EMRP Call 2011 - Health, SI Broader Scope & New Technologies

Selected Research Topic number: **SRT-h10**
Version: 1.0

Title: Metrology for breath analysis

Abstract

Measurement of exhaled breath can be used for early and accurate diagnosis of various kinds of disease. It is a non-invasive technique that provides an alternative to the standard medical diagnostic methods involving blood and urine. A robust metrology framework is required as wrong diagnosis can have a major impact on the patient's well being. Key issues to consider are the standardisation of the sampling and the development of suitable reference materials and sensitive instrumentation. In addition, the concentration profile of a specific species in breath depends decisively on where it is generated in the respiratory system and how it reacts on the way to the mouth. Thus the exact type and timing of the sampling event influences the concentration. Furthermore, reactive species like NH_3, CH_2O and H_2S, adsorb strongly on surfaces and quantitative analysis can only be performed once this effect is minimized and accounted for.

Conformity with the Work Programme

This Call for JRPs conforms to the EMRP Outline 2008, section on "Grand Challenges" related to Health, New Technologies & Fundamental Metrology on pages 8 and 22.

Keywords

Exhaled breath analysis, medical diagnostics, standardisation, validation, laser spectroscopy, real-time analysis, Certified Reference Materials, screening studies, ammonia, hydrogen sulphide, formaldehyde

Background to the Metrological Challenges

Standard medical diagnostics relies heavily on blood and urine testing of patients. Sampling of breath from the patient is an attractive alternative to these two established techniques. Human breath contains hundreds of different compounds, the distribution of which varies greatly from person to person. Some compounds in exhaled breath come from ambient air, some from normal metabolism of the body, and others may be the products of irregularities caused by an illness or medical condition. Endogenous compounds present in the blood are transferred to the lungs through the alveolar-capillary membrane. Therefore, any molecule in the blood stream with significant vapour pressure ultimately ends up in the exhaled breath. Different diseases and conditions alter the metabolic processes of the body in their own characteristic way. Thus, by analysing the composition of exhaled breath it is possible to determine important information about the health status of the person.

Analysis of the exhaled breath presents three fundamental problems. First is the required sensitivity, the biomarkers are often present only at trace levels, from hundreds of parts-per-billion (ppb) down to parts-per-trillion (ppt). Second is the selectivity, concentrations of molecules must be measured independently from each other with as little cross-correlation as possible. Third is the time resolution of the measurement. The time-dependent concentration profile of a normal breath cycle can only be resolved if the experiment reaches a sub-second time resolution.

Nowadays, there are three breath tests used in medical practice; the $^{13}CO_2$ breath test, for the detection of stomach ulcers caused by Helicobacter pylori infection (Nobel Prize 2005), H_2 breath test for lactose intolerance and fractional concentration of nitric oxide (FENO) measurements as a marker for airway inflammation in asthma.

EURAMET, EMRP-MSU
National Physical Laboratory
Hampton Road, Teddington,
Middlesex, TW11 0LW, UK

Phone: +44 20 8943 6666
emrpA169@npl.co.uk
www.euramet.org

EMRP
European Metrology Research Programme
Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

Two available mass-spectrometric techniques fulfil the described needs above: Selected Ion Flow Mass Spectrometry (SIFT-MS) and Proton Transfer Reaction Mass Spectrometry (PTR-MS). Additionally, there are several sensitive laser spectroscopic techniques that have the required sensitivity, selectivity and time resolution. These include Cavity Ring Down Spectroscopy (CRDS), Cavity Enhanced Absorption Spectroscopy (CEAS) and Photoacoustic Spectroscopy (PAS).

Acceptance of new clinical breath tests for these molecules strongly depends on the uniformity of the measurements, measurement techniques and/or interpretation of the results. For many relevant molecules there are currently severe limitations for use in daily practice, due to either lack of suitable devices or technologies or lack of good reference materials. In addition, adsorption of reactive molecules on the surfaces of the measurement apparatus gives rise to further complications. For this reason, any attempt to standardise the breath-sampling event must also be accompanied with sufficient attention being paid to the adsorption/desorption processes taking place in the apparatus.

Scientific and Technological Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the JRP-Protocol.

This JRP shall focus on the traceable measurement and characterisation of species in the human exhaled breath for medical diagnostics.

The specific objectives are:

1. To develop novel methods and systems for real-time and fast exhaled breath monitoring.
2. To develop reference gas standards for exhaled breath analysis instrumentation
3. To design simple and robust sampling techniques that yield reproducible and quantitative concentrations for molecules with complex concentration time-profiles.
4. To develop techniques that minimizes the effect of adsorption of reactive species on the surfaces of the measurement apparatus.
5. To demonstrate the efficacy of the developments through medical pilot studies in association with medical practitioners.

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners and industry is strongly recommended.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond the iMERA-Plus project “T2.J02 - Breath analysis as a diagnostic tool for early disease detection”

The total eligible cost of any proposal received for this SRT is expected to be around the 2.7 M€ guideline for proposals in this call.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community. This may be through the inclusion of unfunded JRP partners or collaborators, or by including links to industrial/policy advisory committees, standards committees or other bodies. Evidence of support from the “end user” community (eg letters of support) is encouraged.

You should detail other impacts of your proposed JRP as detailed in the document “Guide 4: Writing a Joint Research Project”

You should detail how your JRP results are going to:

- feed into the development of urgent documentary standards through appropriate standards bodies
- transfer knowledge to the Medical sector.

You should also detail how your approach to realising the objectives will further the aim of the EMRP to develop a coherent approach at the European level in the field of metrology. Specifically the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of Member States and countries associated with the Seventh Framework Programme whose metrology programmes are at an early stage of development to be increased
- outside researchers & research organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.