BIOMEDICAL APPLICATIONS OF STRUCTURES WITH CARBON NANOTUBES

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ABSTRACT

Excellent physical properties of carbon nanotubes (CNTs) are used for the manufacturing many electronic devices. The single wall version of CNTs is promising for the detection of many important gases including gases exhaled by the living organism. The most promising is the realization of gas sensors based on metal oxides doped with CNTs. Application of CNT-based sensors to breathe analysis, properties of the SWCNTs gas sensors with metal nanoparticles and metal oxides, and CNTs biosensors are reviewed in this paper.

Keywords: Tin dioxide; Acetone; Metal oxide; Gas sensor; Sensitivity; Doping, Carbon nanotube

INTRODUCTION

Carbon nanotubes (CNTs) have excellent mechanical and electrical properties. They allow for the use of CNTs in many applications, for example, for a wide range of electronic devices, including logic circuits [1], light-displaying devices [2], batteries [3], power semiconductor devices [4], and sensors [5-9]. CNTs were discovered about two decades ago [10]. They show a unique structure that can be envisioned as a graphene sheet rolled into a tubular structure. CNTs can be either single-walled (i.e., SWCNT) or multi-walled (i.e., MWCNT) depending on the number of concentric graphitic layers (Fig. 1) [11]. The diameter is typically 1-10 nm for SWCNTs whereas it can be varied from 1 to over 100 nm for MWCNTs. The length of CNTs can also be varied in a broad range from several nm to over 1 mm. The aspect ratio (length vs. diameter) of CNTs can be larger than ~10^6. CNTs are one of the materials with the highest known mechanical strength. The intrinsic tensile strength and Young’s modulus can reach 1 TPa.

Depending on the rolling angle of a graphene sheet (i.e., chirality), CNTs can be either semiconducting or metallic. In their metallic form, CNTs show a very high electrical conductivity with the capability of carrying electrical current over 50 times greater than typical metals. The electrical properties of CNTs are also potentially relevant to biomedical applications. MWCNTs are much less toxic than SWCNTs because of the differences in diameter and surface chemistry. A lot of papers about the technology of preparation of CNTs are known. For example, three papers in this field can be mentioned [13-15].

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CNTs are ideal materials for a new class of molecular sensors. CNT-based gas sensors have sensitive chemical-to-electrical transducer capability, a high degree of chemical functionality options, and potential for miniaturization. Different semiconductor sensors are developed in Yerevan State University (Department of Physics of semiconductors and microelectronics and Research center of semiconductor devices and nanotechnology) in Armenia. Acetone, ammonia, benzene, butanol, i-butane, dichlorethane, dimethyl formamide, ethanol, formaldehyde, gasoline, hydrogen, hydrogen peroxide, iperit, methanol, natural gas , nitrogen oxides, propylene glycol, smoke, sulfurous anhydride , sulfurous oxides, toluene, sarin, etc. nanosensors were developed in YSU [16-19]. Warfare chemical sensors were developed and investigated in the framework of the NATO grant. Besides experimental works, the structure and defects of metal oxide sensors were investigated using the density functional theory and empirical force fields. The electron density of states was computed. Independent testing of chemical warfare and smoke sensors in the USA and Czech Republic were shown promise of their use.

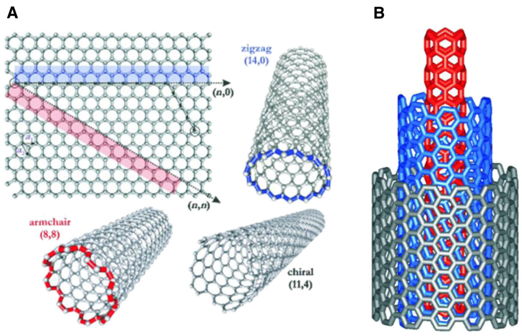

Figure 1: Depiction of (A) SWCNT with zigzag, armchair, and chiral structures, and (B) MWCNT with multiple concentric tubes of graphene [12].

DETECTION OF GASES EXHALED BY THE ORGANISM

Breath analysis is a promising method for rapid, inexpensive, noninvasive disease diagnosis and health monitoring owing to the correlative relationship between breath biomarker concentrations and abnormal health conditions.

Breath biomarkers for various diseases are listed in Table 1 of our papers [20].

Note that scientists have grown interested recently to detect volatile organic compounds (VOCs) for non-invasive diabetes management. The paper [21-27] presents and discusses works carried out both at Yerevan State University and abroad on non-invasive metal oxide sensors (chemiresistors) for acetone exhaled by diabetics. The technologies and parameters of chemiresistors based on tin dioxide, tungsten trioxide, zinc oxide, Fe_2O_3 , In_2O_3 and TiO_2 developed at YSU and in the world are presented. The response of the MWCNT-doped SnO_2 and ZnO chemiresistors measured at a low concentration of acetone allowed us to get the information about diabetics in human organisms at a relatively early stage of the disease.

It was shown that such sensors can be easy prepared by several methods which provided a highly selective analysis of acetone and other VOCs in the breath. Mentioned analytical devices are very sensitive and selective for diagnosis of diabetes mellitus, they are non-expensive, portable, and rather cheap and can be used by patients independently out of hospitals.

Metal oxides doped with semiconducting CNTs are excellent chemical sensing transducers. Doping of metal oxides with carbon nanotubes leads to a large enhancement of gas sensor performance, and can be due to its direct interaction with the gas analysts. Large attention is given in the literature to sensors made from multiwall metal oxides (MWCNTs) doped with CNTs (see, for example, [5-9], but properties of single walls tubes (SWCNTs) and gas sensors based on them did not consider earlier by us.

SWCNTS GAS SENSORS WITH METAL NANOPARTICLES AND METAL OXIDES

Metal nanoparticle (NP) /SWCNT gas were showed the sensitivity (response) to NH_3, NO_2, H_2, and H_2S gases. A metal NP with a lower work function can donate many electrons into the valence band of SWCNTs due to the smaller potential barrier. Zanolli et al. investigated the sensing mechanism of gold-decorated CNTs by experimentally measuring the change of the resistance R of this material exposed to different gases (NO_2, CO, C_6H_6) and calculated the shift in Fermi level upon exposure of each gas [28]. CNTs were first treated with O_2 plasma to create oxygen defects for the purpose of trapping and clustering Au atoms during a thermal evaporation procedure. The Fermi level in the CNT/oxygen defect/Au cluster system was calculated when C_6H_6, CO, or NO_2 gas molecules were contacted the cluster surface. The Fermi level is increased in the case of C_6H_6 and decreased in the case of NO_2. For this system, carbon monoxide did not shift the Fermi level. In the chemiresistor measurements, NO_2 exposure caused a large increase in R. C_6H_6 exposure did not cause a significant change in R, carbon monoxide exposure shows a small increase in R owing to its large binding energy to gold. The sensitivity and selectivity of metal NP receptors can be tailored to specific gases by controlling the size and elemental identity. Penza et al. investigated the effect of different gold nanocluster sizes sputtered on SWCNTs toward different gases [29]. The sizes of gold nanoclusters chosen were 2.5, 5, and 10 nm. Pd had the largest sensitivity toward CO_2. As the affinity gold and sulfur forms Au@S bonds, Au NP/CNTs have been sensitivity to H_2S down to 3 ppb H_2S [30]. Au nanowell (NW)/SWCNTs showed superior sensitivity to low concentrations of H_2S compared with Au NP/SWCNT material. To show that this material could be applied to H_2S sensing in breath, H_2S was successfully detected in an catalytically human breath background of 4% CO_2, 20% O_2, and saturated “flavor” vapors.

Note that palladium is active toward H@H bond dissociation and is significantly cheaper than platinum [30]. These same properties make Pd NPs excellent H_2 sensor receptors. Mubeen et al. prepared an H_2 sensor based on SWCNT networks non-covalently decorated with Pd NPs through electrodeposition [31]. Lundstrçm et al. proposed that H_2 gas molecules adsorbed in the air were dissociated into two adsorbed hydrogen atoms on the surface of Pd NPs [32]. In the presence of O_2, adsorbed H atoms can react with O_2 molecules to produce water molecules. Electron donation from the hydrogen molecules leads to an increase in R proportional to hydrogen concentration. The response of the Pd NPs/ SWCNTs network sensed H_2 was down to 30 ppm. Abdelhalim et al. investigated the role metal identity played toward gas sensitivity by evaporating Au, Ag, and Pd NPs of the same size on CNT films and testing their responses toward four gas molecules (NH_3, CO, CO_2, and ethanol) [33]. Au/CNT films showed the largest responses toward NH_3, CO, and ethanol, whereas Pd had the largest sensitivity toward CO2. Due to the affinity gold and sulfur have to form Au@S bonds, Au NP/CNTs have been used to sense $_{H2S}$ up to down to 3 ppb H_2S [34] and shown a linear chemiresistor response toward H_2S for a dynamic range between 0.2 and 1 ppm. Au NW/SWCNTs showed superior sensitivity to low concentrations of H_2S compared with Au NP/SWCNT material. H_2S was successfully detected in an expected human breath background of 4% CO_2, 20% O_2, and saturated "flavor" vapors [30] These same properties make Pd NPs excellent H_2 sensor receptors. The SWCNT-Cl defect-Pd NP material showed the best sensitivity toward H_2, with a LOD down to 10 ppm [35].

Gong et al. showed that the incorporation of SWCNTs into a sol-gel-prepared SnO_2 film could amplify the sensitivity of SnO_2 toward H_2 [36]. Quantum effects dominate the sensing mechanism of MO/CNT sensors. In the case of a SnO_2 /SWCNT composite, an n/p junction is created between the n-type oxide and the p-type s-SWCNTs. Upon exposure to H_2, the potential barrier between the SnO_2 grain boundaries is lowered. Indium tin oxide (ITO) NPs with SWCNT can sense NH_3 with a limit of detection (LOD) of 13 ppb [37]. ITO has p-type conductivity at low concentrations of NH_3 and humidity; however, at high levels of humidity, it switched to an n-type semiconductor through the hole compensation effect of water. Adsorption of H_2S molecules on the surface of the SnO_2 colloid quantum dots (CQDs) results in a sensor response toward H_2S down to 3.3 ppm. In addition, this composite showed selectivity toward H_2S when compared with the responses of NO_2, NH_3, and SO_2. The Co_3O_4 NPs with 4-8 nm in diameter can be served as CO receptors, achieving sensitivity down to 5 ppm.

The stability of the receptor's attachment to the transducer is crucial for a reproducible sensor response. In addition, the close association between the receptor and transducer is more likely to lead to higher electron delocalization. The titanium oxide NPs / SWCNT was sensitive to acetone vapors down to 400 ppb under UV light. The photoinduced electrons after electron/hole pair generation in the TiO_2 layer are injected into the p-type SWCNT, causing a decrease in conductance and lower current. Acetone adsorption onto TiO_2 /SWCNT prevents electron/ hole recombination; thus causing a detectable drop in conductance. The In_2O_3 /SWCNT composite has a greater responsibility towards ethanol than acetone owing to the dissociative adsorption of ethanol on the surface of (111) In_2O_3 [38].

Short summary of CNT-based sensors of common breath biomarkers is given below in Table 1.

Rather than detecting a single chemical component at a much higher sensitivity to others, the CNT array (e-nose) approach provides a "fingerprint" for a given compound. Such analyses as linear discriminant analysis (LDA) or principal component analysis (PCA) are commonly used to provide a reproducible detection result from the array output [45]. Kubert et al. studied the use of DNA-functionalized SWCNTs as the sensing element in FET devices for VOC differentiation [46]. Chatterjee et al. replaced DNA with a series of different surfactants to create a chemiresistor array of surfactant-functionalized MWCNTs [47]. An array of these sensors was able to differentiate toluene, chloroform, acetone, ethanol, methanol, and water by using PCA. Haick and co-workers successfully applied the array approach toward discriminating the simulated breath patterns of a healthy subject versus a diseased subject [48, 49]. The breath investigations of samples of healthy patients and patients with lung cancer were established 15 VOCs that are significant for lung cancer [48]. When a pre-concentration step was used to separate VOCs from humidity, the healthy and cancerous breath patterns could be easily distinguished with PCA. Impedance metric sensing of NH3 is less susceptible to drift because it is an

AC measurement [50]. A challenge specific to breathe analysis is the confounding effect of high levels of humidity on CNT-based sensors. Therefore, removal or separation of humidity is necessary for most trace breath biomarkers. Methods, such as micro-separation columns, membranes, and the use of silica gel have been also proposed to solve the confounding effect of breath humidity on sensor response. Further clinical research into breath biomarkers and their disease correlations, coupled with advances in CNT-based gas sensors, paves the way toward portable, low-power, non-invasive, point-of-care breath analysis devices.

Composite	Detected gas	LOD [ppm]	Dynamic range [ppm]	Ref
Pd NP/SWCNT	H_2	100	100-1000	[31]
Pd NP/SWCNT	H_2	30	30-10 000	[39]
Au NP/SWCNT	H_2S	0.003	0.02-1	[34]
Au NW/SWCNT	H_2S	0.005	0.005-0.5	[41]
Ag NC/MWCNT	NH_3	10	10-10 000	[40]
SnO2 /SWCNT	H_2	300	300-1500	[36]
TiO2 /ox-SWCNT	acetone	0.4	Feb-20	[41]
ITO NPs/SWCNT	NH_3	0.013	Jan-20	[37]
Co3O4 / MWCNT	CO	5	10-700	[42]
In2O3 /ox-SWCNT	ethanol	2.5	2.5-15	[38]
SnO2 QDs / MWCNT	H_2S	0.043	3.3-100	[43]
CuO/ox-SWCNT	ethanol	2	02-Nov	[44]

Table 1: Summary of CNT-based sensors of common breath biomarkers.

Semiconducting SWCNTs devices can be used as a sensor for chemical nerve agents. Thin-film transistors constructed from random networks of SWCNTs were used to detect dimethyl methylphosphonate (DMMP), simulant for the chemical warfare nerve agent sarin [51]. The devices consist of a lithographically patterned SWCNT network that bridges Ti source and drain contacts. The network is grown on the surface of a thermal SiO2 layer, and the Si substrate serves as a common gate electrode.

These results indicate that the electronic detection of nerve agents and potentially other chemical warfare agents is possible with simple-to-fabricate carbon nanotube devices. Researchers have demonstrated that individual semiconducting SWCNT devices produce a large resistance change in response to certain types of gaseous analytes. In such sensors, the adsorption of an analyst molecule with strong electron donor or acceptor properties results in a partial charge transfer between the analysts and the nanotube that changes its electrical resistance. Autors of [51] found that the electronic properties of the nanotube networks are strongly affected by the presence of DMMP - it readily adsorbs on the SWCNTs, resulting in an effective transfer of negative charge that manifests itself as a shift of the transistor threshold voltage. The molecular adsorption is fully reversible by applying a small positive gate bias that releases the DMMP from the nanotube surface.

The SWCNT-based sensors were reversible and capable of detecting DMMP at sub-ppb concentration levels, and they are intrinsically selective against common interferons. A chemiresistor can detect exposure to 1 ppb DMMP that was delivered for 3000 s. Sensors are intrinsically selective against interfering signals from hydrocarbon vapors and humidity. Such sensors have detected also 0.1 ppb of NO_2, which is superior to current state-of-the-art NO_2 sensors by several orders of magnitude. Note that our chemical warfare detectors developed earlier in the framework of the NATO grant are reported in [52].

CARBON NANOTUBES BASED BIOSENSORS

CNTs based biosensors can be used in ultra-sensitive and ultra-fast biosensing systems [53]. The basic and some newly developed synthetic methods of CNTs are presented in [54]. Note that the concept of CNT-based biosensor was derived from the description of the enzyme electrode by Clark [55]. In general, the CNT-based biosensor includes two parts: biological sensitive element and transducer. The CNT functionalized with biomolecules or bioreceptors, such as proteins, cell receptors, enzymes, antibodies, microorganisms, or even whole biological tissues, which are working as the biological sensitive element [56-58]. The role of the transducer is to convert the concentration of analysts to other physical signals, such as currents, absorbance, or mass. According to the interactions between analysts and the biological sensitive materials, CNT-based biosensors will be separated into two categories: chemical and physical. Among of them, the CNTs-field-effect transistors have superior properties.

The hollow structure of CNTs is good for the adsorption of enzymes. Therefore, CNTs in amperometric CNTs-based biosensors are always used to functionalize with enzymes to generate the enzyme CNT electrodes or to modify the surface of electrodes. CNTs in the CNTFET biosensor configured as FETs offer the advantages of possible biocompatibility, size compatibility, and sensitivity toward minute electrical perturbations for the detection of biological species [59]. They are also low-cost, low-noise and portable [60]. In addition, the effective detect area can be made into the size of a single biomolecule or virus. Because of these unique characteristics, CNTFET biosensor has been widely used in the field of biologies, such as protein, glucose, enzyme, antigen and antibody molecules, DNA molecules, bacteria, and hormones [61, 62]. In the CNTFET biosensor, the preparation of metal electrodes as the source and the drain electrode are prepared on the surface of silicon substrate coated with silicon dioxide insulating layer. The connection of specific CNTs between the two electrodes is acted as a conductive channel, and introducing a gate electrode. The CNTs were synthesized by CVD and the distance between the two electrodes is very small. The specific antibodies can be coated with CNTs, specificity adsorption between antigen and antibody could generate an electric signal that is observed and recorded [59, 63]. According to the different reactants, CNTFETs are divided into different types of FET including enzyme FET, immune FET, organization FET, cell FET, and DNAFET. Over the past decade, many groups have brought significant contributions in the development of CNTFET biosensors. Nanoscale FET devices with SWCNTs were prepared as the conducting channel for the electronic detection of specific protein binding.

Functionalization of CNTs with other nanomaterials, such as polymer, proteins, DNA, enzyme to improve their dispersibility and compatibility with the target biological species [64]. Functionalized CNTs have many improved characteristics, such as large edge plane, high surface activity, high catalytic efficiency, and more functional groups. Using the functionalized CNTs can improve the fixed efficiency of biological recognition of molecules (enzymes, DNA, antigen/antibody, etc.) in biosensors ([65, 66]). Compared with conventional solid-state carbon biosensors, the biosensors made of functionalized CNTs have higher sensitivity, faster response, and a wider detection range. The roles of functionalized CNTs and technologies in how to prepare the functionalized CNTs are discussed in a very interesting and comprehensive review [64, 66, 67].

Note again that investigations of CNTs look like the most exciting areas in current materials sciences, and the development of CNTs for biomolecule detection is particularly important for bioengineering and biomedical applications. Novel nanotechnologies such as nanoimprint lithography and soft lithography are helpful. Both chemical and physical properties of functionalized CNTs strongly depend on the ambient conditions, such as temperature and pH. Some studies have indicated that the sensitivity and the detection limits is significantly enhanced using nanocomposite materials combine with CNTs and metal (Au, Pt, etc.) for biosensor. With the sustainable development of new nanomaterials combined with CNTs, the characterization of these new materials at the molecular level is essential and a key scientific challenge. In parallel with experimental studies, molecular modeling must be further developed as a tool to predict the performance of new materials for given biomolecules. Such computational methods will enable a quick evaluation of new materials. Clearly, the further development of CNT-based biosensors will allow to the fabric of such new micro- /nano-devices as bionanosensors.

Recent developments of novel nanosensors offer promising approaches for improved clinical diagnostics and treatments, with increasing interest in nanomaterials-based biosensors [66-80]. A sensor can include antibodies, aptamers, DNA sequences, molecular imprints, lectins, or synthetic moieties. Various nanoparticles have shown the potential to be highly sensitive and selective, such as metal nanoparticles, quantum dots, nanowires, graphene, graphene quantum dots, and carbon nanotubes that can bind and detect biologically relevant concentrations of a targeting analyst. The use of carbon nanotubes as sensors for biotechnological and biomedical applications is of particular interest [80]. SWCNTs demonstrated long-term stability in vivo [81-83]. The non-photo bleaching, the non-blinking fluorescent emission of SWCNTs allows using them as optical sensors, enabling in situ, label-free, real-time detection with both spatial and temporal resolution [84-86]. Recent studies have demonstrated the detection of proteins using various approaches for surface functionalization, including natural substrates [87-90] and synthetic polymers [84], with the potential to enable long-term continuous monitoring of important biomarkers or to replace costly and time-consuming laboratory testing. The advantages of SWCNTs for in-vivo and in-vitro biomedical applications such as drug delivery, imaging, and sensing, focusing on protein recognition are investigated. Therefore, the properties of SWCNTs make them excellent candidates for sensing proteins and bio-macromolecules, with optical signal transduction, where advancements in nanotechnology design, synthesis, characterization, and modeling will continue to push forward the discovery of new SWCNT-based fluorescent sensors.

OTHER APPLICATIONS OF CARBON NANOTUBES IN MEDICINE

Possibilities to use gas semiconductor detectors for detecting diseases, and, in particular, diabetes, in an organism were discussed above. Note also that detectors made from other metal oxides can serve as analyzers of exhaled (see, for example, [21, 23-26]). So, CNTs an ideal material for the development of a new class of molecular sensors.

Carbon nanotubes (CNTs) are also widely used in dentistry, virology, and cardiology. One of the most active research fields in modern biomedical engineering and clinical practice is the repair and regeneration of hard tissues in the human body such as bone and teeth. Traditional materials that serve as scaffolds in clinical applications include naturally-derived collagen, chitosan, and different synthetic polymers. Of course, it is desirable for the scaffold to be biocompatible and able to control the proliferation and differentiation of cells into the required lineage and structure. The good mechanical strength, flexibility, and lightweight make CNTs ideal materials for use as reinforcement of engineered composites. Today CNTs are used in functional scaffolds for repairing and regenerative purposes [91].

Inorganic composite-based MWCNT hybrid membranes coated with copper(I) oxide, titanium(IV) oxide, and iron(III) oxide nanoparticles were investigated in the removal of viruses (bacteriophages) from contaminated water [92] and used as virus adsorbents.

Injectable polymer/CNT composites are using today for enhancing cardiomyocyte proliferation and function [93], and cardiac differentiation of stem cells [94]. Electrically conductive CNTs can be used in composite scaffolds as synthetic cell culture platforms for enhanced differentiation of human mesenchymal stem cells (hMSCs). Through analysis of fiber morphology, elastic modulus and conductivity, it was established that scaffold properties are affected by the inclusion of CNTs and can be tailored for specific applications. CNTs-based scaffolds have been recently found to support the in vitro growth of cardiac cells: in particular, their ability to improve cardiomyocytes proliferation, maturation, and electrical behavior are making CNTs extremely attractive for the development and exploitation of interfaces able to impact cardiac cells physiology and function.

CNTs are used now as new nanocarriers for drug delivery. Researchers have recently applied CNTs to diagnose and treat cancers such as lung, breast, prostate, liver, colon, etc. [95]. Besides, quantum dots, gold, and magnetic nanoparticles were a series of nanomaterials that could be utilized to detect cancers [96]. The methods of chemotherapy, radiation therapy, and various medications are used for the detection of different cancers (for example, lung cancer [97]). These methods were not highly effective due to the non-targeted and damaging of healthy tissues such as hair follicles. Based on these approaches, damage in the cell cycle, break in the double strands of DNA, inflammatory responses, tissue fibrosis, etc., will have occurred. On the other hand, there were a series of treatment obstacles; low stability, solid solubility in water, and cell resistance to treatment in the chemotherapy method.

Tumor-targeting has many difficulties even with using the specific antibodies to bind to cancer cells; pulmonary tumors are among the invincible types of cancer, on which the researchers work to solve this issue. In fact, CNTs are made in five ways, which are described as arc discharge, laser ablation, chemical vapor deposition, flame synthesis, and silane solution methods. Also, CNTs are purified in three ways as air oxidation, sonication, and acid refluxing. On the other hand, the CNTs are a fascinating substance that can be employed to bind proteins, peptides, nucleic acids, and various drugs. Furthermore, CNTs have a high potential for drug delivery due to their tubular and fiber-like structure. The usable techniques to evaluate the CNTs and drugs with each other were collected as transmission electron microscopy (TEM), scanning electron microscopy (SEM), Raman spectroscopy, Fourier transforms infrared spectroscopy (FTIR), and X-ray diffraction (XRD), etc.

Consider below the pulmonary toxicity assessment of CNTs. CNTs could quickly enter the lungs through the respiratory tract and then rapidly enter and affect the nervous, lymphatic, and circulatory systems, leading to toxic effects [98]. The main reasons for these toxic effects can be durability, the amount of residual oxygen reactive metal, and size. By removing the residual metals and selecting appropriate dimensions, the CNTs can be safe in drug transmission. The smaller sizes were with less toxicity; furthermore, the concentration of metal impurities such as iron did not contribute to toxicity [99]. Indeed, the greater the curvature, the less damage occurred to the cells. Due to the high structural similarity of CNTs with asbestos, which is usually used, similar physiological effects on the human bronchial epithelial cells are shown. In humans exposed to the CNTs, they could induce lung and pleural lesions, inflammation, pleural fibrosis, and lung tumors. The stiffness, hardness, length, width, and CNT longevity are five factors that could induce a harmful effect.

The too-lowest dose of MWCNTs could induce pulmonary fibrosis. Also, MWCNTs, like asbestos, could alter the expression of several genes and cell survival and proliferation [100]. The CNT produced the least toxicity compare with asbestos. On the other side, functional CNT showed less toxicity with higher activity toward CNT without functionalization. The safe applied dose of CNTs was not yet finally determined [101]. Also, researchers can reduce (rule) the toxic effects by choosing the appropriate dimensions (shorter length and higher width), more curved nanotubes, and using the functionalized form [102]. Moreover, the MWCNT was used more efficiently due to less toxicity toward SWCNT. On the other side, there were significant contrasts in using the nanotubes which induced tumor growth and tumor suppressor protein.

Using CNTs in lung cancer treatment is very promising. Generally, lung cancer's clinical manifestations include fatigue, coughing, wheezing, pain in the chest, the brevity of breath, swallowing hardness, anxiety, and yellow fingers. Also, a lung cancer diagnosis is possible with helping 4 methods with the names of radiological, non-radiological imaging such as MRI, endoscopic, and biochemical methods [101-105]. As usual, diagnosis, type, and degree of lung cancer are performed by CNTs scan imaging. [106, 107]. But, unfortunately, too low-dose CNT scans may bring false-positive answers about having lung cancer. Today, the biomarkers of both protein and genetic modifications are known for lung cancer. Numerous biosensors were studied to bind to these biomarkers for non-invasive detection [108-110]. The sensor array of CNTs has demonstrated a discrepancy between the healthy and the patient respiratory sample in the volatile organic components (VOC). Therefore, the detection of VOCs and tumor markers by breath analysis with helping CNT is a modern and studied method [20, 22, 111]. The sensors identify different biomarkers due to the solubility, polarity, and chemical associations, especially for tuberculosis disease. The design of an electronic nose with CNTs to delete the VOC of lung cancer patients was an inexpensive and rapid method. Water, methanol, isopropanol, ethanol, acetone, 2-butanone, and propanol were found as polar vapors lung cancer biomarkers. The CNTs, doped with platinum, can detect styrene and benzene vapors that existed in the exhale of lung cancer patients. This sensitivity was very low in natural nanotubes.

SWCNTs decorated with Pd, Pt, Ru, or Rh elements could also be used to detect toluene gas as an indicator of lung cancer. Research, conducted in [109], stated that a biosensor created by CNT covered with Rh catalyzer can distinguish and absorb C_6H_7N, and C_6H_6 in the exhaled air of lung cancer patients [110]. Another scheme used to enhance lung cancer detection was preparing a combination of SWCNT and chitosan [110]. Due to the differences in nicotinic acetylcholine receptors in normal and small cells of lung cancer, the nanotube-based electrode sensor for the quantitative electrophysiological monitoring of a no adherent cell has been demonstrated [111].

CONCLUSION

Excellent physical properties of CNTs are using for the manufacturing of many electronic devices. Single wall CNTs and gas sensors based on them are also promising for the detection of many important gases including gases exhaled by the organism. The treatment with CNT is much more effective than the traditional treatments. Using the functionalization, nanotubes with a longer length, more width, and greater curvature partially can be made with lower toxicity. CNTs can be used for effective drug delivery and toxicities of tumor cells without the damage of healthy ones.

Carbon nanotubes (CNTs) are also widely used in dentistry, virology, and cardiology.

Application of CNT-based sensors to breath analysis, properties of the SWCNTs gas sensors with metal nanoparticles and metal oxides and CNTs biosensors are reviewed in this paper.

REFERENCES

1. Geier ML, Prabhumirashi PL, McMorrow JJ, Xu W, Seo JWT, Everaerts K , Kim CH, Marks TJ. Hersam MC (2013) Subnanowatt Carbon Nanotube Complementary Logic Enabled by Threshold Voltage Control. Nano Lett 13: 4810-4816.
2. Zou A, Zhang K, Li J, Zhao Y, Wang Y, Pillai SKR, Demir HV, Sun X, Chan-Park MB, Qing Zhang Q (2015) Carbon nanotube driver circuit for 6× 6 organic light emitting diode display. Sci. Rep 5:11755-11761.
3. Cao Z, Wei BBQ (2013) A perspective: carbon nanotube macro-films for energy storage. Energy EnvironSci 6:3183-3190.
4. Shikata S. (2016) Single crystal diamond wafers for high power electronics Diamond and Related Materials. 65:168-175.
5. Aroutiounian VM (2018) Properties of hydrogen peroxide sensors made from nanocrystalline materials. SensTransducers 223:9-21.
6. Aroutiounian VM, Adamyan AZ, Khachaturyan EA, Adamyan ZN, Hernadi K, Pallai Z, Nemeth Z, Forro L, Magrez

A. (2013) Study of the surface-ruthenated SnO2/MWCNTs nanocomposite thick-film gas sensors. Sens. Actuator B177:308-315.

7. Aroutiounian VM (2018) Properties of hydrogen peroxide sensors made from nanocrystalline materials. SensTransducers 228:1-16.
8. Adamyan ZN, Sayunts AG, Khachatryan EA, Aroutiounian VM (2021) Tin Oxide/Carbon Nanotube Nanocomposite Sensors for Some Toxic VOCs Detection. South Florida Journal of Development, Miami, 2021:2:1067-1093.
9. Aroutiounian V (2020) Acetone sensors based on tin dioxide. J Nanomedicine, Nanotechnology and Nanomaterials 1:1-11.
10. Harris P. (1999) Carbon nanotubes and related structures. Cambridge University Press, 279 pp.
11. Hopley EL, Salmasi Sh, Kalaskar DM, Seifalian M (2014) Carbon nanotubes-leading the way forward in new generation 3D tissue engineering. Biotechnology Advances A 32:1000-1014.
12. Masikini M, Chowdhury M, Nemraou O. (2020) Application in exhaled breath acetone chemiresistive sensors. J. Electrochem Society 167:037537.
13. Yang N, Chen X, Ren T (2015) Carbon nanotube based biosensors. Sens. Actuators B 207: 690-701.
14. Szabó A, Perri C. Csató A, Giordano G, Vuono D, Nagy JB (2010) Synthesis methods of carbon nanotubes. Diamond and Related Materials 3:3092- 3140.
15. Berki P, Nemeth Z, Reti B, Berkesi O, Margez A, Aroutiounian V, Forro L, Hernadi K (2013) Preparation and characterization of multiwalled carbon nanotube/In2O3 composites. Carbon 60:266-272.
16. Aroutiounian VM Hydrogen sensors. In: Dekker Encyclopedia of Nanoscience and Nanotechnol. Second Edition, Taylor and Francis: New York, 2012.
17. Aroutiounian VM (2013) Porous silicon gas sensors. In: Semiconductor gas sensors, Woodhead Publishing Series in Electronic and Optical Materials N 38, chapter 12: 408-420.
18. Arouriounian VM (2007) Metal oxide hydrogen, oxygen, and carbon monoxide sensors for hydrogen setups and cells. Int. J. Hydrogen Energy 32:1145-1155.
19. Aroutiounian VM (2019) Gas Nanosensors Made from Semiconductor Metal Oxides. J Cont Physics (Armenian Academy of Sciences) 54:356-378.
20. Aroutiounian VM (2020) Microelectronic gas sensors for non-invasive analysis of exhaled gases. J Nanomed Nanotechnol 11:1-7.
21. Aroutiounian VM (2021) On non-invasive measurements of exhaled acetone using metal oxide nanosensors. J Nanomed & Nanotechnol 2: No 560.
22. Aroutiounian VM (2019) Semiconductor gas sensors detector using Arduino NANO. Biomedical J. Sci. & Tech. Res:12: 28 3-287-291.
23. Alizadeh N, Jamalabadi H, Tavoli F (2020) Breath acetone sensors as non-invasive health monitoring systems. IEEE Sensors J 20: 5-31.
24. Saasa V, Malwela Th, Beukes M, Mokgotho M, Liu CP, et al. (2018) Sensing technologies for detection of acetone in human breath for diabetes

diagnosis and monitoring. Diagnostics 8: 12-29.

25. Ta L, Chang Sh, Chen CJ, Liu JT (2020) Non-invasive blood glucose monitoring technology. Sensors 20:6925 - 6957.
26. Rydosz A (2018) Sensors for enhanced detection of acetone as a potential tool for non-invasive diabetes monitoring. Sensors 18:2298-2312.
27. Ellis JE, Star A (2016) Carbon nanotube based gas sensors toward breath analysis. Chem Plus Chem 81:1248-1265.
28. Zanolli Z, Leghrib R, Felten (2011) A gas sensing with Au-decorated carbon nanotubes. ACS Nano 5:4592-4599.
29. Penza M, Rossi R, Alvisi M (2009) Functional characterization of carbon nanotube networked films functionalized with tuned loading of Au nanoclusters for gas sensing applications. Sens. Actuators B140:176-184.
30. Shao MJ (2018) Palladium-based electrocatalysts for hydrogen oxidation and oxygen reduction reactions. J Power Sources 196:2433-2444.
31. Mubeen S, Zhang T, Yoo B (2014) Palladium nanoparticles decorated single-walled carbon nanotube hydrogen sensor. JPhysChem C 111:6321-6327.
32. Lundström I, Spetz A, Winquist F (1990) Catalytic metals and field-effect devices-a useful combination. Sens Actuators B 1:15-21.
33. Abdelhalim A, Abdellah A, Scarpa G, Lugli P (2014) Metallic nanoparticles functionalizing carbon nanotube networks for gas sensing applications. Nanotechnology 25: 055208.
34. Mubeen S, Zhang T, Chartuprayoon N, Rheem Y, Mulchandani A (2015) Sensitive detection of H2S using gold nanoparticle decorated single-walled carbon nanotubes. Analytical chemistry 82:250-257.
35. Goldsmith BR, Coroneus JG, Khalap VR, Kane AA, Weiss GA, Collins PG (2007) Conductance-controlled point functionalization of single-walled carbon nanotubes Science 315(5808):77-81.
36. Gong J, Sun J, Chen Q (2008) Micromachined sol-gel carbon nanotube/SnO2 nanocomposite hydrogen sensor SensActuators B130: 829-842.
37. Rigoni F, Drera G, Pagliara S, Goldoni A, Sangaletti L (2014) High sensitivity, moisture selective, ammonia gas sensors based on single-walled carbon nanotubes functionalized with indium tin oxide nanoparticles. Carbon: 356-363.
38. Ellis JE, Green U, Sorescu DC, Zhao Y, Star A. (2015) Indium oxide-single-walled carbon nanotube composite for ethanol sensing at room temperature. J. Phys. Chem. Lett.6:712-717.
39. Sun Y, Wang HH (2007) High-performance, flexible hydrogen sensors that use carbon nanotubes decorated with palladium nanoparticles. Adv. Mater.19:2818-2830.
40. Cui S, Pu H, Lu G (2012) Fast and selective room-temperature ammonia sensors using silver nanocrystal-functionalized carbon nanotubes. ACS Appl. Mater. Interfaces 4:4898-4912.
41. Ding M, Sorescu DC, Star A (2013) Photoinduced charge transfer and acetone sensitivity of single-walled carbon nanotube-titanium dioxide hybrids J. Am. Chem. Soc.135: 9015-9022.

42. Dang L, Zhang G, Kan K (2014) Heterostructured Co3O4/PEI-CNTs composite: characterization and CO gas sensors at room temperature. J. Mater. Chem. A:2:4558-4567.
43. Liu H, Zhang W, Yu H (2016) Solution-processed gas sensors employing SnO2 quantum dot/MWCNT nanocomposites. ACS Appl. Mater. Interfaces 8:840-848.
44. Peng G, Wu S, Ellis J. E (2016) Single-walled carbon nanotubes templated CuO networks for gas sensing. J. Mater. Chem. C 4:657-682.
45. Jurs PC, Bakken GA, McClelland HE (2000) Computational methods for the analysis of chemical sensor array data from volatile analytes. Chem. Rev. 100 :2649-78.
46. Kubert NJ, Lerner MB, Yodh JS, Preti G, Johnson ATC (2013) Differentiation of complex vapor mixtures using versatile DNA-carbon nanotube chemical sensor arrays. ACS Nano7:2800-2807.
47. Chatterjee S, Castro M, Feller JF (2015) Tailoring selectivity of sprayed carbon nanotube sensors (CNT) towards volatile organic compounds (VOC) with surfactants. Sens Actuators B 220:840-849.
48. Peng G, Tisch U, Haick H (2009) Detection of nonpolar molecules by means of carrier scattering in random networks of carbon nanotubes: Toward diagnosis of diseases via breathe samples. Nano Lett. 9:1362-1369.
49. Peng G, Trock E, Haick H (2008) Detecting simulated patterns of lung cancer biomarkers by random network of single-walled carbon nanotubes coated with non-polymeric organic materials. Nano Lett 8:3631-3642.
50. Hong HP, Kim JH, Lee CJ, Min NK (2015) In-plane impedance metric ammonia sensing of solution-deposited, highly semiconductor-enriched single-wall carbon nanotube submonolayer network gas sensors. SensActuators B 220:27-32.
51. Novak JP, Snow ES, Houseret EJ (2003) Nerve agent detection using networks of single-walled carbon nanotubes. Applied Physics Letters 8: 4026-4028.
52. Aroutiounian VM (2018) Semiconductor gas sensors for detection of chemical warfare agents and toxic industrial chemicals. Int. Sci. J. Alternative Energy Ecology 249-251:38-45.
53. Yang N, Chen X, Ren T (2015) Carbon nanotube based biosensors. Sens Actuators B 207:690-704.
54. Clark LC, Lyons (1962) Electrode systems for continuous monitoring in cardiovascular surgery. Ann. N. Y. Acad. Sci 10: 29-38.
55. Raicopol M, Pruna A, Damian C, Pilan L (2013) Functionalized single-walled carbon nanotubes/polypyrrole composites for amperometric glucose biosensors. Nanoscale Res. Lett 316:1-12.
56. Guo X. (2013) Single-molecule electrical biosensors based on single-walled carbon nanotubes. Adv. Mater 25:3397-3409.
57. Allen BL, Kichambare PD, Star A (2007) Carbon Nanotube Field-Effect-Transistor-Based Biosensors. Adv. Mater 19:1439-1446.
58. Thévenot DR, Toth K, Durst RA, Wilson GS (2001) Electrochemical biosensors: recommended definitions and

classification. Biosens. Bioelectron 16:121-131.

59. Byon HR, Choi HC (2006) Network single-walled carbon nanotube-field effect transistors (SWNT-FETs) with increased Schottky contact area for highly sensitive biosensor application. J. Am. Chem. Soc 128:2188-2202.
60. Tang XW, Bansaruntip S, Nakayama N, Yenilmez E, Chang YL, Wang Q (2006) Carbon nanotube DNA sensor and sensing mechanism. Nano Lett.6:1632-1636.
61. Kim MB, Woo S, Kim JW, Ahmed S, Subramanian S (2020) A review of review on applications of carbon nanotubes and their modifications for different comtaminants removal. J. Critical reviews 7:2923-2928.
62. Gruner G (2006) Carbon nanotube transistors for biosensing applications. Analyt. Bioanalytical Chemistry 384:322-335.
63. Nie C, Pan L, Li H (2012) Electrophoretic deposition of carbon nanotubes film electrodes for capacitive deionization. J. Electroanal. Chem 666:85-98.
64. Hendler-Neumark A, Bisker G. (2019) Fluorescent single-walled carbon nanotubes for protein detection. Sensors 19:5403-5412.
65. Zhang S, Wong CL, Zeng Sh, Bi R, Tai K, Dholakia K, Olivo M. (2020) Metasurfaces for biomedical applications: imaging and sensing from a nanophotonics perspective .
66. Anker JN, Hall WP, Lyandres O (2009) In:Nanoscience and Technology; Co-Published with Macmillan Publishers Ltd.: London, UK:308.
67. Farrera C, Torres A, Feliu F (2017) Carbon nanotubes as optical sensors in biomedicine. ACS Nano 11:10637-10643.
68. Shao D, Gao Y,Yan F (2011) Semiconductor quantum dots for biomedicial applications. Sensor 11:11736 -11761.
69. Ramgir NS,Yang Y, Zacharias M (2010) Nanowire-based sensors. Small 6:1705-1721.
70. Chen Z, Zhang XX, Yang R, Zhu Z, Chen Y, Tan W. (2011) Single-walled carbon nanotubes as optical materials for biosensing. Nanoscale 3:1949-56.
71. Liu Y, Dong X, Chen P (2012) Biological and chemical sensors based on graphene materials Chem. Soc. Rev 41: 2283-2299.
72. Shen J, Zhu Y, Yang X, Li A (2012) Graphene quantum dots: emergent nanolights for bioimaging, sensors, catalysis and photovoltaic devices. Chem. Commun. 48:223-232.
73. Gao C, Guo Z, Liu JH, Huang XJ (2012) The new age of carbon nanotubes: an updated review of functionalized carbon nanotubes in electrochemical sensors. Nanoscale 4:1948-1965.
74. Liu Z, Tabakman S,Welsher K, Dai H (2009) Carbon nanotubes in biology and medicine: In vitro and in vivo detection, imaging and drug delivery. Nano Res 2:85-92.
75. Caoa Q, Hensleyb DK, Lavrik N, Ventona BJ Carbon nanospikes have better electrochemical properties than carbon nanotubes due to greater surface roughness and defect sites Angew. Chem. Int. Ed. 2019:49:2114-2123.
76. Boghossian AA, Zhang J, Barone P (2011) Near-Infrared Fluorescent Sensors based

on Single-Walled Carbon Nanotubes for Life Sciences Applications. ChemSusChem 11:848- 856.

77. Kim SJJ, Choi SJJ, Jang JSS (2017) Striking sensing improvement. AccChemRes 50:1587-1596.
78. Alvarez M.M, Aizenberg J, Analoui M (2017) Emerging Trends in Micro- and Nanoscale Technologies in Medicine: From Basic Discoveries to Translation. ACS Nano11:5195-5214.
79. Kruss S, Hilmer AJ, Zhang J, Reuel NF, Mu B, Strano MS (2013) Carbon nanotubes as optical biomedical sensors. AdvDrugDelivRev 65:1933-1950.
80. Eatemadi A, Daraee H, Karimkhanloo L, Kouli M, Zarghami N, Akbarzadeh A, Abasi Y, Hanifehpour B, Joo SW (2014) Carbon nanotubes: properties, synthesis, purification, and medical applications. Nanoscale Research Letters 4:393
81. Iverson NM, Barone PW, Shandell M. (2013) In Vivo Biosensing Via Tissue Localizable Near Infrared Fluorescent Single Walled Carbon Nanotubes Nat. Nanotechnol 8:873-880.
82. Ménard-Moyon C, Kostarelos K, Prato M (2010) The alluring potential of functionalized carbon nanotubes in drug discovery. Expert Opin. Drug Discov. 5: 691-705.
83. Wu Y, Phillips JA, Liu H (2008) Carbon nanotubes protect DNA strands during cellular delivery. ACS Nano 2:2023-2030.
84. Hendler-Neumark A, Bisker G (2019) Fluorescent single-walled carbon nanotubes for protein detection. Sensors 19: 5403-5425.
85. Bisker G, Dong J, Park HD (2016) Protein-targeted corona phase molecular recognition. Nat . Commun. 7:1-8.
86. Salem DP, Landry MP, Bisker G, Ahn J, Kruss S. (2016) Chirality dependent corona phase molecular recognition of DNA-wrapped carbon nanotubes. Carbon 97: 147-153.
87. Beyene AG, Delevich K, Yang SJ, Landry MP (2018) New Optical Probes Bring Dopamine to Light. Biochemistry 57: 6379-6381.
88. Dinarvand M, Neubert E, Meyer G, Selvaggio A (2019) Near-infrared imaging of serotonin release from cells with fluorescent nanosensors Nano Lett 19:6604-6618.
89. Ahn JH, Kim JH, Boghossian AA (2011) Label-free, single protein detection on a near-infrared fluorescent single-walled carbon nanotube/protein microarray fabricated by cell-free synthesis. Nano Lett.11:19-27.
90. Reuel NF, Ahn JH, Boghossian AA. Nanotube array for optical detection of protein-protein interactions. USA patent US10,215,752.
91. Han Z. J, Rider A, Ishaq M, Kumar Sh, Kondyurin A, Bilek M, Levchenko I, Ostrikov K (2013) Carbon nanostructures for hard tissue engineering. RSC Adv 3: 11058-11072.
92. Nemeth Z, Perter N, Szekeres G, Schabikowski M, Schrantz K, Traber J, Pronk W, Hernardi K, Graule TR (2016) Enhanced virus filtration in hybrid membranes with MWCNT nanocomposite. R. Soc. Open Sci 6:181294.

93. Meng X, Stout DA, Sun L, Beingessner RL, Fenniri H, Webster TJ (2013) Novel injectable biomimetic hydrogels with carbon nanotubes. J Biomed Mater. Res 101A:1095- 1102.
94. Sheikhpour M, Golbabaie A, Kasaeian A. (2017) Carbon nanotubes: a review of novel strategies for cancer diagnosis and treatment. Mater. Sci. Eng. C 76:1289-1304.
95. Badrzadeh F, Rahmati-Yamchi M, Badrzadeh K (2016) Drug delivery and nanodetection in lung cancer. Artif. Cells. Nanomed. Biotechnol 44:618-634.
96. Sheikhpour M, Naghinejad M, Kasaeian A, Lohrasbi A, Shahraeinis S.S, Zomorodbakhsh S (2020) A Critical The Applications of Carbon Nanotubes in the Diagnosis and Treatment of Lung Cancer. A Critical Review Intern. J. Nanomedicine 15:7063-7078.
97. Kayat J, Gajbhiye V, Tekade RK (2011) Pulmonary toxicity of carbon nanotubes: a systematic report. Nanomedicine 7:40-49.
98. Kim S, Song K.S, Joo H.J (2010) Determination of cytotoxicity attributed to multiwall carbon nanotubes (MWCNT) in normal human embryonic lung cell (WI-38) line. J. Toxical Environ. Health A 73:1521-1529.
99. Pacurari M, Castranova V, Vallyathan VJ (2010) Single-and multi-wall carbon nanotubes versus asbestos: are the carbon nanotubes a new health risk to humans? J. Toxical. Environ. Health. A 73:378-395
100. Nasser I.M, Abu-Naser SS (2019) Lung cancer detection using artificial neur learning instantaneously al network. Int J Eng Inf Syst 3:17-23.
101. Zhou J, Huang ZA, Kumar U, Chen DD (2017) Review of recent developments in determining volatile organic compounds in exhaled breath as biomarkers for lung cancer diagnosis. AnalChimActa 996:1-9.
102. Shakeel PM, Burhanuddin MA, Desa MI (2019) Lung cancer detection from CT image using improved profuse clustering and deep trained neural networks. Measurement 145:702-712.
103. Stueckle T.A, Davidson DC, Derk R (2017) Effect of surface functionalizations of multi-walled carbon nanotubes on neoplastic transformation potential in primary human lung epithelial cells. Nanotoxicology 11:5:613-624.
104. Gasparri R, Sedda G,. Spaggiari L (2018) The Electronic Nose's Emerging Role in Respiratory Medicine. Sensor 18: 029-3030.
105. Khanmohammadi A, Aghaie A, Vahedi E (2020) Electrochemical biosensors for the detection of lung cancer biomarkers: a review. Talanta 206:120251.
106. Zhou L, Forman HJ, Ge Y (2017) Multi-walled carbon nanotubes: a cytotoxicity study in relation to functionalization, dose and dispersion. Topical in Vitro 42:292-298.
107. Choudhary M, Singh A, Kaur S (2014) Enhancing lung cancer diagnosis: electrochemical simultaneous bianalyte immunosensing using carbon nanotubes-chitosan nanocomposite. Appl. Biochem. Biotechnol 174:1188-1197.
108. Wan Q, Xu Y, Chen X (2018) Exhaled gas detection by a novel Rh-doped CNT

biosensor for prediagnosis of lung cancer: a DFT study. Mol Phys 116: 2205-2212.

109. Aasi A, Aghaei SM, Panchapakesan B (2020) A Density functional theory (DFT) study on the interaction of toluene with transition metal decorated carbon nanotubes: a promising platform for early detection of lung cancer from human breath. Nanotechnolog 12:2818-2829.

110. Park C.H, Schroeder V, Kim B. J (2018) Ionic liquid-carbon nanotube sensor arrays for human breath related volatile organic compounds. ACS Sensors 3: 2432-2437.