Review

Understanding the Potential of WO$_3$ Based Sensors for Breath Analysis

Anna Staerz $^{1,2,†}$, Udo Weimar $^{1,2,†}$ and Nicolae Barsan $^{1,2,*}$

$^1$ Institute of Physical and Theoretical Chemistry (IPTC), University of Tuebingen, Auf der Morgenstelle 15, D-72076 Tuebingen, Germany; anna.staerz@ipc.uni-tuebingen.de (A.S.); upw@ipc.uni-tuebingen.de (U.W.)

$^2$ Center for Light-Matter Interaction, Sensors & Analytics (LISA+), University of Tuebingen, Auf der Morgenstelle 15, D-72076 Tuebingen, Germany

* Correspondence: nb@ipc.uni-tuebingen.de; Tel.: +49-7071-297-8761

† These authors contributed equally to this work.

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Abstract: Tungsten trioxide is the second most commonly used semiconducting metal oxide in gas sensors. Semiconducting metal oxide (SMOX)-based sensors are small, robust, inexpensive and sensitive, making them highly attractive for handheld portable medical diagnostic detectors. WO$_3$ is reported to show high sensor responses to several biomarkers found in breath, e.g., acetone, ammonia, carbon monoxide, hydrogen sulfide, toluene, and nitric oxide. Modern material science allows WO$_3$ samples to be tailored to address certain sensing needs. Utilizing recent advances in breath sampling it will be possible in the future to test WO$_3$-based sensors in application conditions and to compare the sensing results to those obtained using more expensive analytical methods.

Keywords: WO$_3$; breath analysis; gas sensors; SMOX based sensors

1. Introduction

Breath analysis is an extremely interesting application field for gas sensors. The ability to monitor diseases and identify exposure to toxins via breath would revolutionize modern healthcare. It had been known since antiquity that human breath contains information about a person’s health, but it was not until the renaissance of analytical chemistry that the constituents of breath were really be identified [1]. In the 1970s Pauling et al. identified over 250 different substances using gas-liquid partition chromatography [2]. Today, with the help of modern technology, such as electrochemical and infrared detectors or sensitive mass spectrometers, thousands of different compounds have been identified in human breath [1]. As the analytical methods became more sensitive, the need for accurate sampling became apparent. In 1994, using an “alveolar gradient” (the difference between the amount in breath and in air), Phillips et al. tried for the first time to identify which compounds in human breath have an endogenous or exogenous origin [3,4]. As the origins of different biomarkers were discovered, it became clear that the breath sampling method must be customized for different biomarkers and should not influence the composition of the sample. Only once breath is properly sampled can a sensor quantitatively identify a specific biomarker. Today different commercially available breath samplers exist e.g., for NO or ethanol detection. These devices usually couple accurate samplers with sophisticated and expensive analytical methods. For widespread application, more compact and less expensive detector options are needed. Semiconducting metal oxide (SMOX)-based sensors are an attractive option for application in breath analysis devices because they are cheap, compact, robust, show high sensor responses, and allow for real-time measurements. Gaseous breath samples can be analyzed using SMOX-based sensors. Research has been conducted regarding the application of different oxides, e.g., ZnO for toluene [5] and SnO$_2$/In$_2$O$_3$ [6] for ethanol. The review paper by
Righettoni et al. provides a general overview of metal oxides’ potential use for breath analysis [7]. The high humidity (practically ~90%) and the presence of many interfering gases make breath analysis challenging. In 2012, despite the difficult conditions, Righettoni et al. reported the successful detection of acetone in human breath using a sensor based on Si-doped WO$_3$ [8]. Today there is extensive research on WO$_3$-based sensors for breath analysis. Through variation in doping, crystal structure, and morphology, changes in selectivity e.g., high sensor signals to different breath analysis relevant gases, are reported (see Table 1).

Table 1. In this table different breath analysis relevant gases which have reportedly been detected using WO$_3$-based sensors are listed.

| Gas          | Biomarker Origin          | Concentration          |
|--------------|---------------------------|------------------------|
| Ethanol [9–11] | Blood Alcohol Concentration | >130–650 ppm [12] |
| Acetone [13–18] | Diabetes                  | up to 3.73 ppm [19]  |
| NH$_3$ [20–24]    | Renal Failure             | around 4.8 ppm [25]  |
| Toluene [26–29]  | Exposure to Toxin         | >56 ppm                |
|                | Lung Cancer               | 80–100 ppb [28]       |
| Nitric oxide [30–32] | Asthma                   | >30 ppb [31]          |
| H$_2$S [33–35]  | Halitosis                 | >20.6 ppb [36]        |

WO$_3$ has fascinated scholars since the 18th century [37], and is widely used today [38]. In addition to its electrochromic and photocatalytic properties [38], WO$_3$ is a commonly used material for commercial SMOX-based sensors. WO$_3$ is an oxygen-deficient n-type semiconductor. Its resistance decreases when exposed to a reducing gas and increases in the presence of oxidizing gases [39]. Some basic research exists on the interaction of the WO$_3$ surface with gases. For example, it has been shown using operando diffuse reflectance infrared (DRIFT) spectra conducted on sensors that CO reduces the WO$_3$ lattice [40]:

$$CO_{gas} + O_O \rightarrow CO_{gas}^{2+} + V_O + e^-$$  \hspace{1cm} (1)

Akamatsu et al. examined and compared the surface reaction of WO$_3$ with NO$_2$ and NO using DRIFT spectroscopy on WO$_3$ powder [41]. An oxidation of the surface was visible in the DRIFT spectra taken during exposure to NO$_2$, indicating the following reaction [41,42]:

$$NO_{2}^{Gas} + V_O + e^- \rightarrow NO_{Gas}^{Gas} + O_O$$  \hspace{1cm} (2)

A slight reduction was visible with NO [41]. Overall the sensor signals to NO$_2$ were much higher than to NO. The competing surface reactions of NO with NO$_2$ make sensing NO difficult. This example shows that it is important to consider not only how the test gases interact with the surface, but also to understand what effect surface reaction products may have on the sensor. In the case of H$_2$S detection at low temperatures, the presence of atmospheric oxygen is necessary [43]. This is indicative of the oxygen-adsorbed model more closely described by Barsan et al. using the example of SnO$_2$ [44]. Readers are referred to this article for more information on the general working principle of SMOX [44]. A more thorough examination and better understanding of surface reactions will enable a more deliberate and directed optimization of sensors in the future.

WO$_3$ crystals are made up of corner-sharing WO$_6$-octahedrals. The crystal structure of WO$_3$ is temperature dependent, see Table 2 [38]. It has been reported that these phases are reversible [45–47]. In addition, a metastable hexagonal structure has been reported [48]. Different crystal structures can have different sensor characteristics, e.g., sensitivity and selectivity. In addition, like all SMOX-based sensors, the sensor characteristics of WO$_3$ samples can be adjusted through different synthesis paths, resulting in morphology changes, etc. [39].
A short review of the human respiratory system will illustrate the complexity of sampling human breath. During inhalation air enters through the mouth and nostrils into the pharynx, then passes the epiglottis into the trachea, and finally enters the bronchi which branch into bronchioles that end in clusters of alveoli (see Figure 1). The exchange of air with the bloodstream takes place in the alveoli [49]. The total exhaled breath contains a combination of the alveolar air and the air originating from the physiological dead space (air originating from the nasal/oral cavity, pharynx, larynx, trachea and bronchi). Depending on the origin of the biomarker, human blood or physiological dead space, different fractions of breath must be sampled. In the following different biomarkers will be examined. Existing sampling methods and possible coupling with WO₃-based sensors will be described.

![Figure 1. Basic picture of the respiratory system (Wikicommons: Respiratory).](image-url)

**Table 2.** WO₃ has several different stable crystal phases [38,48].

| Crystal Phase | Symmetry | Temperature    |
|--------------|----------|---------------|
| ε-WO₃        | Monoclinic | Under −40 °C  |
| δ-WO₃        | Triclinic | −40–17 °C     |
| γ-WO₃        | Monoclinic | 17–320 °C     |
| β-WO₃        | Orthorhombic | 320–720 °C   |
| α-WO₃        | Tetragonal | Over 720 °C   |
| h-WO₃        | Hexagonal | Metastable    |

2. Biomarkers

2.1. Ethanol (C₂H₅O)

Today, one of the most commonly used breath analysis devices is the breathalyzer. It determines breath alcohol concentration (directly correlates to the blood alcohol level) [50]. Draeger is one of the largest suppliers of small portable breath alcohol detectors. Accurate determination of blood alcohol via breath analysis requires the alveolar air to be sampled [50]. Most of the Draeger systems have a plastic disposable mouthpiece into which the test person must blow evenly and without stopping for several seconds [50]. The mouthpiece measures the temperature and the volume of breath. A certain volume and flow rate, dependent on the age and sex of the test person, is necessary before a
measurement can be completed [50]. More information about the Draeger samplers can be found on the Draeger homepage. The sampling method coupled with an electrochemical sensor gives accurate results [51].

Breathalyzers, for personal use, that couple alveolar breath samplers with SMOX-based sensors are commercially available [52]. In 2015, Rosenberg et al. compared the AL5500 from ACE Instruments (Freilassing, Germany), a detector containing a SMOX-based sensor, to 10 different fuel cell-based analyzers [52]. Overall, the AL5500 was more accurate than approximately half and more precise than two of the other analyzers (see Table 3) [52]. The SMOX-based detector is by far the cheapest of the commercially available alcohol testers. This difference in cost is substantial as small portable inexpensive personal sensors become more marketable (see Table 3).

Table 3. The table shows a comparison of different accuracies/precisions to price/detector type. The higher the accuracy value and the lower the precision value, the better the detector.

| Manufacturer | Model       | Detector Type | Price in € | Accuracy [52] | Precision [52] |
|--------------|-------------|---------------|------------|---------------|----------------|
| ACE          | II Basic    | Fuel Cell     | ~99 a      | 95.7%         | 2.6%           |
| ACE          | III Basic   | Fuel Cell     | ~110 a     | 99.0%         | 1.3%           |
| ACE          | III Premium | Fuel Cell     | ~150 a     | 95.6%         | 2.6%           |
| ACE          | III Premium | Fuel Cell     | ~160 a     | 86.2%         | 29.7%          |
| ACE          | AF-33       | Fuel Cell     | ~100 a     | 97.9%         | 2.6%           |
| ACE          | Alco 5500   | SMOX          | ~36 a      | 96.2%         | 17.9%          |
| ACE          | Pro Med Basic | Fuel Cell   | ~250 b     | 88.5%         | 20.6%          |
| ACE          | One         | Fuel Cell     | ~120 a     | 98.6%         | 2.0%           |
| Draeger      | Alcotest 3000 | Fuel Cell   | ~300 a     | 98.9%         | 2.7%           |
| ACE          | Public V    | Fuel Cell     | ~1400 a    | 98.0%         | 2.8%           |
| ACE          | Stationary Alcohol Analyzer | Fuel Cell | Not Found | 77.1%         | 1.4% |

a Price is that listed on www.Amazon.de on 21 September 2016; b Price found on http://www.alkomat-shop.at on 21 September 2016.

Current research focuses on tailoring SMOX materials, in general, to better detect ethanol in breath [6,53,54]. Research exists on the suitability of WO3-based sensors for breath alcohol detection, see Table 4. Sensors based on pure WO3 respond to the presence of ethanol [9,10]. The selectivity, sensitivity, and stability of SMOX-based sensors are dependent on the material design [55]. Dopants can be used to alter the sensor characteristics of SMOX. Labidi et al. found that doping with Au increased the response of the WO3-based sensors to ethanol, while it decreased as a result of Pd doping [9]. Nayak et al. found that sensors based on WO3-(0.54)SnO2 nanostructures show better sensor signals than those made from pure WO3 and SnO2 [11]. In addition the sensors are also reportedly selective to ethanol in the presence of other volatile organic compounds, e.g., ammonia, acetone, chloroform, hexane, and toluene [11]. Another interesting method for increasing the sensor response of SMOX-based sensors is fluctuation-enhanced sensing (FES). Irradiation with ultraviolet (UV) light has a photocatalytic effect on resistive gas sensors [56]. Through irradiation of Au-NP decorated WO3 with two different lasers it is possible to increase the sensor signals to both low (>20 ppm) and higher (>50 ppm) ethanol concentrations [56]. The effect of humidity on the sensor response was not considered in any of the research. This aspect is highly important for medical diagnostics as human breath is saturated with humidity. It will have to be examined and addressed in the future. Using modern nanoscience, material synthesis can be better controlled at a molecular level [57]. As the field advances, it will be possible to lower power requirements, and to raise the sensitivity and selectivity of materials [57]. In the future, WO3-based sensors can be more ideally tailored for ethanol detection in breath. The commercially available breath alcohol detectors provide a proof of concept that SMOX-based sensors can successfully be coupled with existing breath samplers. Although the concentrations of most other biomarkers in breath are lower (see Table 1), experience with the sampling and sensing of ethanol provides a good foundation for the sensing of other gases in breath.
Table 4. A list of different samples used to detect ethanol.

| Sample                  | Nanostructure                        | Crystal Structure | Ethanol Concentration          |
|-------------------------|--------------------------------------|-------------------|-------------------------------|
| Au:WO$_3$ [9]           | Nanoparticles 40 nm (Crystallites)   | Unknown           | 2% in Dry Air                 |
| WO$_3$ [10]             | Nanorods 50 nm (Diameter)            | Monoclinic WO$_3$ | 12.5–31.25 ppm               |
| WO$_3$-SnO$_2$ [11]     | Nanoplates                           | Monoclinic WO$_3$ | 180–2800 ppm                 |
| Au-NP Decorated WO$_3$ [56]| Nanowires ~5 µm (Length) 60–120 nm (Diameter) | Unknown          | With UV Irradiation 25–75 ppm |

2.2. Acetone ($C_3H_6O$)

Patients with diabetes are either unable to make or effectively use insulin. As a result their body burns fat instead of glucose for energy leading to heightened acetone concentrations in blood [19]. As with ethanol, the concentration of acetone in the alveolar breath reflects the arterial concentration [58]. Deng et al. examined the concentration of acetone in human breath using gas-chromatography-mass-spectroscopy (GC-MS). Sick patients were found to have a concentration of acetone between 1.76 and 3.73 ppmv. In the healthy control group the range was much lower, between 0.22 and 0.80 ppmv [19].

In 2015 Righettoni et al. coupled a sensor based on an ε-phased Si-doped WO$_3$ with a sophisticated breath sampler marketed under the name SOFIA) from the company Loccioni, Angeli di Rosora, Italy [13]. The sampler was similar to those used for ethanol detection. The end tidal and dead volume fractions of the breath are distinguished based on the CO$_2$ concentration [13]. The sampler has two major components, the handheld sensing and sampling unit (SSU) and the portable process control unit (PCU). For more details and pictures of the sampler, readers are referred to the research of Righettoni et al. [13] or the homepage of Loccioni (http://humancare.loccioni.com). The repeated results from individual subjects were similar. The SOFIA breath sampler is modular and further metal oxide gas sensors could easily be integrated [13]. This is important for future research, because numerous other WO$_3$ samples show promise as acetone sensors, see Table 5 For example, Li et al. reported that sensors based on WO$_3$ hollow spheres have much better responses to organic gases than sensors made from traditional WO$_3$ particles [14]. The sensors based on the hollow spheres from Li et al. were, however, not selective and also showed high signals to ethanol, CS$_2$, and other organic gases [14]. In 2014, Choi et al reported that Rh loading increased the sensor response and selectivity of these WO$_3$ hollow spheres to acetone. The effect of humidity on the sensor responses was also decreased through Rh loading [15]. Rhodium is believed to influence the surface reactions during sensing. Due to its strong affinity for water, rhodium is believed to suppress the reaction between the sensing surface and humidity, which explains why the sensor response is no longer humidity dependent [15]. In addition to changing the surface reactions, dopants are reported to alter basic material characteristics. Like Righettoni et al., Wang et al. reported the stabilization of ε-WO$_3$ above room temperature using dopants [16,17]. The results of Righettoni et al. are shown in Figure 2. Wang et al. used Cr to stabilize the ε-phase, which is usually only stable below −40 °C, at RT. The addition of Cr is reported to introduce distortions into the WO$_3$ matrix repelling the tungsten atoms from the centric positions in the octahedral WO$_6$. Cr-doped (10 at%) WO$_3$ showed high signals and selectivity to acetone, and against ethanol, methanol, NO, NO$_2$, NH$_3$, and CO. The acentric structure of the ε-phase is thought to be highly selective to acetone [17].

Recently, methods have been developed to better control and optimize doping, for example by Kim et al. who created sensors based on Pt-functionalized WO$_3$ [18]. It is known that through the agglomeration of the catalytic nanoparticles, the sensing properties decrease. Kim et al. encapsulated the Pt nanoparticles in an apoferritin template to prevent large agglomerates. Using this method they attained a very narrow size distribution for the nanoparticles, between 1 and 3 nm [18]. The sensors
showed high signals to acetone and low signals to many other breath analysis relevant gases, e.g., H2S, toluene, ethanol, and ammonia. The high humidity of human breath was taken into consideration, and all measurements were done at 90% RH [18].

![Image](image_url)

**Figure 2.** (A) The response of WO3-based sensors at 400 °C to 600 ppb of acetone are depicted with respect to Si-content and relative background humidity. A sensor based on 10% mol Si-doped WO3 is optimal. (B) Using this sensor it was possible to detect ultralow concentrations of acetone (20–90 ppb) in 90% RH [16]. The figure is reprinted from [16]. Copyright 2010 American Chemical Society.

| Sensor                | Nanostructure          | Crystal Structure       | Acetone Concentration                        |
|-----------------------|------------------------|-------------------------|---------------------------------------------|
| 10 mol% Si:WO3 [16]   | 12 nm                  | Monoclinic ε-WO3        | 100–600 ppb in Dry Air to 90% RH             |
| WO3 [14]              | Hollow Spheres 400 nm (Diameter) 30 nm (Shell) 12 nm (Crystallites) | Monoclinic (JCPDS card no. 72-0677) | 50–500 ppm                                  |
| Rh-Loaded WO3 [15]    | Hollow Spheres 25 nm (Shell) | Orthorhombic β-WO3     | 0.2–20 ppm in Dry Air up to 80% RH           |
| 20 at% Cr-Doped WO3   | Nanoparticles 20 nm (Crystallites) | ε-WO3                  | 0.2–1 ppm                                   |
| 0.022 wt% Pt Loaded WO3 [18] | Nanoparticles 28 nm (Crystallites) | Not Defined            | 0.1–5 ppm                                   |

Righettoni et al. coupled the sophisticated breath sampler with Si-doped WO3 to detect acetone as a proof of concept [13]. In the future additional measurements can be done using this modular sampling device to examine which samples of WO3 are best suited to detect acetone in breath. Furthermore, the sampler can be used to examine the breath analysis of other biomarkers present in alveolar air, e.g., ammonia and toluene.

2.3. Ammonia (NH3)

Davies et al. found that heightened concentrations of ammonia in human breath are characteristic of end stage renal failure [25]. Urea accumulates in the blood as a result of kidney failure [59]. In the gastrointestinal tract the excess urea is then decomposed into ammonia [59]. Saliva bacteria can also decompose excess urea [59], presenting the possibility of contamination. The ammonia concentration in the alveolar air in patients suffering from renal disease is in the ppm range [25].

WO3 based samples show promise for use in breath ammonia detection, see Table 6. As early as 1992, Maekawa et al. reported that Au-doped WO3 samples show good signals to NH3 [20].
The measurements were done in air and the best results were attained with sensors operated at 450 °C. Sensors based on their Au-loaded sample showed better responses to NH$_3$ than sensors based on pure WO$_3$, as well as samples doped with Rh, Ru, Pd, and Ag. No characterization of the material was published [20], so no information is present on the crystal phase of the sample or how exactly the sample was doped.

### Table 6. A list of different samples used to detect ammonia.

| Sensor | Nanostructure | Crystal Structure | Ammonia Concentration |
|--------|---------------|------------------|-----------------------|
| 0.4 wt% Au loaded WO$_3$ [20] | Unknown | Unknown | 0.001–100 ppm |
| WO$_3$ [21] | Carnation 500 nm (Length) 80 nm (Diameter) | Hexagonal h-WO$_3$ | 10–100 ppm |
| WO$_3$ [22] | Nanorod 30–100 nm (Diameter) 100–300 nm (Length) Nanoparticles 10–40 nm | Hexagonal h-WO$_3$ | 80–200 ppm |
| Cu and V Modified WO$_3$ [24] | Nanoparticles 19–64 nm | Monoclinic γ-WO$_3$ and Triclinic δ-WO$_3$ | 500 ppm |

In 2000, Llobet et al. reported for the first time that sensors based on pure WO$_3$ respond to ammonia. When operated at 300 °C, the sensors were selective to ammonia in the presence of toluene, ethanol, and benzene. The base resistance of the samples was found to change as a result of background humidity; the effect on the sensor response was not evaluated. The crystal phase of the WO$_3$ samples was not determined [21]. Recently, however, Takács et al. and Wang et al. reported that the metastable hexagonal phase of WO$_3$ shows very good sensor responses to ammonia [22,23]. Wang et al. report that through acid precipitation, it is possible to synthesize the metastable hexagonal structure. Under the same sensing conditions the signals of sensors based on the hexagonal sample were higher than those based on γ-WO$_3$ (monoclinic) [23]. Takács et al. synthesized h-WO$_3$ samples with different morphologies [22]. The nanorods showed better responses than the carnation-formed particles [22]. The decrease in the resistance of WO$_3$-based sensors is caused by the NH$_3$ oxidation on the surface of the metal oxide grains [60]. A possible oxidation product of NH$_3$ is NO [61]. NO can react to NO$_2$ in the presence of atmospheric oxygen. WO$_3$ is known to respond to the NO$_2$ [41]. Jiménez et al. reported signal instability as a result of the ammonia oxidation and the NO$_2$ adsorption, i.e., reduction [24]. Epifani et al. was able to eliminate the signal instability by measuring at higher temperatures and through loading with Cr [60]. Epifani et al. reports better sensor responses for sensors based on Cr-doped WO$_3$ than those based on pure WO$_3$. Based on X-ray diffraction (XRD) measurements it was determined that the WO$_3$ sample is in the δ monoclinic phase and that the Cr is predominantly interstitially incorporated [60]. In addition to catalyzing the oxidation of NH$_3$, interstitial Cr decreased the number of oxygen vacancies, lessening the adsorption sites of NO$_2$ [60]. This is a perfect example of how advancements in synthesis methods have allowed researchers to address issues by “tuning” materials.

The reactivity of NH$_3$ makes sampling particularly challenging [62]. A modular breath sampler from Loccioni, Angeli di Rosora, Italy was used. Solga et al. found that for reproducible results of exhaled breath ammonia, the temperature of the breath sampler, the mode of breathing, and mouth pH must be controlled [62]. For more details on the difficulty of detection NH$_3$ in breath please refer to the work by Solga et al. [62]. Although the results were promising, there are important limitations. In particular, the study was done on only one subject and the role of diet or testing time was not considered [62].
In the case of exhaled NH$_3$, an optimal sampling protocol must still be developed and tested. Only once sampling is accurate and reproducible will it be possible to examine if and which sensors based on WO$_3$ are optimal for exhaled NH$_3$ monitoring.

2.4. Toluene (C$_7$H$_8$)

Biomarkers in breath can not only be used to monitor diseases but also to detect exposure to hazardous substances. Toluene is a commonly used colorless industrial solvent that has neurotoxic and narcotic properties [63]. The Occupational Safety and Health Administration of the United States (OSHA) has limited toluene exposure to an 8-h weighted average of 200 ppm (1910.1000 Table Z-2). Carlson et al. report that roughly 28% of the inspired toluene concentration is still present 30 min after exposure in the alveolar air [64]. This would be over 56 ppm if toluene concentrations over the OSHA limit are present. Sensors based on differently modified WO$_3$ samples are reported to show good signals to toluene within the relevant concentration range [26,27], see Table 7. For example, Miao et al. report that the sensors based on anisotropic WO$_3$·H$_2$O nanoplatelets operated at 300 °C show high signals to toluene (between 10 and 100 ppm) [26]. The nanoplatelets were synthesized using a hydrothermal synthesis with malic acid. The anisotropic nanoplatelets which have more of the (0 1 0) facet, show higher responses to toluene than the less anisotropic nanocubes. The explanation provided by the authors theorizes that during the adsorption of toluene on the (0 1 0) facet of orthorhombic WO$_3$·H$_2$O more electrons are extracted from the surface than through adsorption on the (1 0 0) and (0 0 1) facets [26]. Different dopants have also been reported to positively affect the sensor characteristics of WO$_3$ for toluene. Vallejos et al. increased the sensor response (for 20–100 ppm of toluene) of WO$_3$ nanoneedles through functionalization with Fe$_2$O$_3$ and Pt [27], see Figure 3.

Table 7. A list of different samples used to detect toluene.

| Sensor                        | Nanostructure              | Crystal Structure          | Toluene Concentration |
|-------------------------------|----------------------------|----------------------------|-----------------------|
| WO$_3$·H$_2$O [26]            | Nanoplates                 | Orthorhombic β-WO$_3$      | 10–200 ppm            |
|                               | 20–30 nm (Thickness)       |                            |                       |
|                               | 150–200 nm (Length)        |                            |                       |
| Fe$_2$O$_3$@WO$_3$·x [27]     | Nanoneedles                | Monoclinic ([P21/n], ICCD card no. 72-0677) | 20–100 ppm            |
|                               | 50–100 nm (Diameter)       |                            |                       |
|                               | ~10 µm (Length)            |                            |                       |
| 0.5 wt% Pd-nanoparticles/0.5 wt% Pd-embedded WO$_3$ [28] | Nanofibers                | Monoclinic (PDF#43-1035)  | 1–5 ppm               |
|                               | 300–600 nm (Diameter)      |                            |                       |
|                               | 17.4–32.59 nm (Crystallites)|                           |                       |
| Pd loaded WO$_3$ [29]         | Nanofibers                 | Unknown                    | 0.1–5 ppm in 90% RH   |
|                               | 200–300 nm (Diameter)      |                            |                       |

By functionalizing WO$_3$ nanofibers with Pd and measuring at 350 °C, Kim et al. detected between 1 and 5 ppm in a background of 90% RH [28]. As a result the sensor response to acetone and H$_2$S drastically decreased. Choi et al. were able to further increase the positive effect of Pd doping on the sensing characteristics by using a new catalyst functionalization method [29]. Thin-walled Pt and Pd were selectively embedded at the pore sites of electrospun WO$_3$. Choi et al. were able to get visible sensor signals to as low as 100 ppb toluene [29]. This was achieved by using polystyrene colloid templates [29].

This concentration range is lower than expected in breath after prolonged exposure to high concentrations of toluene. In fact, it is almost low enough to be suitable for a different sensing objective. Heightened concentrations of toluene are found in patients suffering from lung cancer [28]. The survival rate of lung cancer is very low compared to other cancers because it is often diagnosed in late stages (American Cancer Society Cancer Facts and Figures American Cancer Society). Detection using breath analysis would allow lung cancer to be more easily diagnosed and could potentially raise
the survival rate. The exhaled breath of lung cancer patients contains approximately 80–100 ppb of toluene (two- or three-fold higher than the concentrations found in healthy people) [28].

![Figure 3. STEM and HRTEM of the WO$_{3-x}$ nanoneedles functionalized with Fe$_2$O$_3$. The figure is reprinted with permission from [27]. Copyright 2015 American Chemical Society.](image)

As the understanding of WO$_3$-based sensors grows, it may be possible to not only detect exposure to harmful concentrations of toluene but to also screen patients inexpensively for lung cancer. In 2012, Itoh et al. examined how aging affects WO$_3$-based sensors’ ability to detect toluene. They found that the signals of non-aged sensors to toluene were humidity-dependent while those that underwent a high-moisture heat treatment (aging) showed stable sensor responses. The moist heat treatment is believed to promote the adsorption of water molecules resulting in the formation of hydroxyl groups that block the adsorption sites of water, therefore, eliminating the effects of humidity [65]. This is an example of how knowledge about how sensing takes place could be useful for optimizing sensors in the future.

The sensing of toluene in human breath via WO$_3$-based sensors, both to identify elongated exposure to the toxin and to monitor disease, shows great promise.

2.5. Nitrogen Monoxide (NO)

Sampling of breath for NO detection is very difficult because different technical sampling factors can drastically alter the results [66]. Nitrogen monoxide is produced in the body during the enzymatic oxidation of L-arginine [67]. Fractional exhaled NO (FENO) is a biomarker for inflammation [68]. Concentrations of NO over 50 ppb in breath indicate airway eosinophilia [69]. Patients with stable asthma are reported to have NO breath concentrations between 20 and 25 ppb [69]. Normal nasal NO concentrations of children are very high, around 450 ppb [70]. This makes it extremely important to prevent nasal air contamination during sampling [71]. In addition it was found that the ambient NO concentration can be in the ppb range [70]. Due to the high risk of falsified results through contamination, standardization of measurements was critical so that NO measurements could be
compared or even reproduced [69]. This standardization is believed to be a key reason why, in 2003, the FDA approved a NO breath detector from Aerocrine (Solna, Sweden) as a medical diagnostic tool [71,72].

The breath sampling used by the Aerocrine detector is highly sophisticated [73]. The inhaled air is scrubbed to prevent contamination through ambient NO. A flow control keeps the exhalation rate constant at 50 mL/s and closure of the velum prevents contamination with nasal NO. The exhalation is set to 10 s and the NO plateau is between 7 s and 10 s [73] to ensure accurate sampling. The NIOX MINO from Aerocrine couples this sampling method with an amperometric liquid electrolyte sensor. Although the device is relatively compact (230 mm × 128 mm × 96 mm) the analyzer costs upwards of $2000 (listing number 1491060 on dotmed.com). For more information please refer to the homepage of Aerocrine. This cost and size could potentially be reduced using a SMOX-based sensor. The use of different WO₃ based samples appears promising for the detection of breath NO, see Table 8.

| Sensor | Nanostructure | Crystal Structure | NO Concentration |
|--------|---------------|-------------------|-----------------|
| WO₃ [30] | Nanoparticles 15–20 nm | Monoclinic γ-WO₃ | 0.3–1 ppm |
| WO₃ [31] | Villi (Single Crystalline) 40–50 nm (Diameter) | Monoclinic WO₃ | 0.2–1 ppm in 80% RH |
| WO₃ with a Filter and Oxidizing Agent (KMnO₄) [32] | Unknown | Unknown | 60 ppb |

Gouma et al. reported that a stoichiometric phase pure (monoclinic) WO₃ sample showed a high sensor response to NO and low responses to other breath analysis-relevant gases (see Figure 4) [30]. A NO concentration range between 1 ppm and 300 ppb in dry air was examined. Moon et al. reported selective sensors based on 1D villi-like nanostructured WO₃ with which they could successfully detect down to 200 ppb of NO in a background humidity of 80% RH [31].

**Figure 4.** Gouma et al. has found that the gas selectivity is strongly dependent on the crystal phase. (A) A raman spectrum taken of the monoclinic γ-WO₃ sample; (B) A XRD spectrum taken of the monoclinic γ-WO₃ sample; (C) Gas sensing response of the monoclinic γ-WO₃ sample to 10 ppm NO, 10 ppm acetone, 10 ppm isoprene, 50 ppm ethanol, 50 ppm methanol, and 50 ppm CO in synthetic air; (D) Gas sensing response of the monoclinic γ-WO₃ sample to 1 ppm, 500 ppb, and 300 ppb NO in synthetic air. Reprinted from [30] with the permission of AIP Publishing.
In addition to selectivity and the effect of humidity, the effect of NO$_2$ on the detection of NO must be considered. During sensing NO is oxidized to NO$_2$. Many SMOX-based sensors show a sensor response to NO$_2$ [41]. NO is a reducing gas while NO$_2$ is an oxidizing gas, meaning the sensor response is opposite. An overlapping sensor response (of equal strength) to NO and NO$_2$ would result in no signal or a false negative. Fruhberger et al. addressed this issue by using a permanganate oxidizing agent and a Pt/Al$_2$O$_3$ catalyst to convert NO to NO$_2$ [32]. They then detected the NO$_2$ concentration using WO$_3$-based sensors. The WO$_3$ sample used by Fruhberger et al. showed practically no sensor response to NO (eliminating any cross-sensitivity of the sensor to NO produced during the sensing of NO$_2$) [32].

Through standardization it is now possible to sample breath precisely so that even the very low concentrations of NO can be accurately detected. This shows how important it is to understand the origin of the biomarker and sources of possible contamination during sampling. Through proper regulation, breath sampling is a viable option for medical diagnostics. To minimize device cost and size, different possible detectors, for example WO$_3$-based sensors will need to be researched.

2.6. Hydrogen Sulfide (H$_2$S)

Volatile sulfur compounds (VSCs) produced by oral bacteria are responsible for 90% of malodour [74]. Of all of the gases found in human breath VSCs stand out due to their penetrating stench which resembles the smell of rotten eggs. People with bad breath do not notice it themselves, but others are acutely aware of the smell. The concentration of H$_2$S in patients suffering from halitosis (bad breath) is ca. 20.6 ppb [36]. Unlike the previously considered biomarkers, the origin of most VSCs in breath is the oral cavity. Recently, breath and in-mouth sampling were compared. Both methods yield similar results for VSCs [75]. The results indicate that sampling using a syringe is adequate for the detection of malodorous compounds in breath [75]. The suitability of WO$_3$-based sensors for VSCs is well researched for the example of H$_2$S. It has been known for over 20 years that sensors based on WO$_3$ show high signals to H$_2$S [33]. See Table 9 for an overview of promising WO$_3$ samples for the detection of H$_2$S. Mixed tetragonal and monoclinic phase samples have been found to be especially suited for the detection of H$_2$S. For example, Solis et al. report that the detection of 10 ppm H$_2$S at room temperature is possible using sensors based on such mixed-phase samples. The conductance of the film increased three orders of magnitude within 10 min, the very slow recovery time (hours) was increased using a short heating pulse to 530 K for 1 min [76]. Reyes et al. utilized advanced reactive gas deposition to make nanocrystalline films of WO$_3$ out of metallic tungsten and oxygen [43]. Overall, Reyes et al. found that ambient oxygen is vital for the detection of H$_2$S at low operating temperatures [43]. This information could be useful for tailoring H$_2$S sensors in the future. In 2008, Rout et al. even reported that sensors based on WO$_{2.72}$ nanowires are good candidates for sensing concentrations as low as 10 ppm of H$_2$S [34]. The response to H$_2$S was not significantly affected by humidity under 60% RH [34].

Using sensors based on graphite (GR)- and graphene oxide (GO)-functionalized WO$_3$ hemitubes, Choi et al. reported increased sensor signals and were also able to detect levels as low as 1 ppm of H$_2$S [35] (see Figure 5). The sensors based on graphite (0.1 wt%)-WO$_3$ functionalized hemitubes showed higher signals than those containing graphene oxide (see Figure 5). The sensor signals to acetone, however, also increased as a result of functionalization, indicating limited selectivity [35]. Sekhar et al. found that by using WO$_3$ nanoplatelets, they could attain a high sensor response to just 1 ppm of H$_2$S. At higher concentrations they reported that variations in background humidity had a negligible effect on the sensor response [34].

In addition to H$_2$S, other VSCs, such as methyl mercaptan and dimethyl sulfide, are responsible for bad breath [77]. This makes breath analysis difficult for halitosis due to cross-sensitivity. Today commercial options exist, for example the OralChroma™ device from Fis Inc. (Hyogo, Japan) that couples a small gas chromatograph with SMOX-based sensors. Choi et al. used Pt-infiltrated block copolymer microparticles to functionalize macroporous WO$_3$ nanofibers. They created a sensor array
containing sensors based on pristine WO₃, 0.042 wt% Pt-WO₃, and 0.008 wt% Pt-WO₃. Using principal component analysis, Choi et al. were able to distinguish H₂S, methyl mercaptan, acetone, and toluene within a breath analysis relevant concentration range (1–5 ppm) [78]. Using a sensor array it may be possible to accurately detect halitosis in the future. The next vital step will be to examine what effect the different VSCs have on SMOX-based sensors. Only then can sensors be selected. In the case of an array in addition to examining each single sensor the ideal interplay between sensors must also be achieved.

![Figure 5](image)

**Figure 5.** The graphite (0.1 wt%)-WO₃ (A) functionalized hemitubes showed high sensor signals to 2 ppm H₂S than the graphene oxide (0.1 wt%)-WO₃ (B) functionalized hemitubes. All test gases were measured at 2 ppm and a background humidity of 85%–95%. The figure is reprinted with permission from [35].

In the future, perhaps through morphology control, doping, and a clever combination of WO₃-based sensors, chromatographs may no longer be necessary to detect halitosis.

### Table 9. A list of different samples used to detect H₂S.

| Sensor          | Grain Size           | Crystal Structure                | H₂S Concentration |
|-----------------|----------------------|----------------------------------|-------------------|
| WO₃ [33]        | Unknown              | Unknown                          | 10–100 ppm        |
| WO₂₋₀.₇ [34]    | Nanowires (Single Crystal) 5–15 nm (Diameters) | Monoclinic (JCPDS no: 36-101) | 1–1000 ppm        |
| Graphene Functionalized WO₃ [35] | Hemitubes 200–300 nm (Crystallites) | Monoclinic (JCPDS no: 43-1035) | 1–5 ppm           |
| WO₃ [76]        | Nanoparticles ~11 nm (Crystallites) | Monoclinic and Tetragonal WO₃   | 10 ppm            |
| WO₃ [43]        | Nanoparticles ~10 nm (Crystallites) | Monoclinic and Tetragonal       | 10 ppm            |
| Pt Functionalized WO₃ [78] | Nanofiber ~900 nm (Diameter) | Unknown                          | 1–5 in Dry Air to 95% RH |

3. **Conclusions**

It has been known since antiquity that human breath contains information about a person’s wellbeing. As analytical methods developed, it became possible to identify, and even quantify, gaseous components in breath. As the detection methods became more precise, it was recognized that, for breath analysis, more exact sampling methods were necessary. In the last few years great progress has been made in breath sampling and, now accurate modular samplers exist for different biomarkers. Today accurate sampling and detection is possible. The next step in breath analysis will be towards miniaturization and cost reduction. For this, SMOX-based sensors are an attractive option because they are small, inexpensive, robust, and sensitive.
In particular, WO$_3$-based sensors show promise for implementation in breath analysis. WO$_3$ is already a widely used material for commercially available SMOX-based sensors. A survey of existing research revealed that WO$_3$ shows high sensor responses to several breath analysis-relevant gases, e.g., acetone, H$_2$S, and toluene. Modern material science methods for the synthesis of WO$_3$ show promise for increasing the selectivity and sensitivity of sensors. Through functionalization with different additives it was possible to tailor different WO$_3$ materials for the detection of certain gases within specific concentration ranges. Despite promising results within laboratory settings for different WO$_3$ samples, several issues continue to remain unresolved, in particular, cross-sensitivity to water and other gases in breath. Using existing modular breath samplers WO$_3$-based sensors can be tested in application conditions, allowing the accuracy and precision of WO$_3$-based sensors to be compared to more expensive analytical methods. Through the continued advances of material science more modification possibilities will be developed to tailor WO$_3$ samples. By better understanding how sensing works and what factors play a role, WO$_3$ materials can be strategically altered. For example certain crystal phases appear to be better suited for certain gases. This basic understanding of sensing with WO$_3$ is still relatively limited and will need to be further expanded in the future. Once the sensors are comparable in quality to more sophisticated analytical methods, they can be used for breath analysis.

In summary, as the digitalization era continues, and the application of sensors becomes more widespread, the role of SMOX sensors will increase. In this review, the viability of WO$_3$-based sensors for breath analysis was explored. Although currently no WO$_3$-based sensors are commercially available for medical diagnostics, their use in the future seems highly promising. The use of WO$_3$ based sensors will allow for the production of small, inexpensive, and portable health screening devices.

Conflicts of Interest: The authors declare no conflict of interest.

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