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Electronic-nose Applications in Forensic Science and for Analysis of Volatile Biomarkers in the Human Breath

Wilson AD [*, a]

a Forest Insect and Disease Research (FIDR), Southern Hardwoods Laboratory, Stoneville.

* Corresponding authorauthor: Wilson, AD. Ph.D., Principal Research Pathologist, USDA Forest Service, Southern Hardwoods Laboratory, Stoneville, MS 38776-0227, Tel: +1 662 6863180, Fax: +1 662 6863195, E-mail: dwilson02@fs.fed.us

Abstract The application of electronic-nose (E-nose) technologies in forensic science is a recent new development following a long history of progress in the development of diverse applications in the related biomedical and pharmaceutical fields. Data from forensic analyses must satisfy the needs and requirements of both the scientific and legal communities. The type of data collected from electronic-nose devices provides a means of identifying specific types of information about the chemical nature of evidentiary objects and samples under investigation using aroma signature profiles of complex gaseous mixtures containing volatile organic compounds (VOCs) released from manufactured products and parts of the human body. E-nose analyses also provide useful qualitative information about the physicochemical characteristics and metabolic conditions of human subjects without the need for time-consuming analyses to identify all chemical components in human-derived volatile mixtures. E-nose devices are capable of providing information for a wide range of forensic applications, useful for answering many types of questions relating to past events and details of circumstances and conditions that led to criminal activities involving human subjects and the perpetrators involved. E-nose devices have been used to help locate live subjects, buried in the rubble of collapsed buildings following natural disasters, as well as hidden bodies and the human remains of victims of accidents and crimes of aggression. The noninvasive analysis of gaseous mixtures in the human breath and lungs of living and deceased individuals provides a means for identifying the existence of diseases or adverse physiological conditions of human subjects (both before death and postmortem) potentially useful in determining the cause of death, time of death, and pertinent factors contributing to lethal events such as homicides and other violent crimes.

Keywords: Forensic science, Artificial olfaction; Biomarker indicator compounds; Breath gas analysis; Cadaverine; Disease diagnostics; Electronic aroma detection; E-nose; Metabolomics; Respiratory gas metabolites; Volatile organic compounds.

1 Introduction

The continuous improvement in methods and tools used to facilitate the acquisition of evidence gathered in criminal, forensic and cause-of-death investigations requires the recognition and implementation of new technologies that provide either new types of information, corroborative evidence, or more detailed information by more accurate, rapid or efficient means. The development and use of new forensic analytical technologies ultimately expedite the progress of criminal investigations, leading to more rapid and conclusive resolutions of judicial processes through litigations. Many new forensic tools for chemical analyses have been developed over the years to provide more effective analyses of different sample types. Electronic-nose (E-nose) instruments represent new types of electronic aroma detection (EAD) technologies that are being developed for numerous applications in the fields of forensics and criminology [1,2], and related biomedical and pharmaceutical industries [3,4]. There are many different types of E-nose devices including surface acoustic wave (SAW), quartz crystal microbalance (QMB), metal oxide semiconducting (MOS), conducting polymers (CP), and others[5], as well as the more recent carbon nanotube types (see paper by Kybert et al. in this same issue-Sniffing Out Human Odor).

Electronic-nose devices generally are used primarily to detect and identify specific gaseous mixtures of volatile chemical compounds, including organic and inorganic chemicals released from material sources, rather than identify individual chemical compounds present

in sample mixtures. Thus, the sensor output from an E-nose analysis of a sample reflects the combined aroma characteristics of all the chemical constituents present in the sample as a whole. This information is different from most conventional forensic chemical analyses required to determine the precise chemical composition of evidentiary samples involved in criminal cases. However, E-nose instruments are capable of identifying individual organic and inorganic compounds present in pure form or in simple gaseous mixtures when trained to do so. An E-nose device identifies specific gaseous mixtures or individual compounds in the sample by comparing the output from the E-nose sensor array to reference databases, produced by instrumenttraining to recognize known mixtures or compounds, based on mathematical and statistical processes involving pattern recognition algorithms [5].

This review provides a synopsis of some potential E-nose applications available for chemical analyses in the fields of forensic science, criminology, and medical diagnostics (autopsies etc.) that complement conventional chemical methods used to analyze different forensic sample types. The remainder of this review focuses on specific examples of electronic-nose applications for the detection and analysis of volatile metabolites in the human breath, particularly biomarkers (respiratory metabolites and other respired chemicals), that serve as indicators of specific causes of human ailments, including diseases and metabolic disorders, that contribute to information pertinent to the causes of natural fatalities or deaths associated with various types of forensic investigations.

2 Potential E-nose applications in forensics

Electronic-nose instruments recognize precise gaseous mixtures of volatile organic compounds (VOCs) by the unique "fingerprint" pattern or sensor profiles resulting from sensor responses to VOC gases generated from the collective output of crossreactive sensors in an E-nose sensor array. The combined output pattern (aroma profile) from the multisensor array is produced in response to all of the VOCs present in the sample mixture as these compounds are adsorbed and detected by individual sensors in the sensor array. Different types of electronic-nose instruments utilize different mechanisms for detection although most Enose detection systems include a transducer that converts the electronic detection signal from sensors into digital output values to record individual sensor responses that makeup the combined aroma output pattern. The many and varied types of E-nose instruments available for chemical analyses have been summarized previously [5].

The types or chemical classes of VOCs detected in forensic, criminology, and diagnostic investigations vary widely depending not only on the many different forensic sample types being chemically analyzed, such as human manufactured products and human body-derived samples (tissues, fluids, and exhaled gases), but also the purpose or investigative intent of the chemical analysis. E-nose instruments, utilizing different chemical-detection mechanisms and technologies, are capable of sensing a wide range of volatile inorganic compounds (VICs) and VOCs from a large diversity of chemical classes. A wide range of E-nose instrument types are available for EAD analyses of samples from many different types of forensic and criminal investigations. The chemical constituents present in evidentiary samples, range from VOCs released from manmade products to respiratory metabolites from living human patients and microbial degradation products released from dead human remains. Some of the major chemical classes of VICs and VOCs analyzed in various types of forensic chemical analyses (based on sample types) are listed in Table 1 along with conventional analytical methods used for identification and some potential corresponding E-nose methods available for detections and identifications of each sample type.

Because certain types of E-nose devices are capable of detecting a wide range of compounds [17,52], they are commonly used to detect hazardous chemicals in the environment including industrial and sanitation wastes (air, water, and soil pollutants) [17], pesticides [62,63], medical wastes [64], and toxins [52]. Forensic sample types containing inorganic materials include firearm discharge residues (FDRs), non-firearm discharge residues (NFDRs), heavy metal toxins, primary explosives, particulates in pigments and extenders, glass, and soil samples [6]. Chemical explosives consist of compounds with inorganic or organic oxidized functional groups such as acetylides, azides, chlorates, fulminates, nitrates, nitrites, ozonides, perchlorates, and peroxides. Thus, E-nose instrument types that detect VICs are potentially useful for gathering forensic evidence when inorganic compounds are involved in criminal fatalities. Most other forensic sample types consist of VOCs from numerous chemical classes.

Conventional analytical methods utilized in forensic sample analyses usually require several different steps and multiple analytical instruments for VOC identifications and for confirmation of sample composition. Each instrument provides a different type of information about the chemical composition and physicochemical characteristics of forensic samples. Consequently, different forensic sample types must be analyzed by different combinations of analytical instruments due to differences in the chemical properties of compounds (analytes) present in the samples and the chemical-detection limitations of analytical instruments as determined by instrument design, operating principles and mechanisms of chemical detections. For example, illegally manufactured drugs must be further analyzed to determine the source

or origin of the material, usually based on the occurrence of specific types, concentrations and mixtures of impurities or contaminants within the sample that are unique to a source, batch, or location from which the sample originated. The analysis of the precise types and concentrations of impurities found in forensic samples is referred to as composition profiling or chemical profiling. Chemical profiling of sample impurities is a key method used in the analysis of certain types of explosives, drugs, and trace materials where answering questions concerning origin are important in determining the involvement of suspects in various criminal activities. Chemical profiling also is necessary for analysis of amphetamines, cocaine, cannabis, and heroin drugs to determine the particular source and batch of these products, manufactured in illegal drug operations. Drugs usually are the most common type of toxic materials analyzed by forensic toxicologists. Besides the analysis of drug impurities, chemical profiling of drugs may also involve the detection of other variations in drug composition such as drug purity, the ratio of actual drug to excipients (tablet bulking, fillers, or dilution agents), degree of hydration, form (acid, base, or salt), as well as the presence of trace alkaloids and isomers [6].

Electronic nose instruments are particularly suited for chemical profiling because these tools provide information about the aroma characteristics of the entire headspace derived from forensic samples including all impurities present. The presence of specific types and combinations of impurities provide important clues about the particular processing methods used to produce the sample such as specific chemical or manufacturing processes, providing an effective means of distinguishing between forensic samples from different sources of origination or manufacture. Thus, chemical profiling-type analyses will likely be among the major roles that E-nose devices will offer and contribute to forensic science and sample analyses in the future. Because many E-nose instrument types are very sensitive to moisture content of the sample, the moisture content of the carrier gas (filtered air) must be controlled and standardized to eliminate variations in E-nose signal output due to water vapor interactions with the sensor array [65].

E-nose detection of human scents

Detections of scents or vapors released from the human body provide very useful information for locating individuals, particularly victims of crimes, and for evaluating the physiological condition (e.g. use and exposure to drugs) and general state of health of individuals involved in crimes, including both victims and perpetrators of crimes. For this reason, E-nose instruments increasingly have been used in the medical industry to facilitate disease diagnoses, obtain assessments of human health in point-of-care patient examinations, and other applications in the biomedical field [3]. Progress in E-nose applications in the medical industry is beginning to spill over into new related applications for forensic science.

One new significant area of potential forensic applications for E-nose instruments is in the detection and location of buried individuals (both living and deceased) as well as the human remains of victims of violent crimes. Individuals who become buried in the rubble of collapsed buildings and other structures as a result of natural disasters (such as earthquakes, floods, avalanches of soil or snow, tornados, hurricanes or other violent natural calamities or weather events) or intentionally buried by violent criminals, generally must be located in a relatively short period of time after the burial event to be successfully rescued from all potential hazardous forces that can threaten a victim's life in such situations. A relatively new approach for detecting living victims that are buried in rubble is to develop chemical detection devices to replace sniffer dogs that usually require frequent rest intervals after periods of active searches. Electronic-nose instruments are not subject to operator fatigue.

Currently, buried human remains most often are detected using ground-penetrating radar (GPR), manual probing techniques, and trained 'cadaver dog' canines. It is not well understood which specific chemicals are detected by cadaver dogs to locate human remains, but the high success rate of trained canines has demonstrated the effective use of human scent as targets of detection. Trained dogs have been very useful in discriminating scents and for detecting explosives, accelerants, narcotics and other drugs, as well criminals and missing persons on foot. Certain canines are capable of discriminating between human remains and other mammals, odors emitted by live individuals, recently deceased, and human remains in various stages of decomposition. Unfortunately, canines used for human-remains detection are a minor portion of the law enforcement canine population due to the high costs associated with the purchase, training, and care of these animals. Neverthelsess, canines possess keen olfactory discrimination capabilities that often are far more sensitive and discriminative than many analytical instruments.

Different approaches for detecting and locating living buried victims using E-noses depend on the different types of target compounds intended to be detected based on VOCs released from the victim's bodies in response to stress, oxygen deprivation, excretions, and other adverse conditions associated with being trapped for prolonged periods of time. The bodies of individuals that are subject to variable degrees of suffocation, dehydration, wounding, and starvation or prolonged exposure to adverse elements (temperature extremes, toxic fumes etc.) produce and release different types of gases as a result of various types of metabolic and physiological changes that occur in the body in response to physical afflictions, deprivations and associated stresses. The categories of bodily gases released in association with different adverse

conditions are summarized in the upper section of Table 2.

A recent study by Mochalski et al.[93] has revealed some interesting points relating to the sensing of buried human victims. They found that among the VOCs (composing human scent) that serve as potential markers of human presence during Urban Search and Rescue (USR) operations, organized following natural or man-made disasters (e.g. earthquakes, explosions and terrorist attacks), breath volatiles and to a lesser extent skin volatiles are the principal sources of human scent constituents. Their reasoning was that trapped victims have to breathe and that breath constituents, as long-lasting emission sources of VOCs, can help to discriminate between living humans and corpses. They concluded that even though blood and urine in the close vicinity of victims usually offer only temporary sources of human volatiles for detection, these human fluid sources of VOCs should not be underestimated because earthquake and explosion victims frequently are severely injured with blood volatiles comprising a significant important reservoir of human scent VOCs. Consequently, baseline knowledge of all human scent profile constituents, along with the contribution of particular sources in the human scent pool, is critical in order to determine the most appropriate USR sensing targets for E-nose sensing of human bodies trapped by various causes and in different circumstances and conditions.

The recovery of the bodies of victims who die as a result of exposure to adverse conditions or injuries due to burial may be detected with E-noses using a different set of VOCs than are used for buried live victims. The particular types of VOCs released from the decomposing bodies of victims of natural disasters and violent crimes depend on the type of chemical processes involved in decomposition. Some of the major chemical constituents released from human cadavers, produced primarily as a result of microbial decomposition, include such chemicals as cadaverine, putrescine, etc. as indicated in the lower section of Table 2. Very similar chemical classes of VOCs are released from the decomposing bodies and remains (carrion) of large non-human vertebrates, such as dogs and pigs, and the scent markings of wild mammals [94,95].

3 E-nose detections of breath volatiles

The investigation of chemical indicators (bioindicators) of human metabolism or physiology through a specialized analysis approach, known as metabolic profiling, is a relatively new research area that has received considerable attention due to the potential for simplifying many human-scent related chemical analyses. The investigation of human scents using metabolic profiling is recognized as a way to rapidly and noninvasively detect gaseous mixtures released from the human body that provide significant information about general health, physiological condition, presence of disease, exposure to toxic substances, and many other exogenous factors that influence the outcomes of crime-related events of interest to forensic scientists who are primarily responsible for determining the precise conditions and events that occurred in a criminal case and the factors that affected the ultimate outcome for victims of criminal activities.

Phillips et al. [96] found over 2,000 VOCs in the human breath of healthy individuals using two-dimensional gas chromatography coupled with time-of-flight mass spectrometry (GCxGC-TOF MS), a powerful new tool for multidimensional analysis of complex chemical mixtures. About fifty of these VOCs had the highest alveolar gradients (abundance in breath minus abundance in ambient room air) mostly comprised of benzene derivatives, acetone, methylated alkane derivatives, and isoprene. Some very specific metabolites in the human breath have been highly correlated with certain types of human pathogens, diseases and metabolic disorders [3,97].

Bioindicators of human diseases and causes of death

The specific classes of VOCs comprising the major groups of abnormal chemicals (those not normally found in a healthy body) that are expired in the breath from the body in association with various diseases, genetic disorders, microbial infections (bacterial, fungal, and viral), and metabolic byproducts of microbial degradation of deceased individuals are presented in Table 3. These major groups of abnormal VOCs are released from the human bodies of living patients who are either not in good health or have adverse physiologies as a result of various diseases. Abnormal VOCs often persist in the bodies of postmortem patients for an indefinite period of time following death. Also, the composition of VOCs released from the body changes over time following death, resulting in different metabolic profiles revealed in E-nose analyses. Consequently, the composition and ratio of chemical constituents present in the volatile gases released from corpses over time can serve as useful signatures to help determine the time that has elapsed following death (time since death) or postmortem interval (PMI). The PMI is a useful time reference used by forensic scientists and law enforcement personnel to compare against the activities and whereabouts of potential suspects (and their alibis) and to help identify the victims and perpetrators of criminal activities.

Breath profile analysis

The mixture of chemicals released in the human breath is very complex, contains thousands of VOCs that are constantly changing, and is representative of the large complement of biochemical or physiological processes occurring in the entire body [96]. The composition of expired air in the human breath also varies depending on a person's health status and unique body chemistry. Various metabolic processes within the body produce VOC products that are released into

Table 1. Identification of components in forensic sample types (human manufactured products and body fluids containing volatile organic or inorganic compounds) using conventional chemical analyses and new potential electronic-nose technologies.

Sample types[1]	Categories	Chemical classes[1]	Example compounds[2]	Conventional analyses[1]	Conv. Refs.	E-nose Refs.[3]
Arson	Accelerants (ignitable liquids)	HC fuels	petrol (gasoline), kerosene, paint thinners	PVD, GC, GC-MS, GC-IRMS	[6,7]	[8-11]
CTE	Fiber dyes	triazines	dichlorotriazine	TLC, HPLC, SERRS, RR, LC-MS	[6,12-14]	NR
	Paint pigments, extenders, binders	organic/inorganic particulates	Volatile paints/solvents, non-volatile particulates	PLM, FM, FTIR, XRD, XRF, SEM-EDS, LAICP-MS, PGC, PMS	[6,15]	[16,17]
	Glass	inorganics	Non-volatile inorganics	GRIM, SEM-EDS, XRF, ICP-AES, ICP-MS, LAICP-MS, SEM,	[6,18,19]	NR
	Soil	inorganics, organics	non-volatile inorganics, various VOCs	ICP-AES, ICP-MS	[6,20]	[17,21]
	Cosmetics	liquids and solids emitting VOCs	face powder, lipstick, mascara, eye liner, nail polish, perfumes, lotions	XRD, XRF, SEM/EDS, SERRS	[6,13]	[22,23]
	Shoe polish	various HCs	waxes, pigments, analine dyes; nitrobenzene	XRD, XRF, SERRS	[6,13]	[24]
Documents	Inks, solvents	various HCs	Ink pigments, 2-phenoxyethanol	VLMS, TLC, RM, SERRS, LC-MS	[6,13,25-28]	[29,30]
	Paper	VOCs	Volatile byproduct residues in manufactured paper	FTIR	[31]	[32]
Explosives	Primary	inorganics	Lead azide, tetrazene, mercury fulminate	XRF	[6]	[17]
	Secondary	aromatic HC	nitrocellulose, HMX, TNT, TATB, PETN, RDX, picric acid, tetryl	IMS, HPLC, MS, GC-TEA, LC-MS	[33-36]	[37-41]
	Propellants	organics	black powder (potassium nitrate, charcoal, sulfur), nitrocellulose	HPLC, GC-TEA, LC-MS, XRF	[6,36,42]	[43,44]
FDRs	Primers	inorganics	lead styphnate, antimony sulfide, barium nitrate; also Zn- and Ticontaining particles	SEM-EDS,	[45]	[17]
	Propellants	organics	nitrocellulose, nitroglycerine, nitroguanidine	HPLC, GC-TEA, LC-MS, XRF	[25,45]	[46-48]
Human body fluids	Blood, excrement, oral fluid, semen, sweat, urine, sputum, etc.	DNA, VOCs, inorganics	nucleic acids, complex VOCs profile, inorganic contaminants	DNA profiling, XRF	[6]	[3,4]
NFDRs	Pyrotechnics, fireworks, automobile brake pads	inorganics	lead styphnate, antimony sulfide, barium nitrate	XRF	[45,49]	[17]
Toxins	Alcohol	aliphatic alcohol	ethanol	SFST, DRE, FIT	[6,18]	[17,50-52]
	Drugs	phenethylamines	amphetamine, MDA, MDMA, epinephrine, norepinephrine, Dopamine	MT, TLC, GC-MS, NMR, HPLC, EIA, RM	[53-55]	[3,5]
		barbiturates	Phenobarbital, Barbital, Alphenal	LC-MS, HPLC, GC-MS, IRS	[33]	[3]
		benzodiazepines	Diazepam, Lorazepam	GC-MS, HPLC-uv	[6,33]	NR
		opioids	Morphine, Fentanyl, Etorphine, Heroin, Methadone (synthetic)	XRD, MT, HPLC, GC-MS, EIA	[6,33,37,53-55]	NR
		tropane alkaloids	Cocaine, Ecgonine, Norcocaine, Benzoylecgonine, Truxillines	CIT, ST, TLC, GC-MS, SIRMS, EIA, NMR	[6,33,37,56-58]	[59]
		cannabinoids	Cannabis (Δ^9-THC)	TLC, EIA, GC-MS, HPLC	[6]	[60]
	Heavy metal poisoning	inorganics	Arsenic, cadmium, lead, mercury, osmium, thallium, vanadium	XRF	[61]	[17]

[1] **Abbreviations:** CIT = Cobalt Isothiocyanate Test; CTE = Chemical Trace Evidence; DRE = Drug Recognition Examinations; EIA = Enzyme Immunoassay; FDRs = Firearm discharge residues; FIT = Field Impairment Testing; FM = Florescence Microscopy; FTIR = Fourier Transform Infrared Spectroscopy; GC-MS = Gas Chromatography with Mass Spectroscopy; GC-TEA = Gas Chromatography with Thermal Energy Analysis; GRIM = Glass Refractive Index Measurement; HC = Hydrocarbons (organic compounds containing carbon and hydrogen); HPLC = High Performance Liquid Chromatography with amperometric detection; ICP-AES = Inductively Coupled Plasma Atomic Emission Spectroscopy, ICP-MS Inductively Coupled Plasma Mass Spectrometry; IMS = Ion Mobility Spectrometry; IRS = Infrared spectroscopy; LA-ICP-MS = Laser Ablation-Inductively Coupled Plasma Mass Spectrometry; LC = Liquid Chromatography; LC-MS = Liquid Chromatography with Mass Spectrometry; MT = Marquis Test; ; NFDRs = Non-firearm discharge residues; NMR = Nuclear Magnetic Resonance; PGC = Pyrolysis Mass Chromatography; PLM = Polarized Light Microscopy; PMS = Pyrolysis Mass Spectrometry;

Table 2. Potential E-nose forensic applications for the location of human bodies and remains through the detection of complex gaseous mixtures of VOCs released from these sources under various conditions and situations.

Applications	E-nose detection	Substrates/ Applications E-nose detection Physiology†	Compounds present	Chemicals classes	Example compounds (VICs and VOCs)	References
Location of cadavers and human remains	Decomposition (by autolysis)	soft human tissues	478 VOCs (identified by GC-MS)	Oxides Benzene deriv. Aliphatic HC Polycyclic AH Heterocyclic HC Methyl esters Cl-, F-aliphatic HC	Sulfur dioxides dimethy benzene, toluene undecane naphthalene methenamine hexadecanoic acid methyl ester	[1,2, 66-68]
			Small mol. wt. gases	Oxides Simple HC Sulfides Ammonium	carbon dioxide methane hydrogen sulfide ammonia	[69-72]
	Putrefaction (by microbial action)	Proteins (amino acids)	Aliphatic amines Aromatic, heterocyclic	Diamines Indoles	cadaverine putrescine skatole	[73-77] [78]
		Fatty acids	Short chain organic acids	Carboxylic acids	propionic acid butyric acid	[72,79,80]
Location of live trapped persons	Respiration gases	Inorganics	Small mol. wt. gases	Oxides	carbon dioxide	[81,82]
	Stress compounds	Oxidative stress	Aliphatic HC	Aldehydes	hexanal	[83,84]
		Dehydration				
		Ketosis (starvation)	Aliphatic HC	Ketone	acetone	[86-88]
	Wound compounds	Contusions, lacerations, ischemia	Aliphatic	Complex VOCs mixture	tritetracontane, nonahexacontanoic acid, 4-(2,6-dimethyl-1-cyclohexen-1-yl) morpholine	[89,90]
	Waste excretion	Urination	Aliphatic	Carbamide	urea	[91,92]

† **Number of sensors and sensor type abbreviations:** Carbon black composite (CBC), Carbon dioxide sensor (CO_2), Conducting polymer (CP), electrochemical (EC), Metal oxide semiconductor (MOS), Metal oxide semiconductor field effect transistor (MOSFET), Quartz crystal microbalance (QMB), surface acoustic wave (SAW), and Tin dioxide (SnO_2), a type of MOS sensor.

PVD = Portable Vapor Detector; RM = Raman Spectroscopy; RR = Resonance Raman Spectroscopy; SEM-EDS = Scanning Electron Microscopy with Energy Dispersive Spectroscopy; SERRS = Surface Enhanced Resonance Raman Scattering Spectroscopy; SIRMS = Stable Isotope Ratio Mass Spectrometry; FST = Standardized Field Sobriety Tests (SFST); SEM = Scanning Electron Microscopy; ST =Scott test; TLC = Thin Layer Chromatography; VLMS = Visible Light Microspectrophotometry; VOCs = Volatile Organic Compounds; XRD = X-ray powder diffraction; XRF = X-ray Fluorescence.

[2] **Chemical abbreviations:** HMX = octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine or cyclotetram ethylenetetranitramine; MDA = 3,4-methylenedioxyamphetamine; MDMA = 3,4-methylenedioxymethylamphetamine; PETN = pentaerythritol tetranitrate; RDX = cyclotrimethylene-trinitramine; TATB = triamino-2,4,6-trinitrobenzene; tetryl = trinitrophenylmethylnitramine; Δ9-THC = Δ9 – tetrahydrocannabinolic acid; TNT = trinitrotoluene. VOCs = volatile organic compounds.

the blood and eventually are passed on to the airways once the blood reaches the lungs. When normal human physiological processes break down or are altered by disease (pathogenesis) or metabolic disorders, the mixture of gases released by the lungs in the breath changes because of the altered chemical pathways resulting from the abnormal metabolic changes caused by these various maladies. Consequently, by frequent monitoring and analyzing the changes in composition and amounts of VOCs present in exhaled breath air, commonly referred to as metabolomics (breathomics) or VOC profiling, it is possible to determine a clinical diagnosis to explain the chemical or biological cause(s) of abnormal alterations in breath-air composition. Boots et al. [219] described some of the currently available methodologies for breath sampling, analysis and data processing with indications of their advantages and potential drawbacks as well as different application possibilities of VOC profiling. They pointed out that until recently, VOC profiling has been applied primarily for diagnostic purposes, but it also may be applied as an analytical or monitoring tool to elucidate the heterogeneity observed in chronic diseases, to study the pathogen(s) responsible for reoccurring infections and to monitor treatment efficacy and progress of healing. Thus, VOC components can serve as individual biomarkers of oxidative stress, inflammation, carcinogenesis and many other diseases. The entire compliment of VOCs in breath also can be chemically analyzed as a whole using electronic noses to produce breath patterns or profiles that can be compared to those of healthy individuals or those with differing physiological histories or exposures to different ambient (atmospheric) environments. Breath profiles produced using E-noses are more useful than those produced from conventional analytical instruments such as GC-MS because E-nose breath profiles can be stored and analyzed

Table 3. Potential electronic-nose diagnoses of human organ-related diseases and postmortem causes of death through the detection of volatile biomarker indicator compounds in the human breath, exhaled breath condensate, bronchi, or alveolar air.

Disease/Disorder/Injury/Infection[1]	Organ	Biomarker indicator VOCs[2]	References
AFDL	Liver	Acetaldehyde, isoprene, other VOCs	[98]
AHI	Liver	Ethane, pentane (volatile alkanes)	[99]
ALF	Liver	Complex VOCs profile	[100]
ARDS	Lung	Acetone, isoprene, n-pentane	[101,102]
Aspergillosis (invasive)	Lung	2-pentylfuran	[103]
		Complex VOCs profile	[104]
Asthma	Lung	Pentane, ethane, isoprene	[105-107]
		Leukotriene B4, prostaglandin E2	[108,109]
		8-isoprostane	[110]
		Nitric oxide	[111]
		Complex VOCs profile	[112-116]
BCKD	Systemic, Kidney	2-oxoisocaproic acid	[73]
Cancer	Bladder	Complex VOCs profile	[117]
	Breast	C4-C20 alkanes, monomethylated alkanes	[118]
	Head and neck	4,6-dimethyl-dodecane, 2,2-dimethyl-propanoic acid, 5-methyl-3-hexanone, 2,2-dimethyl-decane, limonene, 2,2,3-erimethyl-, exobicyclo[2.2.1]heptane	[119]
		Dimethyl trisulfide	[120]
	Lung	Alkanes, monomethylated alkanes	[121,122]
		Alkanes, aromatic compounds	[123]
		Aniline, o-toluidine	[124]
		Aliphatic aldehydes	[125,126]
		1-Butanol, 3-Hydroxy-2-butanone	[127]
		Dimethyl sulfide, dimethyl formamide, butane, butanal	[128]
		Ethane	[129]
		Isoprene, acetone, methanol	[130]
		Pentane	[131]
		1-octene	[132]
		Complex VOCs profile	[73,121,130, 131,133-148]
	Skin	Isoamyl alcohol, dimethyldisulfide, trisulfide	[149]
Chronic hepatitis	Liver	Methyl-mercaptan, dimethyl sulfide	[150]
CIP	Lung	Acetone, isoprene, n-pentane	[101]
COPD	Lung	Aldehydes, nitrotyrosine, cytokines	[151]
		Leukotriene B4, 8-isoprostane	[152]
		Hydrogen peroxide	[153,154]
		Nitrate	[155]
		Nitric oxide	[156]
		Ethane	[157]
		Complex VOCs profile	[116,158-164]
CPD	Heart, Lung	Ethanol, acetone	[165]
Cystic fibrosis	Lung	Leukotriene B4, interleukin-6	[166]
		Nitrotyrosine	[151]
		Pentane, propane, methanol, ethanol, acetone, benzene	[167]
		Carbonyl sulphide, dimethyl sulphide, carbon disulfide	[167,168]
		Methyl thiocyanate	[169]
		Ethane	[167,170]
		Isoprene	[167,171]
		Hydrogen cyanide	[172,173]
		Complex VOCs profile	[167,174,175]
Cystinuria	Kidney, ureter, bladder	Cadaverine, piperidine, putrescine, pyrrolidine	[73,74]
Diabetes mellitus	Systemic	Acetone, ethanol, methyl nitrate, complex VOCs	[176,177]
Emphysema	Lung	Complex VOCs profile	[178]
Endocarditis (infective)	Heart	Hydrogen sulfide, methyl mercaptan, dimethyl sulfide	[179-182]
Foetor hepaticus	Liver	Complex VOCs profile	[183]
GERD	Esophagus	Complex VOCs profile	[162]
Hepatic cirrhosis	Liver	Dimethyl sulfide, hydrogen sulfide, mercaptans, fatty acids	[184]
		Dimethyl sulfide, acetone, 2-pentanone and 2-butanone	[185]
		Methyl-mercaptan, dimethyl sulfide	[150,186]
Hepatic coma	Liver	Methyl-mercaptan, dimethyl sulfide	[150,186,187]

as a whole for comparison against application-specific reference (aroma breath profile) databases whereas GC-MS chemical profiles must be analyzed on an individual-compound basis which is considerably more time consuming for routine clinical use where rapid real-time detection and diagnosis is required.

Montuschi et al. [220] found that E-nose breathprints effectively discriminate between patients with different respiratory diseases (including asthma, COPD and lung cancer associated with airway inflammation activity) from healthy control subjects. They also suggested that uses of E-noses could be combined with other '-omics' sensing platform technologies to contribute to the identification of new surrogate markers of pulmonary inflammation and various other respiratory diseases.

Biller et al. [221] evaluated exhaled breath profiles using the Cyranose 320 E-nose, a promising non-invasive diagnostic tool for the discrimination of breath prints between patients with COPD and asthma, to assess whether exhaled breath profile analysis could detect the inflammatory airway response (IAR) induced by ozone inhalation. E-nose signals from exhaled breath profiles showed no significant differences or correlation in the occurrence of IAR between subjects with or without exposure to ozone inhalation. However, independent of ozone exposure, E-nose sensor data did correlate with serum surfactant protein D levels and to a lesser extent with blood neutrophil levels.

One of the biggest technological challenges in developing breath analyzers is to accurately measure a trace amount of VOC analytes in the presence of many interfering gases with a highly concentrated water vapor [222]. Human breath is nearly saturated with water vapor (>95% relative humidity, RH) that often overloads the E-nose sensor array leading to failure of the breath analyzer. This problem can only be solved by proper breath sample conditioning in the mouthpiece before air passes into the sensors for VOC detection. The development of effective and efficient breath-sampling mouthpieces, to filter out interfering water vapor components in the breath, would be very useful in improving VOC breath-analysis methods.

The diagnostic approach of analyzing VOCs in exhaled breath samples constitutes a new frontier in medical diagnostics because it is a noninvasive and potentially inexpensive way to rapidly detect numerous illnesses. Conventional analytical methods for identifying VOCs associated with specific diseases, such as various types of spectroscopy,

Disease/Disorder/Injury/Infection	Organ	Biomarker indicator VOCs[2]	References
Histidinemia	Systemic	2-imidazolepyruvic acid, 2-imidazolelactic acid, 2-imidazoleacetic acid	[73]
Hyperglycemia	Systemic	Methyl nitrate, xylene, ethylbenzene	[177,188]
IBD	Intestine	Pentane, ethane, propane	[189-192]
IHD, angina	Heart	Alkanes, methylated alkanes	[122,193]
ILD	Lung	Ethane	[194,195]
Ketosis, starvation	Systemic	Acetone	[86]
MPM	Lung	Complex VOCs profile	[196-198]
NSCLC	Lung	1-Butanol, 3-Hydroxy-2-butanone	[127]
		Complex VOCs profile	[142,147]
Oxidative stress	Systemic	8-Isoprostane	[110]
		Alkanes, methylated alkanes	[199]
PCD	Respiratory tract	Complex VOCs profile	[175]
Phenylketonuria	Systemic	Phenylpyruvic acid, phenyllactic acid, phenylacetic acid	[73]
PLC	Lung	Formaldehyde, propanol, isoprene, acetone, o-toluidine	[200]
Renal dysfunction	Kidney	Complex VOCs profile	[201]
Respiratory infections	Lung	Complex VOCs profile	[202]
Rheumatoid arthritis	Bone joints, cartilage	Pentane	[203]
Schizophrenia	Brain	Pentane, carbon disulfide, ethane	[204-206]
SFS	Feet	Butyric acid, hexanoic acid; trans-3-methyl-2 hexenoic acid	[207]
TB	Lung	Methyl nicotinate	[208]
		Complex VOCs profile	[86,209-213]
Tyrosinemia	Systemic	p-hydroxyphenylpyruvic acid	[73]
Upper respiratory infections	Respiratory tract	Acetic acid, acetaldehyde, 2-butene,methyl methacrylate, 2,3-butan-edione, 2-butenal, vinyl butyrate	[214]
VAP	Lung	Complex VOCs profile	[215-218]

[1] **Abbreviations:** AFDL = Alcoholic Fatty Liver Disease; AHI = Alcohol-induced Hepatic Injury; ALF = Acute Liver Failure; ARDS = Acute Respiratory Stress Syndrome; BCKD = Branched-Chain Ketoaciduria Disorder (Maple Syrup Urine Disease); CIP = Critically Ill Patients; CPD = Cardiopulmonary Disease; COPD = Chronic Obstructive Pulmonary Disease; GERD = Gastro-esophageal reflux disease; IBD = Inflammatory Bowel Disease; IHD = Isochemic Heart Disease; ILD = Interstitial Lung Disease (includes cryptogenic organizing pneumonia, idiopathic pulmonary fibrosis, sarcoidosis, etc.); MPM = Malignant Pleural Mesothelioma; PCD = Primary Ciliary Dyskinesia; PLC = Primary Lung Cancer; NSCLC = Non-Small Cell Lung Cancer; SFS = Sweaty Feet Syndrome; TB = pulmonary Tuberculosis; VAP = Ventilator Associated Pneumonia.

2Bioindicators are primarily volatile organic compounds (VOCs), initially identified using gas chromatography-mass spectroscopy (GC-MS), or similar analytical instruments, prior to development of corresponding E-nose reference libraries and VOC profiles for application-specific detections.

have shown to be feasible for diagnosing many diseases in all parts of the body using breath-analysis tests, but these traditional approaches require expensive equipment, sophistiated methods, and high levels of expertise to operate effectively in clinical situations. Newer E-nose sensors based on nanomaterials are likely to become the clinical and laboratory diagnostic tools of choice for the future because these instruments are significantly smaller, easier to use, and less expensive than spectrometry or spectroscopy. An ideal nanomaterial-based sensor for breath testing should be sensitive at very low concentrations of VOCs, have a rapid response time, and provide a consistent output for specific mixtures of VOC analytes [223].

The VOCs emitted by the human body have a great potential for medical diagnosis and therapeutic monitoring because their analysis offers a unique insight into biochemical processes ongoing in healthy and diseased humans. Breath analysis holds a distinguished status in this context as it is noninvasive and breath biomarkers can provide valuable information on disease processes, or metabolic disorders occurring even in distant parts of the body away from the lung. Unfortunately, the origin and metabolic fate of numerous breath VOCs have not been elucidated in sufficient depth, thereby limiting the clinical application of breath tests [224]. Consequently, more research is needed to fully elucidate the sources of VOCs in human breath, and establish stronger correlations of bioindicators to specific diseases, so that this information can be used to further advance the application of E-nose technologies to detect specific mixtures of VOCs for disease diagnosis and monitoring.

Disease diagnosis from cell line volatiles

The isolation of diseased human cells in tissue culture lines, as the representative source of tissues where abnormally altered physiological processes are occurring due to disease or metabolic disorders, is another approach for diagnosing diseases using VOCs. In this case, the method is not noninvasive because the removal of tissue samples from the body through surgical biopsies is required to obtain the tissue cell lines for study. This approach is different from breath analysis that usually is noninvasive as a result of simple collection and analysis of VOCs in exhaled breath gases.

Amal et al. [225] built a predictive model to detect metastasis in Hepatocellular carcinoma (HCC), a common and aggressive form of cancer, by using discriminant factor analysis with pattern recognition of VOC fingerprints from HCC cancer and normal cell cultures, analyzed using nanomaterial-based E-nose sensors. The results constitute a proof-of-concept for the in-vitro prediction of the metastatic potential of HCC from VOC fingerprints using nanotechnology that could benefit the development of a fast and potentially inexpensive laboratory test for subclinical HCC metastasis.

Mochalski et al. [224] utilized HepG2 liver cell lines to study VOCs released by the liver which are biomarkers related to products of enzymes involved in drug metabolism (such as cytochrome P450 enzymes). HepG2 is a cell line derived from a 15-year old male patient with a liver carcinoma that possesses an epithelial morphology and secretes a variety of major plasma proteins (e.g., albumin, transferrin and the acute phase proteins fibrinogen, alpha 2-macroglobulin, alpha 1-antitrypsin, transferrin, and plasminogen). The hepatocellular carcinoma (liver cancer) cells were incubated in specially designed headspace 1-L glass bottles sealed for 24 hours prior to headspace analysis. Nine compounds were found to be metabolized and twelve different compounds were released by the carcinoma cells, reflecting the activity of liver enzymes and thus the potential of VOC headspace analysis for the assessment of liver enzyme function.

Pennazza et al. [226] analyzed the VOC mixtures released from well-characterized tumor cells including human melanoma cell lines LOIA, FORM, FIV, a thyroid carcinoma cell line FRO, and synovial sarcoma cell line CME using an E-nose sensor array composed of six crystal quartz microbalance (QMB) sensors, each having a thin surface coating of a different metalloporphyrin to provide differential chemical sensitivity, operating at a 20 MHz resonant frequency. QMB E-noses have quartz crystal resonators that vibrate at a frequency proportional to the mass of the molecules adsorbed to the sensor surfaces. The VOC patterns from the sensor array for the melanoma cell lines were distinctly different from those of the thyroid carcinoma and sarcoma cell lines. Experimental results suggested the possibility of detecting tumors in vivo through the analysis of released VOCs from different body compartments, such as breath and skin.

Single metabolite-specific detection

One of the strong advantages of E-nose detection is the capability of adjusting the chemical sensitivity of individual E-nose sensors in a sensor array in order to tailor the instrument to a very specific narrow range of chemical detection for VOCs in a particular chemical class, or even for a single compound when this is sufficient for detecting certain metabolic or physiological events strongly correlated with release of that compound. Application-specific E-noses with specialized reference databases may focus on a very narrow range of analytes to simplify detection of specific diseases or determine the metabolic health states of organs in the body.

Breath analysis offers the huge potential for early-stage detection and monitoring of diseases to drastically reduce medical diagnostic costs and improve the quality of life of patients suffering from numerous chronic lung illnesses. Righettoni et al. [227] evaluated the detection of the single compound (acetone in the human breath) as a promising noninvasive diagnositic

and painless method for monitoring diabetes. A portable E-nose sensor, consisting of flame-deposited and in situ annealed, 10 mol% Si-doped epsilon-WO3 nanostructured films, was developed with a miniaturized sample chamber volume, sensing temperatures optimized for the low detection limit of acetone (~20 ppb), and short response (10–15 s) and recovery times (35–70 s). Sensor signal (response) was robust in being able to detect and monitor acetone levels continuously at variable exhaled-breath flow rates and at realistic relative humidity ranges (80–90%) in the human breath. This portable experimental nanostructured film sensor device performed comparably to that of state-of-the-art proton transfer reaction mass spectrometry (PTR-MS) and provides an alternative to more elaborate breath analysis techniques. The Si-doped WO3 nanoparticle sensors were highly selective to acetone over ethanol and had sensor-response times below 15s, making these devices attractive for breath analysis. Acetone concentrations were measured with high signal-to-noise ratios >10.

Rogers et al. [228] demonstrated the use of microsensor-based devices, for detecting select biomarkers in exhaled breath, as a fast and inexpensive breath-screening technology. Micro- hotplate elements with three chemi-resistive metal-oxide films (SnO_2, In_2O_3, and CuO) were tested for data acquisition in simulated breath containing single targets [(5 to 20) µmol/mol ammonia, methanol, and acetone], and mixtures of these chemical species. A supervised hierarchical machine-learning algorithm using linear discriminant analysis (LDS) for dimensional reduction of sensing data and discrimination was developed for successful classification and quantification of model biomarkers in validation-set mixtures.

4 Emerging E-nose applications

The potential for the development of new biomedical and forensic (cause of death) applications using E-nose instruments is high given the rapid progress in correlating VOC bioindicators and breath gas profiles to specific causes of disease, death, and health conditions of crime victims. New E-nose devices are being developed with the capability of detecting specific types and patterns of VOC profiles for numerous applications. Barash et al. [229] recently developed a gold nanoparticle (GNP) gas sensor E-nose that could distinguish between healthy lung cells and diseased cells with small-cell lung cancer (LC), non-small cell LC, adenocarcinoma or squamous cell carcinoma. This instrument has the potential to revolutionize LC screening as well as early and differential diagnosis of LC subtypes of unreachable lung nodules based on specific patterns of VOC profiles derived from the analysis of headspace from LC cells. In a similar study, Broza et al. [230] demonstrated the feasibility of using a nanomaterial-based E-nose sensor to identify the breath-print of early stage LC and to assess the difference in LC states before and after lung surgery to remove tumor tissue. They found five VOCs that were significantly reduced after LC surgery (lung resection). Tisch et al. [231] noted that most lung cancers originate from epithelial cells that undergo genetic mutations leading to changes in protein levels and posttranslational protein modifications that presumably generate changes in VOCs (relative to healthy, unmutated epithelial cells) that are released in exhaled air. Xu et al. [232] examined the feasibility of using a non-invasive nanomaterial-based breath test to replace upper digestive endoscopy and biopsy for the detection of gastric cancer.

Several studies have provided evidence to show the potential for using breath biomarkers to detect and diagnose active bacterial infections in the lung. Phillips et al. [211] evaluated breath VOC biomarkers in subjects with active pulmonary tuberculosis (TB), caused by *Mycobacterium tuberculosis*. They found that metabolic products of M. tuberculosis, principally derivatives of naphthalene, benzene, and alkanes, could be reliably used to detect this pathogenic bacterium in subjects with active TB using a six-minute point-of-care breath test developed to detect these TB-specific volatile biomarker metabolites. Španěl and Smith [233] found that hydrogen cyanide was released by Pseudomonas bacteria into the breath of children with cystic fibrosis. They also found other correlations for biomarkers such as the presence of breath acetone that varied with diet, ammonia as an indicator of dialysis efficiency, and hydrogen and CO_2 levels that were related to gastric emptying and bowel transit times. Michael et al. [234] suggested that future bedside VOC profiling would probably enable the rapid characterization of microbe-associated diseases to facilitate diagnosis and treatments by healthcare practitioners. They observed that VOCs are indicative of both healthy and disease states because VOC profiles, for any given anatomical site in the body, are dependent on VOCs produced by both human tissue (host component) and any microbes that are present in these same tissues.

The results from many studies have shown the capability of various E-noses to distinguish between different types of lung diseases. Fens et al. [158] showed that a new experimental E-nose could be used to discriminate between asthma and fixed airways COPD via differences in exhaled breath profiles. Many other examples, demonstrating the use of E-noses to distinguish between different diseases, are listed among the references in Table 3.

The repeated E-nose monitoring of breath gas profiles from individuals has been shown to indicate changes in body biochemistry and health state, providing a means of determining if a person is recovering or getting worse due to particular ailments. Fuchs et al. [235] found that isoprene (2-methybuta-1,3-diene) represents a precursor to isoprenoid and cholesterol biosynthesis and that a decline in exhaled isoprene in LC patients was correlated with

immune activation which they surmised was related to changes in lipid metabolism.

Numerous studies have provided a large amount of evidence to show that the composition of exhaled breath is affected by a person's exposure to exogenous chemicals in inhaled air such as through smoking habits, living near the source of air pollutants, or exposure to smoke from fires. Španěl et al. [236] found that all inhaled exogenous compounds are partially retained in the exhaled breath. Through this understanding, the biochemical background or history of inhaled chemical exposures (from various recent prior exposure events) can be deduced to determine the current state of health of victims, cause of death (through inhalations of toxic gases), or exposure to air pollution, smoke from fires, or indoor-air contaminants. This information provides valuable indications of the prior location of victims, (relative to crime scenes) based on exposure to local or point-sources of pollutants or toxic substances. This information is useful for determining the effects of inhalation factors on crime incidences and whether a victim was moved from the crime scene. Filipiak et al. [237] found that the composition of exhaled breath is considerably influenced by exposure to airborne pollutants, contaminants, and particularly by smoking. They found 80 VOCs that were significantly related to smoking, and suggested that the proper interpretation and full understanding of breath profile data required a careful investigation of the potential biological and chemical origins of breath volatiles, either from endogenous or exogenous sources.

Recent advancements in methods, used to help improve E-nose analyses (correlating breath bioindicators to E-nose patterns) through identification of breath gas VOC components and sampling methods and models, are important in the development of future E-nose applications to forensic science. Filipiak et al. [238] developed an automated adsorption needle trap method to pre-concentrate breath VOCs from critically ill patients in intensive care to improve sensitivity and reproducibility of NT-GC-MS analysis, also applicable to E-nose analyses. Gilchrist et al. [173] investigated the use of three different bag materials, (Nalophan of 25 μm and 70 μm thickness, and Tedlar), for collection and storage of breath-derived samples containing hydrogen cyanide. The latter two bag types performed best, retaining HCN concentrations for up to 24 h. Mochalski et al. [239] investigated the stability of 41 selected VOC breath constituents in three types of polymer sampling bags and found that Tedlar bags were superior to Kynar and Flexfilm sampling bags in terms of background emission, chemical species stability, and reusability.

Ibrahim et al. [115] generated a breath analysis model based on 15 VOCs to classify asthma patients with an accuracy of 85%. This non-invasive disease phenotyping model could lead to clinical application for classifying asthma patients into sputum, neutrophila, and uncontrolled asthma phenotypes. King et al. [240] produced a similar model for the evaluation of isothermal rebreathing, an experimental technique for estimating the alveolar air levels of hydrophilic VOCs in exhaled breath gases. This model clarifies the discrepancy between in vitro and in vivo blood-breath ratios of hydrophilic VOCs and helped to explain the exhalation kinetics of exchange between blood-borne and exhaled breath VOCs. King et al. [241] previously had developed a mathematical method for the sampling of other trace gases in exhaled breath, especially VOCs like acetone that reflect ongoing metabolism. Koc et al. [242] developed the first mathematical model for isoprene in exhaled breath that provides supportive evidence for a peripheral (extrahepatic) source of isoprene, the most abundant exogenous VOC contained in human breath which is considered a potentially useful biomarker for diagnostic and monitoring purposes. Martinez-Lozano [243] utilized secondary electrospray ionization mass spectrometry (EIMS) to quantify and identify the abundance of carboxylic acids (organic acids) in the breath following sucrose intake. Rapid increases in the concentrations of propionic and butanoic acids in the breath were attributed to bacterial activity in the mouth and pharynx. Carboxylic acids in the breath are readily detectable by certain E-nose instruments and could be used to diagnose bacterial infections in the lung, upper respiratory tract, as well as in the mouth and throat.

Phillips et al. [161] examined machine-learning approaches to analyze breath data for the diagnosis of COPD in patients based on unique combinations of VOCs found in the breath. They found that a patient's smoking status affected COPD-classification, requiring cross-validation with appropriate controls. Ulanowska [144] applied statistical methods, such as discriminant analysis (DA) and the CHAID model tree, to breath-profile data in order to identify patients with lung cancer. Their results indicated that patients with lung cancer had higher concentrations of certain VOCs (ethanol, acetone, butane, dimethyl sulfide, isoprene, propanal, 1-propanol, 2-pentanone, furan, o-xylene, and ethyl benzene) compared to healthy nonsmokers. A few other VOCs (pentanal, hexanal, and nonane) were found only in the breath of people who suffered from cancer. They also discovered higher concentrations of acetonitrile, benzene, and furan derivatives in nonsmokers. DA showed that butyrolactone, carbon disulfide, and dimethyl sulfide had to be considered in breath analysis in order to definitively recognize and distinguish between healthy subjects (with different smoking habits) from those suffering from cancer.

Filipiak et al. [218] identified specific pathogen-derived volatile biomarkers in breath that could be used for the early and noninvasive diagnosis of ventilator associated pneumonia (VAP). In vitro experiments using cultures of

bacteria most frequently associated with VAP patients, i.e. *Staphylococcus aureus* and *Pseudomonas aeruginosa*, were performed to investigate the release or consumption of specific VOCs associated with these species. They found many distinct differences in VOCs released from cultures of these two bacteria for aldehydes, carboxylic acids, alcohols, ketones, hydrocarbons, esters, volatile sulfur compounds (VSCs) and volatile nitrogen compounds (VNCs) chemical classes. The results provided strong evidence to suggest that the detection and identification of pathogenic bacteria could be achieved by determination of characteristic volatile metabolites useful in clinical breath-gas analysis as a non-invasive method for the early detection of bacterial lung infections.

5 Confirming E-nose analyses

Electronic-nose instruments could potentially be used in combination with other forensic instruments in several ways. E-nose devices could be used for the initial testing of forensic samples to provide a preliminary indication of the chemical nature of the VOCs present. This information can be used to help direct the types of subsequent analytical tests that need to be performed using conventional analytical instruments. New multiple-detector E-nose instruments are being developed with the capability of simultaneous detection of multiple types of volatile gases [5]. Other instruments with E-nose detectors interfaced in tandem with analytical instruments, similar to GC-MS and LC-MS, are possible. E-noses also may be used to confirm diagnoses and interpretations of chemical analyses made from determinations using conventional analytical instruments [3,4].

6 Admission of E-nose evidence in criminal litigations

Forensic evidence based on analytical data from E-nose devices hitherto has not been introduced, used, or admitted into the evidentiary record at any significant level for criminal litigations in the United States. There are also many other analytical methods, still considered in the experimental or unproven stage, that have not yet been established as proven and completely reliable to the extent that they are recognized as acceptable evidence for routine admittance in US courts; such as is currently recognized for numerous molecular biology methods that provide many types of DNA evidence.

In 2000, Rule 702 of the Federal Rules of Evidence for assessing the admissibility of scientific expert testimony was amended to include the Daubert standard. The Daubert standard provides a rule of evidence regarding the admissibility of expert witnesses' testimony (based on analytical methods) in United States federal legal proceedings. A Daubert motion, usually introduced by a defense lawyer, is a special case of motion raised before or during a trial to exclude the presentation of unqualified evidence to the jury. Once certain types of scientific evidence (derived from specific methods or instruments) have been excluded by a Daubert motion because they fail to meet relevancy and reliability standards, they can be challenged when introduced again in another trial as testimony or evidence based on the method. Even though a Daubert motion is not binding in other courts of law, other judges may choose to follow that precedent if certain types of scientific evidence are found untrustworthy by a different court. The U.S. Supreme Court listed some guidelines to help in evaluating the soundness of novel science methods used in forensic analyses. The Supreme Court agreed that before scientific evidence could be admitted as scientific expert testimony, the following principles should apply: 1) the trial judge is the gatekeeper who must assure that scientific expert testimony truly proceeds from scientific knowledge; 2) the trial judge must ensure that the expert's testimony is relevant and rests on a reliable foundation, and the expert testimony cannot be simply referred to the jury as a question of weight; 3) a conclusion will qualify as scientific knowledge if the proponent can demonstrate that it is a product of sound scientific methodology derived from the scientific method; in which 4) the scientific methodology is defined as: a) the process of formulating hypotheses and then conducting experiments to prove or falsify the hypothesis, b) that the hypothesis is considered relevant for establishing the "validity" of scientific testimony based on empirical testing (whether the theory or technique is falsifiable, refutable, and/or testable), and c) the method has been subjected to peer review and publication, has a known or potential error rate, has maintenance standards and controls concerning its operation, and the theoretical basis of the technique is generally accepted by a relevant scientific community.

The Supreme Court further ruled that nothing in the Federal Rules of Evidence governing expert evidence "gives any indication that 'general acceptance' is a necessary precondition to the admissibility of scientific evidence". By requiring experts to provide relevant opinions grounded in reliable methodology, proponents of Daubert were satisfied that these standards would result in a fair and rational resolution of the scientific and technological issues. The Supreme Court explicitly cautioned that the Daubert list should not be regarded by judges as "a definitive checklist or test...". Yet in practice, judges have judged the admissibility of scientific evidence using the "Daubert factors" as a checklist. Even though the Daubert standard is now the law in federal courts and in over half of U.S. states, the Frye standard remains the law in some jurisdictions including California, Illinois, Maryland, New York, New Jersey, Pennsylvania, and Washington state.

The absence of agreed upon protocols for the validation of scientific techniques, prior to their being admitted in court, has been considered entirely unsatisfactory and unfair in courts of

law. Judges are not well qualified to determine scientific validity without input from scientists. Thus, some countries have recommended that a Forensic Science Advisory Council be established to develop "gate-keeping" tests for expert evidence. This process should be accomplished in partnerships between judges, scientists and other key players in the criminal justice system. In 2005, the United Kingdom House of Commons Science and Technology Committee recommended the creation of a Forensic Science Advisory Council to regulate forensic evidence in the UK. A similar science-based advisory council would be very useful and instrumental in establishing the validity of data and evidence from new, emerging scientific methods and technologies in the United States. The Law Commission for England and Wales has proposed a consultation paper (No.190) to adopt a criterion like the Daubert Standard to help reform the law of evidence in regards to the admissibility of scientific evidence.

Thus, the validation of E-nose evidence, based on standardized methods of acquisition, must first be established with reliable and consistent standardized methods and with Daubert-standard certifications to assure the strength and validity of E-nose data in criminal investigations and court proceedings. Once E-nose methods have been validated and introduced as reliable evidence with increasing frequency in criminal litigations, these instruments should provide valuable additions to the tools available to forensic scientists of the future.

7 Future potential E-nose applications

Human breath analysis, a promising new field of medicine and medical instrumentation, potentially offers noninvasive, real-time, point-of-care (POC) disease diagnostics and metabolic status monitoring for many illnesses [244]. Numerous breath biomarkers were detected and quantified previously using GC-MS techniques [245], Proton Transfer Reaction MS (PTRMS) [246], and selected ion flow tube mass spectrometry, SIFT-MS [247]. Recently, high-sensitivity laser spectroscopic techniques, including tunable diode laser absorption spectroscopy (TDLAS), cavity ringdown spectroscopy (CRDS), integrated cavity output spectroscopy (ICOS), cavity enhanced absorption spectroscopy (CEAS), cavity leak-out spectroscopy (CALOS), photoacoustic spectroscopy (PAS), quartz-enhanced photoacoustic spectroscopy (QEPAS), and optical frequency comb cavity-enhanced absorption spectroscopy (OFC-CEAS) have been reported [244].

Santonico et al. [248] simultaneously tested the validity of two different E-nose instruments on selected target compounds. A gas sensor array based on the quartz crystal microbalance E-nose (ROTV E-nose) with transducers functionalized with metalloporphyrins, and a Cyranose E-nose were used simultaneously in calibration tests to demonstrate that limits of detection down to tens of ppb are possible. This study provided the first steps towards quality assurance of E-nose data for use in the biomedical field.

Valera et al. [249] evaluated the potential application of a new E-nose for the diagnosis of respiratory tract diseases. It is a simple, portable instrument that may be easily used in daily practice. Other positives include quick results and high reproducibility between instruments over different days. For definitive implementation of this new tool, additional studies are necessary with sufficiently large case volumes in order to determine the more specific VOC patterns of each disease.

The diagnostic accuracy of a sophisticated experimental E-nose (DiagNose, C-it BV) using exhaled air to detect tuberculosis was recently tested [212] The DiagNose uses a measurement method that enables transfer of calibration models between devices thus eliminating the most common pitfall for large scale implementation of E-noses in general. The portability and fast time-to-result of the DiagNose provides a proactive screening search for new TB cases in rural areas, without the need for highly-skilled operators or a hospital center infrastructure.

Other future potential new E-nose applications include detection of head trama severity associated with athletic physical-contact injuries, heart disease (such as infective endocarditis) based on the presence of resident oral bacterial populations (releasing halitosis-related VOCs), and other postmortem analyses for specific information relating to causes of death (disease, physiological or genetic disorder, toxins, poisons, physical trama, drug related, organ failure, injuries) or time of death.

8 Conclusions

E-nose devices are relatively new analytical tools that may soon be added to the arsenal of methods and techniques useful to forensic scientists and investigators in recreating crime scenes and events based on chemical evidence derived from the analysis of many different types of crime-scene samples that release volatile gases. E-nose instruments potentially offer new types of evidence and provide additional information that can be used in combination with data and evidence collected from conventional analytical instruments utilized in the chemical analysis of forensic samples.

Even though exhaled breath analysis is the least invasive diagnostic method, it is still not yet the preferred, routine method used in clinical practice. The gap standing between breath printing and disease diagnosis is mainly due to the complexity of the many variables affecting the composition of breath gases and the huge variety of available techniques that are still largely confined to research. Bridging this gap will require standardization of sample collection methods, sensor technology and data analysis. Narrowing the gap will require cooperation between

researchers and healthcare professions to agree on a unified path for breath analysis methodologies through development of common technological platforms and a shared list of standard operating procedures [250].

The pattern of exhaled breath VOCs represents a person's whole-body metabolic signature (overall physiological health condition) with the potential for identifying and characterizing different types of human diseases including lung cancers. A breath biosignature-based classification of homogeneous subgroups (types) of lung cancer may be more accurate than a global breath signature [148]. Thus, more application-specific E-nose referenced databases of breath profiles used for the single application intended, such as for a specific type of cancer, will usually provide more effective and reliable diagnoses, better predictive results, greater reproducibility (precision), and significant reductions in false positive determinations. Application-specific reference databases (breath profiles) for specific diseases are constructed from the analysis of breaths from subjects with confirmed known diagnoses for each corresponding type of disease (such as lung cancers) included in the reference database. Broader-based reference breath-profile libraries could be constructed for various lung diseases or other diseases of the body. Broader reference databases are useful for initial diagnoses to narrow down the list of possible causes to explain current symptoms and to provide a strategy for subsequent diagnostic tests.

This review has described some potential new methods and solutions that are needed to improve and standardize the processes used in the analysis of breath profiles and VOCs, including the greater integration and utilization of E-nose devices. Applications of E-nose instruments will no doubt lead to even more effective early detections of human diseases and metabolic disorders as scientific breakthroughs in knowledge of bioindicator compounds, correlations with disease incidence, and improvements in gas-detection methods advance with new research. All of these biomedical applications are potentially useful in forensic science investigations to help solve crimes requiring information relating to human health and causes of death.

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