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Exhaled breath analysis: The new interface between medicine and engineering

Alquam Mashir^a and Raed A. Dweik^{a,b,*}

^aDepartment of Pathobiology/Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, United States

^bDepartment of Pulmonary and Critical Care Medicine/Respiratory Institute, Cleveland Clinic, Cleveland, OH 44195, United States

Abstract

Exhaled breath testing is becoming an increasingly important non-invasive diagnostic method that can be used in the evaluation of health and disease states in the lung and beyond. Potential advantages of breath tests over other conventional medical tests include their non-invasive nature, low cost, and safety. To advance in this area further, however, there has to be a close collaboration between technical experts and engineers who have devices looking for clinical application(s), the medical experts who have the clinical problems looking for a test/biomarker that can be helpful in diagnosis or monitoring, and industry/commercial experts who can build and commercialize the final product.

Keywords

Exhaled breath; Volatile organic compounds; Medicine; Engineering

As we breathe out we expel thousands of molecules into the air. When correctly captured and analyzed these molecules make a “breath-print” that can tell a lot about the state of our health [1]. The synergies between medicine and engineering in this area have the potential to revolutionize the way we monitor health and disease and allow us to provide personalized care for each individual based on his or her own “breath-print” [1].

The current conditions in the breath analysis field could not be better: the science is mature, the technology is exploding, industry is interested, and the medical community is embracing this noninvasive method of testing. Thanks to major engineering and breakthroughs in the 20th century including new technologies (infrared, electrochemical, chemiluminescence, and others) and the development of very sensitive modern mass spectrometry (MS), gas chromatography (GC) and gas chromatography mass spectrometry (GC–MS) instruments, we can now identify thousands of unique substances in exhaled breath. These substances include elemental gases like nitric oxide and carbon monoxide and a multitude of volatile organic compounds (Table 1). Furthermore, exhaled breath also carries aerosolized droplets collected as “exhaled breath condensate” that have non-volatile compounds that can be captured by a variety of methods and analyzed for a wide range of biomarkers from metabolic end products to proteins to a variety of cytokines and chemokines and the possibilities continue to expand

[2,3]. With various technologies available to test for any and all of these exhaled breath components (Table 2), several methods are now in clinical use or about ready to enter that arena. Breath analysis is now used to diagnose and monitor asthma, to check for transplant organ rejection, and to detect lung cancer, to mention a few applications. Thus, the 21st century promises to deliver a revolution in our understanding of the constituents of exhaled breath and the advancement of the field of breath analysis and testing.

While the concept of using breath analysis as a medical test may be a surprise to engineering professionals, it is an easier to accept fact for medical professionals. The history of medicine is replete with discoveries that led to our current day understanding of the diagnostic potential of exhaled breath. Hippocrates described feto oris and feto hepaticus in his treatise on breath aroma and disease, Lavoisier and Laplace in 1784 showed that respiration consumes oxygen and eliminates carbon dioxide [4], Nebelthau in mid 1800s showed that diabetics emit breath acetone [5], and Anstie in 1874 isolated ethanol from breath (which is the basis of breath alcohol testing today) [6]. A major breakthrough in the scientific study of breath started in the 1970s when Linus Pauling demonstrated that there is more to exhaled breath than the classic gases of nitrogen, oxygen, carbon dioxide and water vapor. Using gas-liquid partition chromatography analysis, Pauling demonstrated the presence of 250 substances in exhaled breath [7].

The upward trajectory of the breath analysis field and related product development and manufacturing was very clear after a three-day Breath Analysis Summit hosted at the Cleveland Clinic in November 2007. The Summit was perhaps a turning point in the field as it attracted participants from 22 countries and 18 states [1]. The Summit brought together industry executives and entrepreneurs with scientists, engineers, and clinicians to discuss key trends, future directions, and upcoming technologies in breath analysis and medicine. The major focus of the Summit was on new technologies and medical applications and to address the major hurdles that faced this field as it transitions from the laboratory to clinical testing. Topics included exhaled nitric oxide, exhaled breath condensate, electronic nose and sensor arrays, mass spectrometry and bench top instrumentation, and cutting edge sensor technologies. Medical applications that were covered included asthma, COPD, pulmonary hypertension, other respiratory diseases, gastrointestinal diseases, occupational diseases, critical illness, and cancer [1]. The major conclusions of the summit were clear. Multidisciplinary collaboration is the only way to keep moving the field forward and to allow breath analysis and testing to achieve their potential and hold their rightful place among other accepted medical tests. The members of this team need to include scientist and engineers who have the technical knowledge and can build the appropriate devices, medical professionals who understand the disease processes and know the areas of greatest medical need, as well as industry to build devices for testing and later distribute the successful ones to a national and worldwide healthcare market. This is where the synergy between medicine and engineering is at its best.

Most likely to succeed in these endeavors are integrated multidisciplinary teams that join colleagues in industry and academia for the focused purpose of rapid development and commercialization of urgently needed non-invasive devices that will guide the diagnosis and monitoring of different diseases by exhaled breath testing. While each of these team members can independently make major contributions to their respective fields, the potential for having them work together is enormous and cannot be overstated. The process could start with a clinical need as identified by a physician; the appropriate sensor(s) can then be developed by team members with biochemical and engineering expertise. It is not uncommon, however, for the process to start from the engineering end when a new technology or device is found to be particularly sensitive or specific to detect a certain molecule or group of molecules and the medical team is approached for a possible medical application of this new technology. Regardless of where the process starts, however, it is likely to need continuous work and

refinement from all involved. Once a sensor is developed a prototype is built and validated by an industrial partner and sent to the medical team for human testing. Depending on the human test results, the device may be sent back for further refinement and retesting. This process/cycle is repeated until a sensor/device achieves its expected goals. Once a device is ready, it goes back to the industry partner(s) for production on larger scale for clinical trials that will be needed for regulatory approval.

One great example of how the collaboration between technical, medical, and commercial professionals has resulted in a clinically useful tool is the measurement of exhaled nitric oxide (NO) in exhaled breath for monitoring airway inflammation. The advent of chemiluminescence analyzers in the early 1990s allowed the detection of low (ppb) levels of NO in exhaled breath [8]. This was quickly followed by the observation that patients with asthma had higher than normal levels of NO in their exhaled breath that was later linked to eosinophilic airway inflammation [9,10]. Standardization of the gas collection methods and measurement techniques allowed the industry to build the next generation of analyzers suitable for use in the clinical setting [11-14]. In 2003 the FDA approved the first desktop NO analyzer for monitoring airway inflammation in asthma [15]. This new test has evolved into an important tool in the modern management of asthma and airway inflammation. The use of exhaled NO in monitoring asthma is useful for several reasons. It is non-invasive, it can be performed repeatedly, and it can be used in children and patients with severe airflow obstruction where other techniques are difficult or not possible to perform. Exhaled NO may also be more sensitive than currently available tests in detecting airway inflammation which may allow more optimum therapy [13,16-22].

As breath analysis offers a window on lung physiology and disease, exhaled breath testing is becoming an increasingly important non-invasive diagnostic method that can be used in the evaluation of health and disease states in the lung and beyond. Potential advantages of breath tests over other conventional medical tests include their non-invasive nature, low cost, and safety. This is an area where the modern day advances in technology and engineering meet the ever expanding need in medicine for more sensitive, specific and non-invasive tests which makes this area a major front in the interface between medicine and engineering.

References

1. Dweik RA, Amann A. *J Breath Res* 2008;030301.
2. Horvath I, Hunt J, Barnes PJ, Alving K, Antczak A, Baraldi E, Becher G, van Beurden WJ, Corradi M, Dekhuijzen R, Dweik RA, Dwyer T, Effros R, Erzurum S, Gaston B, Gessner C, Greening A, Ho LP, Hohlfeld J, Jobsis Q, Laskowski D, Loukides S, Marlin D, Montuschi P, Olin AC, Redington AE, Reinhold P, van Rensen EL, Rubinstein I, Silkoff P, Toren K, Vass G, Vogelberg C, Wirtz H. *Eur Respir J* 2005;26:523-548. [PubMed: 16135737]
3. Grob NM, Aytekin M, Dweik RA. *J Breath Res* 2008;037004.
4. Duveen DI, Klickstein HS. *Bull Hist Med* 1955;29:164-179. [PubMed: 14363986]
5. Hubbard RS. *J Biol Chem* 1920;43:57-65.
6. Baldwin AD. *Am J Public Health* 1977;67:679-681. [PubMed: 327838]
7. Pauling L, Robinson AB, Teranishi R, Cary P. *Proc Natl Acad Sci USA* 1971;68:2374-2376. [PubMed: 5289873]
8. Gustafsson LE, Leone AM, Persson MG, Wiklund NP, Moncada S. *Biochem Biophys Res Commun* 1991;181:852-857. [PubMed: 1721811]
9. Kharitonov SA, Yates D, Robbins RA, Logan-Sinclair R, Shinebourne EA, Barnes PJ. *Lancet* 1994;343:133-135. [PubMed: 7904001]
10. Persson MG, Zetterstrom O, Agrenius V, Ihre E, Gustafsson LE. *Lancet* 1994;343:146-147. [PubMed: 7904005]
11. *Am J Respir Crit Care Med* 1999;160:2104-2117. [PubMed: 10588636]

12. Am J Respir Crit Care Med 2005;171:912–930. [PubMed: 15817806]
13. Grob NM, Dweik RA. Chest 2008;133:837–839. [PubMed: 18398112]
14. Grob NM, Dweik RA. J Breath Res 2008;037002.
15. Gill M, Graff GR, Adler AJ, Dweik RA. J Asthma 2006;43:731–734. [PubMed: 17169823]
16. Dweik RA. Cleve Clin J Med 2001;68:486, 488, 490, 493. [PubMed: 11405609]
17. Dweik RA, Comhair SA, Gaston B, Thunnissen FB, Farver C, Thomassen MJ, Kavuru M, Hammel J, Abu-Soud HM, Erzurum SC. Proc Natl Acad Sci USA 2001;98:2622–2627. [PubMed: 11226289]
18. Guo FH, Comhair SA, Zheng S, Dweik RA, Eissa NT, Thomassen MJ, Calhoun W, Erzurum SC. J Immunol 2000;164:5970–5980. [PubMed: 10820280]
19. Khatri SB, Ozkan M, McCarthy K, Laskowski D, Hammel J, Dweik RA, Erzurum SC. Am J Respir Crit Care Med 2001;164:1844–1848. [PubMed: 11734434]
20. Khatri SB, Hammel J, Kavuru MS, Erzurum SC, Dweik RA. J Appl Physiol 2003;95:436–440. Discussion 435. [PubMed: 12576414]
21. Dweik, RA. Disease Markers in Exhaled Breath: Basic Mechanisms and Clinical Applications. In: Marczin, N.; Yacoub, MH., editors. NATO Science Series. IOS Press; Amsterdam, Netherlands: 2002. p. 159–166.
22. Ozkan M, Dweik RA. Clin Pulmonary Med 2001;8:199–206.
23. Buszewski B, Keszy M, Ligor T, Amann A. Biomed Chromatogr 2007;21:553–566. [PubMed: 17431933]
24. Barker M, Hengst M, Schmid J, Buers HJ, Mittermaier B, Klemp D, Koppmann R. Eur Respir J 2006;27:929–936. [PubMed: 16455833]
25. Miekisch W, Schubert JK, Noeldge-Schomburg GF. Clin Chim Acta 2004;347:25–39. [PubMed: 15313139]
26. Phillips M, Cataneo RN, Ditkoff BA, Fisher P, Greenberg J, Gunawardena R, Kwon CS, Rahbari-Oskoui F, Wong C. Breast J 2003;9:184–191. [PubMed: 12752626]
27. Kneepkens CM, Lepage G, Roy CC. Free Radic Biol Med 1994;17:127–160. [PubMed: 7959173]
28. Mendis S, Sobotka PA, Euler DE. Free Radic Res 1995;23:117–122. [PubMed: 7581809]
29. Scholpp J, Schubert JK, Miekisch W, Noeldge-Schomburg GFE. J Neurotrauma 2004;21:667–677. [PubMed: 15253795]
30. Larstad MA, Toren K, Bake B, Olin AC. Acta Physiol (Oxf) 2007;189:87–98. [PubMed: 17280560]
31. Aghdassi E, Allard JP. Free Radic Biol Med 2000;28:880–886. [PubMed: 10802218]
32. Mohler ER 3rd, Reaven P, Stegner JE, Fineberg NS, Hathaway DR. J Chromatogr B Biomed Appl 1996;685:201–209. [PubMed: 8953161]
33. Skeldon KD, McMillan LC, Wyse CA, Monk SD, Gibson G, Patterson C, France T, Longbottom C, Padgett MJ. Respir Med 2006;100:300–306. [PubMed: 16002272]
34. Manolis A. Clin Chem 1983;29:5–15. [PubMed: 6336681]
35. Cope KA, Watson MT, Foster WM, Sehnert SS, Risby TH. J Appl Physiol 2004;96:1371–1379. [PubMed: 14672964]
36. Poli D, Carbognani P, Corradi M, Goldoni M, Acampa O, Balbi B, Bianchi L, Rusca M, Mutti A. Respir Res 2005;6:71. [PubMed: 16018807]
37. Droz PO, Guillemin MP. J Occup Med 1986;28:593–602. [PubMed: 3746479]
38. Ross BM. BMC Res Notes 2008;1:41. [PubMed: 18710494]
39. Phillips M, Cataneo RN, Condos R, Ring Erickson GA, Greenberg J, La Bombardi V, Munawar MI, Tietje O. Tuberculosis (Edinb) 2007;87:44–52. [PubMed: 16635588]
40. Michael P. J Chromatogr B 1999;729:75–88.
41. Sanchez JM, Sacks RD. Anal Chem 2006;78:3046–3054. [PubMed: 16642992]
42. Qin T, Xu X, Polak T, Pacakova V, Stulik K, Jech L. Talanta 1997;44:1683–1690. [PubMed: 18966907]
43. Reimann I, Mergemeier S, Ebner I, Scholz F, Fresen J. Anal Chem 1995;353:206–210.
44. Belda-Iniesta C, de Castro Carpeno J, Carrasco JA, Moreno V, Casado Saenz E, Feliu J, Sereno M, Garcia Rio F, Barriuso J, Gonzalez Baron M. Clin Transl Oncol 2007;9:364–368. [PubMed: 17594950]

45. van den Velde S, Quirynen M, van Hee P, van Steenberghe D. *J Chromatogr B Analyt Technol Biomed Life Sci* 2007;853:54–61.
46. Mitsubayashi K, Matsunaga H, Nishio G, Toda S, Nakanishi Y. *Biosens Bioelectron* 2005;20:1573–1579. [PubMed: 15626611]
47. Van den Velde S, Nevens F, Van Hee P, van Steenberghe D, Quirynen M. *J Chromatogr B Analyt Technol Biomed Life Sci* 2008;875:344–348.
48. Phillips M, Cataneo RN, Ditkoff BA, Fisher P, Greenberg J, Gunawardena R, Kwon CS, Tietje O, Wong C. *Breast Cancer Res Treat* 2006;99:19–21. [PubMed: 16502014]
49. Manne J, Sukhorukov O, Jager W, Tulip J. *Appl Opt* 2006;45:9230–9237. [PubMed: 17151764]
50. Rolla G, Bruno M, Bommarito L, Heffler E, Ferrero N, Petrarulo M, Bagnis C, Bugiani M, Guida G. *Eur J Clin Invest* 2008;38:728–733. [PubMed: 18837798]
51. Thorpe MJ, Balslev-Clausen D, Kirchner MS, Ye J. *Opt Express* 2008;16:2387–2397. [PubMed: 18542317]
52. Cao W, Duan Y. *Clin Chem* 2006;52:800–811. [PubMed: 16513771]
53. Roberge MT, Finley JW, Lukaski HC, Borgerding AJ. *J Chromatogr A* 2004;1027:19–23. [PubMed: 14971479]
54. Ledochowski M, Widner B, Murr C, Sperner-Unterweger B, Fuchs D. *Scand J Gastroenterol* 2001;36:367–371. [PubMed: 11336160]
55. Minocha A, Mokshagundam S, Gallo SH, Rahal PS. *Am J Gastroenterol* 1994;89:1797–1800. [PubMed: 7942670]
56. Minocha A, Siddiqi S, Rahal PS, Vogel RL. *Dig Dis Sci* 1994;39:1613–1617. [PubMed: 8050308]
57. Babusikova E, Jesenak M, Durdik P, Dobrota D, Banovcin P. *J Physiol Pharmacol* 2008;59(Suppl 6):9–17. [PubMed: 19218629]
58. Scherer JJ, Paul JB, O'Keefe A, Saykally RJ. *Chem Rev* 1997;97:25–52. [PubMed: 11848864]
59. Wyse CA, Preston T, Yam PS, Sutton DG, Christley RM, Hotchkiss JW, Mills CA, Glidle A, Cumming DR, Cooper JM, Love S. *Vet Rec* 2004;154:353–360. [PubMed: 15074325]
60. Sandrini A, Johnson AR, Thomas PS, Yates DH. *Respirology* 2006;11:325–329. [PubMed: 16635093]
61. M.M.R.a.P. HERING. *Mid-Infrared Coherent Sources and Applications*. 2008:535–555.
62. Pleil JD, Lindstrom AB. *Clin Chem* 1997;43:723–730. [PubMed: 9166222]
63. Levitt MD, Furne JK, Kuskowski M, Ruddy J. *Clin Gastroenterol Hepatol* 2006;4:123–129. [PubMed: 16469670]
64. Christl SU, Murgatroyd PR, Gibson GR, Cummings JH. *Gastroenterology* 1992;102:1269–1277. [PubMed: 1551534]
65. Chatterjee S, Park S, Low K, Kong Y, Pimentel M. *Am J Gastroenterol* 2007;102:837–841. [PubMed: 17397408]

Table 1

Markers identified in exhaled breath with their chemical structure, the associated medical conditions, and the techniques used to measure them.

Breath marker	Condition(s)	Technique(s)	References
<i>hydrocarbons</i>			
Methane CH ₄	Oxidative stress, irritated bowel syndrome, breast cancer, heart transplant rejection, bronchial asthma, rheumatoid arthritis, schizophrenia, acute myocardial infarction	GC-MS, laser spectroscopy, mid infrared technology, methane breath test, GC-FID	[23,63-65]
Ethane C ₂ H ₆	Oxidative stress, breast cancer, diabetes COPD, heart transplant rejection, OSA acute myocardial infarction ARDS, schizophrenia, rheumatoid arthritis bronchial asthma, scleroderma/systemic sclerosis lipid peroxidation of unsaturated fatty acids	GC-MS, GC-FID MIR, laser absorption spectroscopy cavity ring down spectroscopy cavity leak-out spectroscopy (CALOS)	[23-28]
Propane C ₃ H ₈	Oxidative stress, lipid peroxidation of unsaturated fatty acids	GC-MS, laser spectroscopy	[24,23]
Butane C ₄ H ₁₀	Lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[25,26]
Pentane C ₅ H ₁₂	Oxidative stress, cystic fibrosis, bronchial asthma, breast cancer, heart transplant rejection, rheumatoid arthritis acute myocardial infarction, SIRS, cigarette smoking, lipid per oxidation of unsaturated fatty acids	GC-MS, laser spectroscopy, SIFT-MS, CALOS analyzer automated thermal desorption GC-FID GC-PID	[23,24,26-32]
Hexane C ₆ H ₁₄	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[23,26,33]
Heptane C ₇ H ₁₆	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[23,26,33,34]
Octane C ₈ H ₁₈	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[23,26,33]
Nonane C ₉ H ₂₀	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, GC-time of flight, automated thermal desorption	[23,26,33]
Decane C ₁₀ H ₂₂	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[23,26,33]
Undecane C ₁₁ H ₂₄	Lung cancer, lipid peroxidation of unsaturated fatty acids	GC-MS, automated thermal desorption	[23,26,33]
1-Methyl-2-pentylcyclopropane C ₁₀ H ₁₂	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[26,33,23]
Isoprene 2-methyl-1,3-butadiene C ₅ H ₈	Lung cancer, breast cancer, hypercholesterolemia, oxidative stress	GC-MS, automated thermal desorption, laser spectroscopy, SIFT-MS	[24,35,28,26,36,23]
2-Methylpropane CH ₃ -CH(CH ₃)CH ₃	Breast cancer	GC-MS, automated thermal desorption	[33,23,26]

Breath marker	Condition(s)	Technique(s)	References
2-Methylpentane $\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_3$	Lung cancer, breast cancer, pulmonary TB	GC-MS, automated thermal desorption	[26,36,33,23,44]
Methylcyclopentane $\text{C}_5\text{H}_{10}(\text{CH}_3)$	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[34,23,26,33]
1,4-Dimethylcyclohexane	Pulmonary TB	GC-MS	[44]
2,5-Dimethylhexane $\text{C}_6\text{H}_{12}(\text{CH}_3)_2$	Active/passive smoking	GC-MS, GC-time of flight automated thermal desorption	[26,33]
Cyclohexane C_6H_{12}	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[33,23]
2-Methylheptane $\text{C}_7\text{H}_{15}(\text{CH}_3)$	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[26,33,23]
3-Methylheptane	Pulmonary TB	GC-MS	[44]
2,2,4,6,6-Pentamethyl heptane $\text{CH}_3-\text{C}(\text{CH}_3)_2-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{C}(\text{CH}_3)_2-\text{CH}_3$	Pulmonary TB, lung cancer, breast cancer	GC-MS, automated thermal desorption	[36,23,44]
2-Methyloctane $\text{CH}_3-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[26,23]
3-Methyloctane $\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[33,23]
3-Methylnonane $\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$	Lung cancer, breast cancer	GC-MS, automated thermal desorption	[26,23]
3-Methylundecane $\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)\text{C}_8\text{H}_{17}$	Breast cancer	GC-MS, automated thermal desorption	[33]
5-Methyltridecane	Breast cancer	GC-MS, automated thermal desorption	[26]
3-Methylnonadecane $\text{CH}_3-\text{CH}_2-\text{CH}(\text{CH}_3)\text{C}_{16}\text{H}_{33}$	Breast cancer	GC-MS, automated thermal desorption	[26]
4-Methyldodecane $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}(\text{CH}_3)\text{C}_{10}\text{H}_{21}$	Breast cancer	GC-MS, automated thermal desorption	[26]
Methylcyclohexane	Pulmonary TB	GC-MS	[44]
Ethylene	Anesthetics inhalation	GC-MS	[34]
Butadienes $\text{CH}_2=\text{CH}-\text{CH}=\text{CH}_2$	Periodontal disease	SIFT-MS	[23]
1-Hexene C_6H_{12}	Lung cancer, breast cancer	GC-MS	[23]
1-Heptene C_7H_{14}	Lung cancer, breast cancer	GC-MS	[23]
1-Octene	Lung cancer	GC-MS	[44]
Benzene C_6H_6	Lung cancer, breast cancer, smoke exposure	GC-MS, SIFT-MS	[24,37]
Trimethylbenzene $\text{C}_6\text{H}_5(\text{CH}_3)_3$	Lung cancer, breast cancer	GC-MS	[36,23]
1,2,3,4-Tetramethylbenzene	Pulmonary TB	GC-MS	[44]

Breath marker	Condition(s)	Technique(s)	References
Ethylbenzene $C_6H_5-C_2H_5$	Lung cancer, breast cancer	GC-MS	[23,44]
Propylbenzene $C_6H_5C_3H_7$	Lung cancer, breast cancer	GC-MS	[23,44]
Toluene $C_6H_5CH_3$	Lung cancer	SIFT-MS, GC	[24,37,38]
<i>o</i> -Toluidine 2-amino-1-methylbenzene C_7H_9N	Lung cancer	GC-MS	[34]
<i>m</i> -Toluidine 3-amino-1-methylbenzene C_7H_9N	Lung cancer	GC-MS	[34]
Aniline $C_6H_5NH_2$	Lung cancer	Gas chromatography	[34]
Styrene $C_6H_5CH=CH_2$	Lung cancer	GC-MS	[36,34,23]
Xylenes $C_6H_4(CH_3)_2$	Lung cancer	GC-MS, SIFT-MS	[38,23]
Naphthalene $C_{10}H_8$	Occupational exposure pulmonary TB	GC-MS	[34,39]
<i>Heteroarenes</i>			
Pyridine C_5H_5N	Periodontal disease	GC-MS	[40]
2-Methylfuran C_5H_6O	Smoking	GC-MS, GC-TOF, automated thermal desorption	[34,41]
2,5-Dimethylfuran C_6H_8O	Smoking	GC-MS, GC-time of flight automated thermal desorption	[41]
2,3-Dihydro-1-phenyl-4(1 <i>H</i>)-quinazoline $C_8H_6N_2$	Lung cancer	GC-MS	[23]
Indole C_8H_7N	Liver disorders cirrhosis	GC-MS, SIFT-MS	[38,34]
Skatole C_9H_9N	Aminuria	Gas chromatography	[34]
<i>Alcohols</i>			
Methanol CH_3OH	Overgrowth of intestinal bacterial flora	SIFT-MS, GC-MS	[24,23,35,42]
Ethanol C_2H_5OH	Overgrowth of intestinal bacterial flora, alcohol consumption	SIFT-MS GC-MS, SPME GC-MS, GC-PID	[24,23,42,43,44,35]
<i>n</i> -Propanol C_3H_7OH	Lung cancer	GC-MS	[42,45]
2-Propanol $CH_3CH(OH)CH_3$	Acetone reduction by bacterial flora, lung cancer, breast cancer, stomach cancer	GC-MS, SIFT-MS, SPME GC-MS	[24,44,23,53]
Dodecanol $C_{12}H_{25}OH$	Ovulation	GC-MS	[34]
Tetradecanol $C_{14}H_{29}OH$	Ovulation	GC-MS	[34]
<i>Aldehydes</i>			
Formaldehyde HCHO	Lung cancer, prostate cancer, bladder cancer	GC-MS, laser photoacoustics-quartz PTR-MS	[23]
Acetaldehyde CH_3CHO	Lung cancer, alcohol consumption	GC-MS	[34,23,46]
Malondialdehyde $CH_2(CHO)_2$	Oxidative stress	GC-MS	[25]

Breath marker	Condition(s)	Technique(s)	References
Hexanal $C_6H_{12}O$	Lung cancer	GC-MS	[23]
Heptanal $C_7H_{14}O$	Lung cancer, breast cancer	GC-MS	[23,53]
Nonanal	Pulmonary T.B.	GC-MS	[44]
<i>p</i> -Tolualdehyde $CH_3-C_6H_4-CHO$	Unknown	GC-MS	[34]
<i>Ketones</i>			
Acetone 2-propanone $OC(CH_3)_2$	Diabetes mellitus, ketosis, halitosis	GC-MS, SIFT-MS laser spectroscopy, SPME GC-MS CALOS analyzer, CRDS	[24,23,35,47,45,44,34,42]
1-Phenylethanone $C_6H_5COCH_3$	Lung cancer, breast cancer	GC-MS	[23,48]
2-Butanone $CH_3C(O)CH_2CH_3$	Liver function disorder, lung cancer, halitosis	GC-MS	[47,45]
Ethyl, methyl ketone	Liver disorders	GC-MS	[34,47]
Penta-2-none $C_5H_{10}O$	Liver disorders, halitosis	GC-MS	[47,45]
1-Methyl,3-heptanone	Pulmonary TB	GC-MS	[39]
2,3-Dihydro-1-phenyl-4(1 <i>H</i>)-quinazolinone	Breast cancer	GC-MS	[48]
<i>Esters</i>			
Isopropyl myristate/ tetradecanoic acid $C_{17}H_{34}O_2$	Breast cancer, lung cancer	GC-MS	[23,53]
<i>Carboxylic acids</i>			
C2-C8 normal and branched org. acids	Upper respiratory/oropharyngeal carcinoma	Gas chromatography	[34]
Propanoic acid	Liver disorder	Gas chromatography	[34]
Butyric acid $CH_3-CH_2-CH_2-COOH$	Liver disorders	Gas chromatography	[34]
Isobutyric acid	Liver disorders	Gas chromatography	[34]
Isovaleric acid 3-methylbutanoic acid $C_5H_{10}O_2$	Liver disorders	Gas chromatography	[34]
Pentanoic acid	Liver disorders	GC-MS	[34]
<i>Ammonia</i>			
NH_3	Uremia, peptic ulcer, kidney disease	Gas chromatography laser-cavity ring-down spectroscopy	[49,23,34,50,51]
<i>Amines (Ammonia derivatives) $R-NH_2$</i>			
Putrescine/1,4-diaminebutane	Aminuria	Gas chromatography	[34,23]
Cadaverine/1,5-diaminepentane	Aminuria	Gas chromatography CRDS	[34]
Dimethyl amine $(CH_3)_2NH$	Aminuria kidney failure	Gas chromatography CRDS	[23,34]
Trimethyl amine $(CH_3)_3N$	Aminuria kidney failure	Gas chromatography CRDS	[23,34]
^{13}C Urea $CO(NH_2)_2$	Helicobacter pylori	Ammonia/urea breath test	[52]

Breath marker	Condition(s)	Technique(s)	References
<i>Sulfides</i>			
Methylsulfide CH_3S	Intestinal bacterial flora, liver disorder	GC-MS, SIFT-MS	[23]
Dimethylsulfide $\text{CH}_3-\text{S}-\text{CH}_3$	Intestinal bacterial flora, liver disorders, oral infection	SIFT-MS	[34]
Dimethyldisulfide $\text{S}(\text{CH}_3)_2$	Liver disorders, oral infection	GC-MS, SIFT-MS	[24,23]
Methanethiol CH_4S	Liver disorders, ovulation and menstrual cycle	GC-MS, SIFT-MS	[34]
Ethanethiol $\text{C}_2\text{H}_5\text{S}$	Liver disorders	GC-MS	[23,34]
Hydrogen sulfide HS	Periodontal disease, ovulation and menstrual cycle	Gas chromatography	[35,34]
Carbonyl sulfide $\text{O}=\text{C}=\text{S}$	Acute lung transplant rejection	Mid infra red absorption spectroscopy, laser spectroscopy, SIFT-MS	[52]
Carbon disulfide CS_2	Liver allograft rejection, schizophrenia, aminuria	SIFT-MS solid phase microextraction and gas chromatography-mass spectrometry (SPME GC-MS)	[49,45,44]
<i>Hydrogen</i>			
H_2	Disorder in digestion and absorption, small bowel bacterial overgrowth	H-breath test	[53,54-56,63-65]
<i>Oxides of carbon</i>			
Carbon monoxide CO	Differentiation between current/passive smokers, hyperbilirubinemia, hemolysis, lung diffusion capacity, diabetes, asthma, inflammation, oxidative stress	Mid infra red spectroscopy (MIR) IR laser absorption spectroscopy quantum cascade laser technique CRDS QCL based sensor CALOS analyzer	[57,35,58,51]
Carbon dioxide CO_2	Intestinal bacterial flora, H. pylori ($^{13}\text{CO}_2$)	Mid infra red absorption spectroscopy CALOS analyzer	[58,51,59,34,54,63-65]
<i>Oxides of nitrogen</i>			
Nitric oxide (NO)	Asthma, pulmonary hypertension, inflammation, oxidative stress, cystic fibrosis, rhinitis, bronchitis, asbestos related lung disorders, end stage renal disease	MIR, chemiluminescence analyzer, laser-multi pass cell, laser cavity enhanced technique, LMRS, ring down spectroscopy (14NO and 15NO) CALOS, Faraday modulation spectroscopy, NO analyzer	[50,38,60,23]
<i>Nitrogen dioxide (NO_2)</i>			
Nitrate	Airway inflammation	Laser spectroscopy	
Nitrite	Asthma, cystic fibrosis	SIFT-MS	[52]
Nitrous oxide (N_2O)	Asthma, cystic fibrosis	SIFT-MS	[52]
	Airway inflammation	Laser photoacoustics quartz Spectroscopy	[61]

Breath marker	Condition(s)	Technique(s)	References
<i>Alkyl halides</i>			
Vinyl chloride $H_2C=CHCl$	Exposure to VOCs from contaminated water	GC-MS	[62]
Cis-1,2-dichloroethane $C_2H_4(Cl)_2$	Exposure to VOCs from contaminated water	GC-MS	[62]
1,1,1-Trichloroethylene	Exposure to VOCs from contaminated water	GC-MS	[37]
1,1,1-Trichloroethane	Exposure to VOCs from contaminated water	IR-spectrometry	[34]
Tetrachloroethylene	Exposure to VOCs from contaminated water	GC-MS	[37]
Bromodichloroethane $Br-CH_2-CH(Cl)_2$	Exposure to VOCs from contaminated water	GC-MS	[62]
Bromotrichloroethane $Br-CH_2-C(Cl)_3$	Exposure to VOCs from contaminated water	GC-MS	[62]
Dichloroethane	Exposure to VOCs from contaminated water	GC-MS	[34]
Chloroform $CHCl_3$	Exposure to VOCs from contaminated water	GC-MS	[34,62]
Dimethyl selenide	Liver Disorders	GC-MS	[47]

Table 2

Techniques and devices used in breath analysis.

<i>Optical techniques</i>
Laser absorption spectroscopy
Mid infra red absorption spectroscopy
Multi pass cell-laser absorption spectroscopy
Tunable diode-laser spectroscopy
Cavity ring-down spectroscopy
Cavity leak-out spectroscopy
Cavity enhanced comb spectrometer
Integrated cavity output spectroscopy
Laser magnetic resonance spectroscopy (LMRS)
Laser photoacoustics-quartz spectroscopy
Faraday-LMRS
Quantum cascade laser MIR spectroscopy
Proton transfer reaction mass spectroscopy
Faraday modulation spectroscopy
<i>Non-optical techniques</i>
Gas chromatography (GC)
Mass spectroscopy (MS)
GC-MS
GC-flame ionization
GC-photoionization
GC-solid phase micro extraction chromatography
GC-automated thermal desorption chromatography
GC-time of flight
Selected ion flow tube mass spectroscopy (SIFT)
Ion mobility spectrometry (IMS)