-methyl were only detected by active samplers used in air sampling. In contrast, ethion and thiophanate methyl were only detected by high volume samplers, and both types of the samplers detected carbendazim, indicating samplers' complementary nature. However, as described before, active samplers have limited life, and an extra load of battery on the wearer during their daily life activities is cumbersome [31]. Therefore, the use of active samplers has become less common nowadays. Commercially available silicone wristbands are used as samplers for different pollutants such as flame retardants, plasticizers, phenols, OPEs, and pesticides [33,37–41,50]. Silicone wristbands might be a candidate for the most popular air sampler within the next years since, in addition to its simplicity and lightness compared to active samplers, the silicone can extract a wide range of hydrophobic pollutants. However, the performance of this material is inadequate for polar compounds, indicating that there is still room for improvement.

Several other studies that have been performed to evaluate personal exposure were conducted in parallel with active and passive samplers, which allows for cross-checking the reliability of the data obtained by each method. For instance, a study was performed to evaluate the level of VOC exposure of workers working on the recovery of valuable components disposed of electrical and electronic devices [46]. The volunteers carried both active and passive samplers for comparison (Fig. 1). In this study, three types of silicone-based passive samplers were used: wristband, brooch, and armband. In the case of active air samplers, it consisted of a filter, polystyrene/divinylbenzene-based (XAD-2) sorbent, and polyurethane foam (PUF) plug, which allowed the collection of both the gaseous (free) and particle-based (bound) pollutants. The active sampler was connected to an air sampling pump during the sampling at a flow rate of 2 L/min. The sampling with both devices was performed for 8 h when workers performed different tasks. The sorbents/plugs in all devices were extracted with acetonitrile following the sampling and then analyzed by GC-MS. The workers' exposure was monitored by collecting blood (plasma fraction was

used) and urine samples for correlation studies. After evaluating the data, it was found that silicone wristbands, armbands, and brooches accumulated non-halogenated flame retardants, PBDEs, and OPEs. Methylphosphonyl difluorides for most flame retardants were found higher in wristbands than brooches/armbands. This observation might be because wristbands were closer to polluted air, such as workbenches and disassembled equipment. Based on the comparison of paired passive and active air samples it was found that the brooch-type sampler and active sampler had similar results [46]. In the same line, Simons et al. constructed a study to show whether there is a difference in the performance of active and passive sampling methods for air sampling [31]. This study showed monitoring exposure to isopropyl alcohol (IPA) in an industrial setting using a passive (3 M 3520 organic vapor monitor that contains two charcoal adsorbents) and active samplers (coconut shell charcoal solid sorbent tubes). The active sampler was placed over the shoulder of the worker with a belt that held the air pump (Fig. 1). The flow rate was set to 0.09 L/min. The passive sampler was fixed near the sampler tube on the same shoulder. The samplings were performed for 20–29 min (to meet the minimum requirement of volume set by the National Institute of Occupational Safety and Health (NIOSH) 1400) with the active sampler and 8 h with the passive sampler. Based on the obtained data, active and passive samplers provided statistically different results, but a strong linear correlation was found between the samplers. This means that if the concentration of an analyte is known from one sampler, the concentration that will be obtained from the other sampler can be predicted by correlation studies. Another comparative study for active and passive samplers was conducted by Itza et al. In this study, participants wore wristbands and carried an active sampler with a PTFE filter and XAD tubes for 24 h [15].Based on the study results obtained from GC-MS, and as can be expected, each type of sampler provided different limits of quantifications. For instance, the limit of quantifications (LOQs) of PTFE filters were in a range from 0.01 to 0.38 ng/m^3, for XAD adsorbent were in a range from 0.01 to 10.93 ng/m^3, and passive samplers were from 0.03 to 56.85 ng/wristband. Besides, only phenanthrene and fluorene were captured by all devices in all participants. Further investigation on comparing the results of active and passive sampling indicated that the PAHs with small molecular weight showed similar concentration profiles for biphenyl, 1-methylnaphthalene, and 2-methylnaphthalene while the other PAHs varied. This strongly suggests that different results are possible based on the device used and the targeted analyte.

Another valuable sampler suitable and used as a wearable device is a needle trap. In this design, the extractive phase is fixed in a needle tailored in size for thermal desorption in the GC injector port [51]. The NT can be used as a diffusive sampler for TWA concentration measurement (as a passive sampler) or as an active sampler for spot sampling when combined with an air pump. SPME and NT are often considered similar approaches; however, active sampling with NT is a rather exhaustive technique requiring close control of the sample volume to ensure that the breakthrough volume for targeted analytes is not reached [2]. As NT devices can be desorbed directly to the injector port of a GC, it provides an opportunity for sensitive analysis. Although this technique holds many potential advantages described above, only a few applications reported its use as a wearable sampler. In this manner, as a passive sampler, homemade NT device packed with divinylbenzene (DVB) particles with 60–80 mesh size in 7 mm length were used for sampling of VOC in a medical examination center to investigate personnel exposure with a wearable pen-like NT device [52]. The TWA concentration of xylene after 8 h sampling with NTs showed a good agreement with the standard active sampling method (NIOSH 1501), highlighting the advantages of this device for routine exposure studies. The same type of NT device was also investigated for monitoring the exposure of oil painters to organic compounds such as isododecane, which is the main emitted compound from the oil thinners [53]. The obtained results from passive NTs and NIOSH 1501 active sampling generally agreed with slightly higher concentrations obtained by NTs, which was explained by the better efficiency for the extraction with NTs. Although NTs have many advantages, such as being suitable for direct coupling to GC injector port, having pen-like geometry suitable as a wearable device, and commercial availability, they still have not been uncovered as the ideal tool for personal exposure studies.

2.2. Wearable extractive samplers in breath sampling

Breath as a sample matrix is an important source of chemical information. Exhaled breath contains mostly water, but also VOCs and SVOCs are present in the microdroplets. This biological matrix provides valuable information about physiological and pathological diseases and exposure to air pollutants. Tedious sample collection procedures make the collection of compounds in exhaled breath unpractical on a larger scale. A simple way to monitor human exposure to air pollutants is using face masks as wearable passive samplers. The use of protective masks to reduce hazardous pollutants and exposure to pathogens became standard worldwide, especially after the SARS-CoV-2 pandemic. Well-known surgical masks are made from nonwoven fabrics, in which the effectiveness of a mask is enhanced by melt-blown filters made by polypropylene (PP) and polyethylene terephthalate (PET) filaments. As the masks became a crucial part of daily life, using them as passive samplers to monitor environmental exposure via inhaled air and to monitor body response to various stimuli via exhaled breath became rational. For instance, Chan et al. showed the use of face masks to monitor personal exposure to PAHs [54]. In this proof of the concept study, the volunteers first wore the masks in a laboratory environment for 2 h and then in a room influenced by incense burning for 15 min. After the sampling, the analytes adsorbed on the masks were desorbed in methanol and analyzed by high-performance liquid chromatography with a fluorescence detector (HPLC/FLD). Based on the results, naphthalene was the most abundant chemical. Moreover, after 2 h of sampling, nine PAHs were found in detectable amounts. Similar results were obtained by mask sampler and the standard NIOSH method, while the novel method held the advantage of simplicity and shorter sampling time. With a similar approach, Locatelli et al. introduced a novel fabric-phase sorptive membrane (FPSM) which was attached to a mask for *in-vivo* sampling from the exhaled breath aerosol [55]. In this way, a microenvironment was formed inside the facemask suitable for extraction of the exhaled molecules that might contain metabolites and biomarkers important for the exposure analysis and diagnostic purposes. Different sorbents were used in the study to maximize the extraction and coverage of analytes from exhaled breath aerosol. The membranes were inserted on the same side of the facemask by stapling, where each membrane was not in contact with another. The used membranes in the study consisted of PDMS (non-polar), polytetrahydrofuran (PTHF) (medium-polar), polyethylene glycol-polypropylene glycol-polyethylene glycol (PEG–PPG-PEG), and phosphino-polycarboxylic-acid polycarboxylate-polydimethylsiloxane-phosphino-polycarboxylic-acid polycarboxylate (PCAP–PDMS-PCAP), CW20 M (polar), and mixed-mode zwitterionic sorbent, ensuring a wide range of analyte coverage. The masks equipped with membranes (with 1.0 cm in diameter) were used for 8 h by volunteers in their working areas. Based on the results, more than 739 chemicals were detected. Despite of various types of sorptive materials tested in the study, no information was provided on the individual capability of each type of sorbent. With a similar

intention of taking advantage of a face mask, Cai et al. developed a wearable sampler by fixing two paper strips inside and outside of a facemask that adsorbs exhaled and inhaled air [56]. The paper strip exposed to an exhaled aerosol of smoker volunteers was analyzed for nicotine and cotinine, the specific nicotine metabolite. The analysis was conducted in paper spray mass spectrometry (PSMS) without requiring sample pretreatment, making this approach suitable for fast and reliable direct-to-mass spectrometric determinations (Fig. 2). Results revealed the presence of nicotine right after the smoking while cotinine peak appeared 3 h after the smoking. Based on this pilot study, it can be concluded that direct analysis of strips provides an opportunity for the fast and reliable analysis of thermally unstable compounds. Since the mask by nature is used for protection from environmental exposure, a paper strip placed in and out of the mask may provide additional knowledge on the protection capability of the mask. Furthermore, the authors were able to show that when the strip was placed on the outside of the mask show the evidence of oil aerosol exposure in the cooking environment, while the inner strip on the mask showed no evidence of the presence of the same group of analytes. This finding shows that this design would be helpful to study both exhaled body metabolites (inner strip) and personal exposure to environmental pollutants by inhaling (outer strip).

Although the above-mentioned combination of paper and direct to MS analysis provides one of the simpler approaches for sampling and analysis it should be kept in mind that the sorptive property of paper is limited; therefore, it would not be a method of choice when sensitive determination of certain compounds is needed. In this sense, SPME-based technologies that are capable of direct to MS combinations provide a more reliable platform for fast and sensitive analysis. Recently Yuan et al. demonstrated the application of commercial SPME fibers (PDMS/DVB, CAR/PDMS, DVB/CAR/PDMS, and PDMS) immersed in a face mask for exhaled breath analysis (Fig. 1) [57]. Following the sampling, the SPME fibers were coupled with DART-MS for fast direct to MS analysis. In this study, several proofs of the concept experiments were designed and successfully used to demonstrate the detection of drugs, food and smoking-related compounds and metabolites following intake. In addition to varieties of available coating showing sensitivity for different compounds the SPME-based devices used in the study hold the advantage of being reusable.

3. Wearable extractive samplers for skin sampling (Non-invasive sweat sampling)

Body fluids are the source of numerous metabolites related to human health. It is feasible to reach many body fluids from different organs in the human body. One of these organs is the skin, which provides access to body fluids such as blood, interstitial fluid, and sweat. Collecting blood and interstitial fluid can be classified as invasive or minimally invasive techniques [58]. Although they result in minor damage such as perforation of the skin, still, disturb the human subject. However, sweat can be attained from the skin surface in a completely non-invasive way. Sweat secretion is supplied by eccrine glands found widely distributed on the skin (>100 glands/cm^2) [59]. Eccrine sweat glands consist of a secretory coil and dermal duct. The coil produces sweat, and the duct carries it to the skin surface [60]. The primary mechanism of sweat secretion is based on osmotic pressure. The higher sodium and chloride concentration in sweat than in plasma creates an osmolality difference. As a result of this difference, the sweat produced in the secretory coil is pumped through the dermal ducts reaching the skin [61].

Hormones, small proteins, peptides, metabolites such as ethanol, cortisol, glucose, lactate, urea, and electrolytes such as sodium, chloride, potassium, ammonium, and calcium constitute the composition of sweat. During sweat secretion, these molecules pass into the sweat. However, the partitioning of these analytes from blood to sweat depends on three different mechanisms: passive, active, and self-generating [62]. Passive transport occurs as a result of concentration gradient (e.g., potassium, cortisol, ethanol transportation) while active transport occurs by the aid of transportation proteins and the use of cellular energy (e.g., sodium and chloride transportation).

The rich composition of the sweat allows procuring helpful information to monitor various metabolisms reflecting the human body state. Although blood is known to be the gold standard body fluid for health monitoring and disease diagnosis, with the advances in wearable technology; it is very promising that sweat could replace blood. A point to be considered in detecting biomarkers with sweat sampling is the effect of sweat flow rate on the concentration of biomarkers. An unknown dilution in the concentration of the biomarker occurs when the rate of transport of a biomarker into the sweat is slower than the rate of transport of the biomarker to the skin surface. Such situations have led to inadequacies in determining sweat-blood correlations for metabolites [62]. All these developments have necessitated the establishment of blood-sweat correlations for biomarkers that can be determined by sweat [63].

Various formats of extractive phases in the form of thin-film microextraction, solid-phase microextraction, and other patch-type of extractive devices can be used as passive samplers not only for monitoring the exposure of humans/animals to various pollutants and their biological effects but also can be used for prognostic and diagnostic disease monitoring. The sampling devices can be placed directly on the skin surface (TFME membranes) or can be placed on holders (SPME fiber). Besides, they can be worn by a person without significantly distracting her/his daily activities. PDMS films, as biocompatible and flexible materials were among the first samplers used for skin sampling. In an early study with PDMS films, PDMS simply was placed on the skin and fixed in the position with a plaster to sample the sebum [64]. In addition to flexibility in design, the thermal stability of PDMS enables solventless desorption via large volume thermal desorber when combined with GC. Following this application, the possibility to use the PDMS film to sample from the headspace of the skin was demonstrated by Bicchi et al. by use of a bell-shaped glass chamber that could be fixed on the skin surface [65]. The chamber created isolation from the environment as well as an atmosphere reflecting skin metabolome. This design also provided head space sampling opportunity. Holding the PDMS tape in the headspace for 30 min enabled the extraction of volatile compounds. However, impracticality of the design appears as it is quite difficult to consider this design as wearable since a precaution to keep the position of the glass chamber is needed and restricts the daily activities of the wearer. The headspace sampler design for skin sampling further was modified by Jiang et al. by placing the sampler on a mesh separated only few millimeters from the skin and fixed on position by means of an adhesive patch. In this study the DVB particles were also immobilized in the homemade PDMS to improve the extraction ability of the PDMS film without diminishing its flexibility and thermal stability [66]. The prepared films were used to monitor skin metabolome by investigating its capability to extract food-related metabolites after garlic consumption. Several food-related metabolites were detected on the extractive films with GC-MS analysis. Moreover, the authors showed the applicability of the method for alcohol monitoring from the skin following alcohol intake. Results revealed that the alcohol amount excreted on the skin surface increased over time, and it reached a peak value after 40 min, followed by a sharp decline. This proof of the concept study shows the possibility of using such devices for kinetic evaluations

and its potential for roadside testing if a portable instrument suitable for detection is available. The authors also showed that although the PDMS can extract various analytes, the sampler design and its position are critical. For instance, when the samplers were placed directly on the skin, in addition to VOCs, late eluting compounds (high boiling point SVOCs) were observed in the chromatograms. Contrary to the direct sampling from the skin surface, when the sampler was designed to create a small gap between the sampler and the skin surface, only VOCs were observed on the chromatograms. The applicability of PDMS films for skin-related disease diagnosis was demonstrated by Schivo et al. (2017) in an exploratory study performed in the animal model for early diagnosis of skin ulcer resulting from pressure resulting from being immobile in the bed [6]. In this study, the PDMS patches were able to capture oxidative stress-related degradation of lipids as indication of early-stage ulcer. This pilot study highlights the importance of wearable devices in the early-stage diagnosis of wounds in long-term hospitalized patients. Moreover, the advantage of this technology for monitoring the wound healing process was demonstrated in a study performed for monitoring of microbiome and metabolome using PDMS patches as extractive devices. Results of the study were able to show the temporal changes in the wound metabolome as healing proceeds showing the importance of non-selective extractive devices for untargeted monitoring.

4. In vivo low invasive sampling with wearable samplers

In case of in vivo studies, the sample preparation should be as soft as possible in such a way that the sampling is non-invasive or minimal invasive. Moreover, to not alter the existing system equilibrium, the extraction of the analytes should be non-depletive. Therefore, the applicable devices are restricted to SPME and microdialysis (MD). Although this review focuses on wearable extractive samplers, SPME devices can be considered wearable devices for in vivo sampling as once they are immersed in the sampling location, they usually do not affect the daily activities of the wearer. Contrary to SPME, MD requires an infusion pump for circulation of perfusate and dialysate through the system. Therefore, MD was not considered in this review as the focus is on extractive devices that allow sampling and sample preparation simultaneously in freely moving subjects.

4.1. Proof of the concept clinical studies

As stated above, SPME-based techniques are unique as wearable devices suitable for low invasive in vivo applications. SPME devices with 200 μm-diameter bare flexible nitinol fiber coated with ca 45 μm-thick extractive phases on the fiber are commercially available for in vivo sampling. For instance, SPME fibers coated with C18 or C18 with benzenesulfonic acid moieties (known as mixed mode, MM), with 4 mm coating length and with other geometrical parameters described above, were used for in vivo sampling from rat brain [67–71] In some of the studies the performance of SPME was compared to the traditional 'gold standard' microdialysis [67,68]. The study results suggested that SPME can extract and provide information related to a more non-polar fraction of the metabolites present in the brain, while MD is superior for the polar fraction of metabolites indicating the complementarity of the devices. A very similar study with the primary aim to investigate the mechanism behind the deep brain stimulation in major depression was investigated by Reyes et al. using the abovementioned fibers [71]. The samplers were kept for 30 min in the brain region, and after 30 min, the sampler was replaced with a new sampler in order to monitor the stimuli-based metabolic changes. The SPME probes were able to capture various alterations in brain metabolites during the deep brain stimulation process.

Although the abovementioned fibers are promising in general for in vivo sampling, even smaller SPME devices are required when spatial resolution is needed. For instance, SPME fibers with a 3-mm coating length and less than 200 μm of device thickness were prepared for a study aiming to investigate the changes that occur in different brain structures of the Rhesus monkey that is under a cognitive study [72]. In this study, SPME fibers coated with benzene sulfonic acid modified hydrophilic–lipophilic balanced (HLB) polymeric particles were used as extractive phase. Although HLB extractive particles became one of the universal extractive phases in SPME when a wide range of analytes are targeted, still modification with a strong cation exchanger was necessary to ensure sufficient extraction sensitivity for polar neurotransmitters. Results suggest that the wearable SPME device can capture changes in various neurotransmitters during the cognitive task performed by the monkey. All studies suggest that SPME can be considered a wearable device for sampling in situ and in vivo conditions.

4.2. Exposure studies

Early in vivo applications in which monitoring of exposure was realized using SPME-based devices were on proof of the concept levels. These studies were mainly conducted with fish as the primarily affected species from aquatic exposure. In addition, the bioaccumulation of the pollutants in fish muscles may be used to estimate and monitor the secondary exposure of humans by consumption of the fish. One of the preliminary studies that show the applicability of TFME blade, a form of SPME with a larger extraction phase, as a sampler for rainbow trout was performed by Togunde et al. In this study, the bioaccumulation of the drugs under the exposure conditions was investigated as many wastewater treatment plants are discharging the cleaned water to the aquatic system and some compounds cannot be eliminated with the current waste treatment strategies [73]. Although C18-coated TFME blades provide better extraction sensitivity than fibers due to the larger extractive phase deposited on the blades, they are more invasive compared to the small, miniaturized fibers. Still, the sampling was non-lethal to the fish itself and provided information about the bioaccumulation of various drugs in fish tissue. However, when non-invasive and non-depletive sampling representative of the chemical microenvironment of the system is needed, SPME becomes imperative. Especially considering 3R rules adapted for animal studies, SPME fibers may step forward to be suitable for in vivo sampling. Several studies have been published recently with the primary aim of investigating the exposome in aquatic biota are summarized below.

In various studies, it has been proven that in vivo metabolomic profiles may differ from collected samples. The main reason for the difference is the instability of some of the compounds in the collected samples. Therefore, implementation of the SPME for exposure analysis directly in vivo has imperative advantages in terms of metabolism quenching in addition to the advantages described above. For instance, Roszkowska et al. investigated the effect of storage on fish tissue metabolome [74]. In this study, SPME extractions performed with one-year stored fish tissue showed 10-fold fewer features than in vivo SPME extraction. Further analysis of the in vivo SPME extracts showed the presence of various classes of bioactive lipids, which were absent in ex vivo SPME extracts. The advantage of in vivo fish sampling with SPME for exposome analysis was also reported by Bessonneau et al. In this study, in vivo sampling with C18-coated blades (C18-TFME) showed better extraction and stability for reactive molecules (e.g., 1-oleoyl-sn-glycero-3-phosphocholine and 1-palmitoleoyl-glycero-3- phosphocholine) for white sucker collected from Athabasca River (oil

sands region) [75]. The same group also showed that SPME could monitor exosomes in the fish in the same region and fish type [76]. In this study, significant changes were observed for various compounds, including antioxidants, short-lived oxysterols, and other lipids, compounds related to CYP1A1 induction. This strongly suggests the presence of chemical exposure as this enzyme is associated with metabolic clearance of organic toxicants to their more polar forms. Another related study revealed significant changes in features that were tentatively identified as eicosanoids, linoleic acids, and fat-soluble vitamins due to exposure to various environmental toxicants and accumulation of various petroleum-related toxins were identified [77]. The exposure of juvenile rainbow trout to benzo[a]pyrene was also investigated in in vivo sampling with MM-SPME fibers. In this 14-day exposure study, metabolomic differences between the control and exposed group were observed, indicating BaP-altered signaling pathways, including amino acids, lipids, and metabolites involved in osmotic regulation [78].

Although the abovementioned formats of SPME provided satisfactory results, the extractive phase on the device can be damaged when it penetrates through the scale of the fish. The damage on the extractive phase may result in lower reproducibility, diminishing the reliability of the data. Consequently, in a more recent study, Poole et al. developed an arrow-type device in which the extractive phase was built in a groove recessed from the tip [79]. As the SPME extractive phase was protected in the recession and the arrow tip assisted the penetration through the scale, any damage on the extractive phase was eliminated. These devices were also made in such a way that they can be used with bullet gun type shooters and that can be shot directly on the fish. Therefore, it did not require catching, capturing, and keeping immobile the fish for the sampling. After the sampling was completed, the samplers were transferred in dry ice to the laboratory for further analysis, where various pollutants were detected.

Another interesting application of SPME-based in situ sampling performed on Mediterranean Sponges aimed to screen untargeted exometabolome [80]. In this study, three different types of micro-extraction devices were used for sampling from the sponges in the Mediterranean Sea. To monitor the water intake through the sponge pores, SPME fibers; to monitor the exhaled water from the vents, TFME blades; and to monitor the microenvironment to which the sponges are in contact, thin-film membrane was used. Although the study was a proof of the concept study, it revealed the presence of various compounds that indicate the chemical exposure of the sponge. In addition, this study indicates the importance of geometrical flexibility for a wearable sampler when in vivo and in situ sampling is aimed.

5. Future directions

In addition to the sampling approaches described above, novel techniques integrating the extractive phases and chip technology can be considered as one of the future directions for the design of state-of-the-art extractive devices. Based on our search only a single article combining chip technology with extractive devices has been reported [12]. In this preliminary study microfabricated chip-based (μPC) wearable air sampler was prepared using lithography. In this design, heaters were added to the backside of the μPC to heat the sorbent cavity trapping the VOCs in shorter times with poly (2,6-diphenylphenylene oxide) (TENAX TA). This design has the advantage of being programmable for sampling at different flow rates and connected to a global positioning system (GPS) for recording the coordinates. The device was also capable of monitoring temperature and humidity every 10 s. The sampler was tested in a study aiming to monitor personnel's daily exposure to VOCs. The sampling was performed for 12 h with consecutive continuous sampling for 30 min and then turned off for 30 min. The thermal desorption of analytes from the chip to GC was realized using a custom-made thermal desorption system. Using the chip-based sampler, naphthalene, 3-decen-1-ol, hexanal, nonanal, methyl salicylate, and limonene (well defined VOCs in home and working environment released from primary sources such as personal care products, plants, and cleaning chemicals) were detected. For some samplers, high standard deviations were calculated for determined VOCs reflecting the effect of differences in daily activities. The capability of this sampler clearly shows one of the directions in which the technology will be evolved in the future.

In recent works, soft, flexible, and stretchable microfluidic systems have been utilized to realize precise sampling and analysis of sweat [61]. The direct contact of the microfluidic device with the skin enables gathering and storing of sweat without exposing any skin contamination and environmental factor [81]. Such approach has also advantages in extractive samplers. Therefore, the second emerging direction in device design will be applications of microfluidic systems in samplers with primary applications for skin sampling.

Another direction of development will be the integration of extractive wearable devices with sensory detection mechanisms. In this regard, the most significant development is a wearable biosensor that integrates organic electrochemical transistor (OECT) and molecularly selective membrane for non-invasive cortisol sensing [82]., Although several bioreceptors such as enzymes, antibodies, and ionophores can be utilized for selective sensing of the target molecules in the fabrication of OECT-based biosensors [83], in this study, molecularly imprinted polymers that mimic the mechanism of natural receptors were used for the selective detection of cortisol, resulting in molecularly selective OECT (MS-OECT). The fabricated device was a skin-combined patch-type wearable biosensor consisting of several functional layers; laser-patterned microcapillary channels to collect sweat from the skin, sample reservoir to transport the gathered sweat onto the sensor layer, MS-OECT sensor layer, and hydrophobic protection layer (Fig. 3). The sensor layer was built on styrene-ethylene-butylene-styrene (SEBS) elastomer to provide flexibility and stretchability. OECT consisted of gate electrode (Ag/AgCl) and poly (3, 4-ethylenedioxythiophene: polystyrene sulfonate (PEDOT: PSS) semiconductor. The semiconductor was modified with the molecular selective membrane (MSM) to bring about a biological recognition reaction between the synthesized molecularly imprinted polymer (MIP) and cortisol. The working principle of the detection mechanism of cortisol is based on the change in source-drain current. As such, in the absence of the analyte, the movement of the ions causes a significant change in the source-drain current, while the penetration of the analyte into the pores of the MSM inhibits the ion movement. The constructed device showed good reversibility and selectivity in the presence of structurally related analytes such as progesterone, cortisone, and testosterone. Based on proof of the concept application carried out with volunteers who wore the sensor on their forearm during the 20 min running exercise, MS-OECT responded to the cortisol while non-imprinted did not.

Another direction to pursue with wearable technologies is the extension of applicable matrices. More common wearable devices target skin, or they are fixed on the clothes of individuals. In fact, several studies showed the applicability of SPME and TFME to sample saliva in situ, as one of the potential matrices for wearable samplers [84]. Although the samplers were not attached to the body as a wearable device, they could still be kept in the mouth like a lollipop. Using this approach, the authors reported the detection of many salivary metabolites and drugs taken before sampling with TFME. In addition, a recent study reported by Wu et al. illustrated

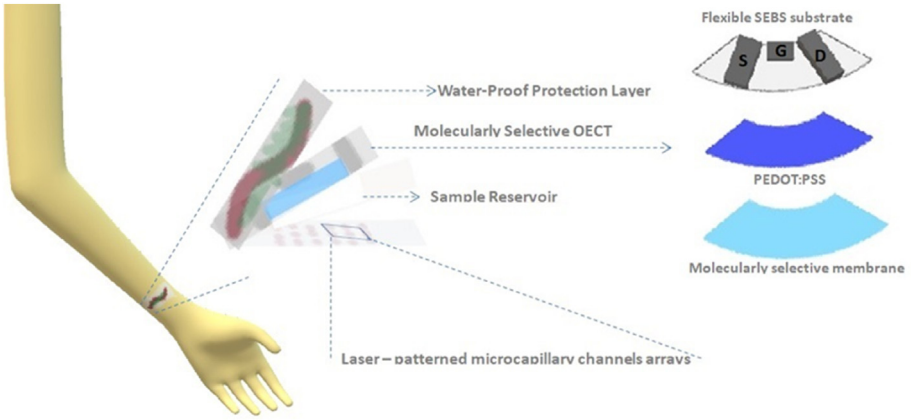

Fig. 3. The OECT device with extractive molecular selectivity [82].

the use of C18-coated SPME fiber integrated on a cotton swap for sampling salivary metabolites. In this design, the cotton swap acted as a sample reservoir during the extraction with SPME in addition to holding the fiber in a position [85]. One advantage demonstrated by the author is the combination of desorption and ionization of the analytes via nano-ESI prior to their direct to MS analysis. However, it should be kept in mind that such devices are not actually wearable and only shows the potential for future developments.

Besides, although there is a plethora of applications related to extractive materials used as transdermal patches for drug delivery the capability of the same patches in unloaded forms for sorption of studies was not investigated despite that the technology is already available.

6. Concluding remarks

Although the active and passive samplers have been known for decades in exposure analyses, their emerging applications as wearable devices suitable for exposome monitoring and clinical investigations come later. Novel geometries (SPME, TFME, film patches, needle traps, wrist bands, brooches, and dog-tag type of samplers) with the same fundamental principles were developed over time to address the practicality needs and a wide range of analyte coverage and compatibility with direct to MS analyses. As mentioned before, the samplers have been in the market for a long time; however, the reported results still suggest that the technology is currently evolving and still is not entirely mature, holding the calibration and cross-verification difficulties among the various designs.

Table 1 in the introduction section summarizes the comparison of various features of passive and active samplers when used as wearable devices. For instance, the cost of passive samplers is relatively cheaper than that of active samplers as no pump is involved for sample collection in passive sampling. Moreover, passive samplers are easy to afford (e.g., TFME) when they are homemade; however, such samplers can be prepared only by proficient personnel. The passive samplers are easy to use without or with minimal disturbance in daily activities. They can be used for long-term monitoring, while active samplers, due to the battery-limited operation of pumps, are restricted to shorter time monitoring. In the case of quantitative data requirements, however, calibration of passive samplers becomes more challenging as the uptake kinetics of the device must be investigated before sampling. Unlike passive sampler calibration, knowing the breakthrough volume of the analyte of interest for the active sampler would be sufficient to calibrate the devices. Nevertheless, both types of samplers require trained personnel for analysis and data evaluation, making it their weakest point against wearable sensory devices. Another disadvantage of extractive samplers compared to sensor-based wearable devices is that 'detection on device' is not possible as each sampler must be coupled to an analytical instrument or desorbed before instrumental analysis, which requires a longer time to complete the analysis. Despite this, the most crucial advantage of wearable extractive devices is that a wide range of analytes can be extracted, allowing to attain more comprehensive information about the investigated system, contrary to wearable sensor-based devices in which the sensors respond only to a specific analyte. Therefore, it provides a substantial advantage in exposome and metabolomic studies. Although sensor-based mechanisms were already exploited in many studies, their limited applications to a single analyte create the bottleneck for producing many different devices for every single application with relatively high cost. On the contrary, wearable extractive devices bear the main advantage of being capable of taking the snapshot of the investigated system when combined with a state-of-the-art instrument. The feature comparison summary in Table 1 clearly illustrates that none of the techniques can be considered standalone, which bears all the merits required for on-site/in situ/in vivo global analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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