EMPIR Call 2015 – Health, SI, Normative and Research Potential

Selected Research Topic number: **SRT-h08**
Version: 1.0

Title: Key reactive molecules as exhaled breath biomarkers for disease diagnostics and monitoring

Abstract

Exhaled breath analysis is a non-invasive diagnostic technique that can be used with patients ranging from the newborn to the elderly and with a potential wide scope of medical applications. However, to support its use a robust metrology framework is needed to facilitate the acceptance of breath analysis in medical practice. In order to achieve this, sensitive instrumentation for key reactive molecules need to be developed and validated, as well as the production of reproducible and accurate sampling and measurement methods and suitable reference materials.

Keywords

Exhaled breath analysis, key reactive molecules, medical diagnostics, laser spectroscopy, e-noses, optical transfer standards, reference materials

Background to the Metrological Challenges

Exhaled breath analysis could be used to replace common invasive methods that often cause considerable discomfort for patients. There are many molecules which could potentially be used as markers of disease in breath analysis. However, care must be taken when interpreting breath analysis data as human breath is a complex mixture containing >300 compounds stemming from inhaled air, drinks, foods and absorption through skin. Furthermore, typical concentrations of key markers in exhaled breath are at (sub) nmol/mol levels, which pose strict requirements on the sensitivity of analytical equipment.

The reliable of breath analysis can be affected by the reactivity of key molecules/markers, such as hydrogen cyanide (HCN) and ammonia (NH_3). HCN can currently be detected in exhaled breath with laser spectroscopic techniques and mass spectrometry however NH_3 is more difficult to measure. For the determination of hydrogen peroxide (H_2O_2) (used as an oxidative marker), exhaled breath condensate is commonly used. However, this method is time consuming and suffers from a lack of standardised samples and methods for normalisation.

Mass-spectrometer based techniques are predominantly used for the measurement of compounds such as volatile organic compounds (VOCs) in breath. In such techniques, exhaled breath is sampled on sorbent tubes and subsequently analysed, however the techniques require complex and time-consuming sample preparation, test procedures and statistical analysis. They are also costly and less suitable for small molecules (due to interference by components in ambient air). In contrast, metal oxide semiconductor (MOX) sensors which can be used as electronic olfactory systems, have generally high sensitivity, but suffer from poor selectivity. To enhance their selectivity a combination of nano-structured sensing materials and pattern recognition algorithms in sensing arrays (so-called “e-noses”) are needed, as well as validation with key reactive molecules.

Finally, for the calibration of breath analysis instruments, there is a need for suitable reference materials based on gravimetric, dynamic methods or optical transfer standards. For a few reactive molecules NMIs have already developed gas reference standards (e.g. NH_3) at µmol/mol levels and higher, but this has not been achieved for the low levels relevant for breath analysis (nmol/mol and below). An alternative could be optical transfer standards however optical transfer standards based on laser spectrometers or FTIR rely on data from spectral databases which are, also not yet traceable or sufficiently developed for breath analysis.

EURAMET MSU, Hampton Road, Teddington, Middlesex, TW11 0LW, UK
Phone: +44 20 8943 6666 Email: msu@npl.co.uk
msu.euramet.org

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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 protocol.

The JRP shall focus on the traceable measurement and characterisation of key reactive molecules, used as exhaled breath biomarkers for disease diagnostics and monitoring.

The specific objectives are

1. To develop novel methods and instrumentation for detection of key reactive molecules in exhaled breath (including HCN, NH_3 and H_2O_2) for real-time diagnostics. Methods and instrumentation should be optimised in terms of sensitivity, selectivity and size (for end-user utilisation).
2. To develop standardised methods for breath sampling and analysis of key reactive molecules.
3. To produce validated and reliable reference standards for the calibration of breath sampling instrumentation. For non-selective techniques such as e-nose, gas reference standards will be produced simulating exhaled breath in terms of humidity and CO_2 and O_2 levels. For potential biomarkers for e.g. lung cancer-related diseases, reference standards will be developed for particular reactive molecules like HCN, various VOCs and H_2O_2.
4. To experimentally demonstrate and validate the performance and effectiveness of the developed technology and measurement methods, clinical tests will be performed in collaboration with the medical sector.
5. To facilitate the uptake of the technology and measurement infrastructure developed by the project by the measurement supply chain (accredited laboratories, instrumentation manufacturers), standards developing organisations (ISO, CEN) and end users (medical practitioners, medical (academic) hospitals and industry).

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, medical (academic) hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

In particular, proposers should outline the achievements of the iMERA-Plus joint research project Breath analysis and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution to the project. Any deviation from this must be justified.

Any industrial partners that will receive significant benefit from the results of the proposed project are expected to be unfunded partners.

Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the medical sector.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”.

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. 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 EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

Time-scale

The project should be of up to 3 years duration.