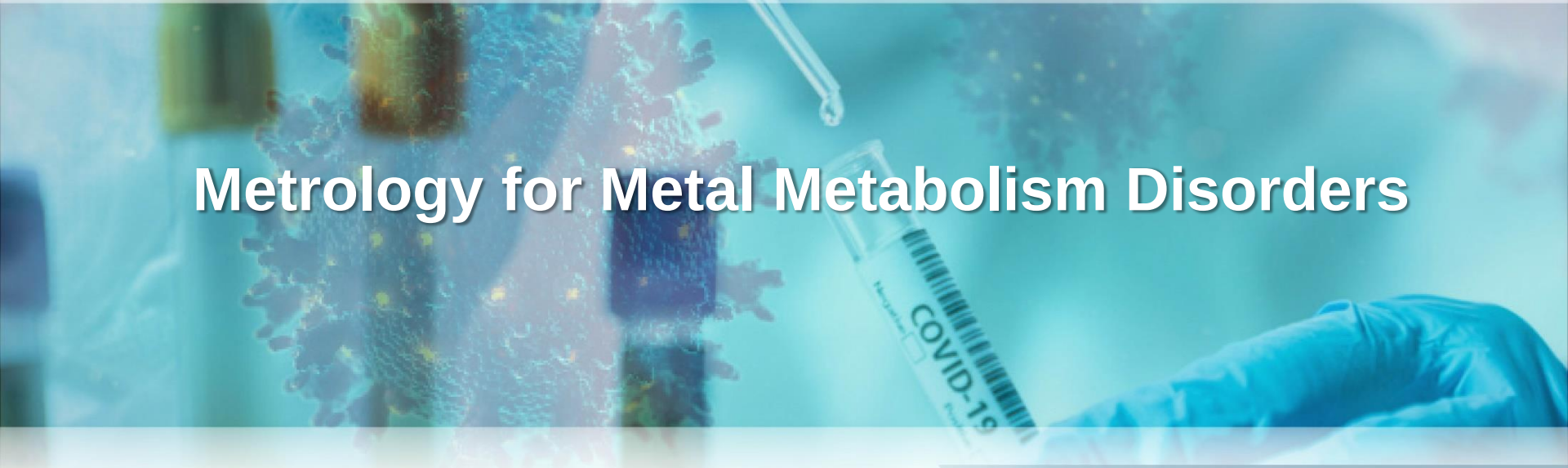
EMN TraceLabMed & TC for Metrology in Chemistry

Stakeholder Workshops on Measurement Challenges

EURAMET



Metrology for Metal Metabolism Disorders

EUROPEAN METROLOGY NETWORKS

TRACE LAB MED

METROLOGY IN CHEMISTRY

Heidi Goenaga Infante, LGC NML, UK

Email: Heidi.Goenaga-Infante@lgcgroup.com

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Pandemics | Laboratory Medicine

Background

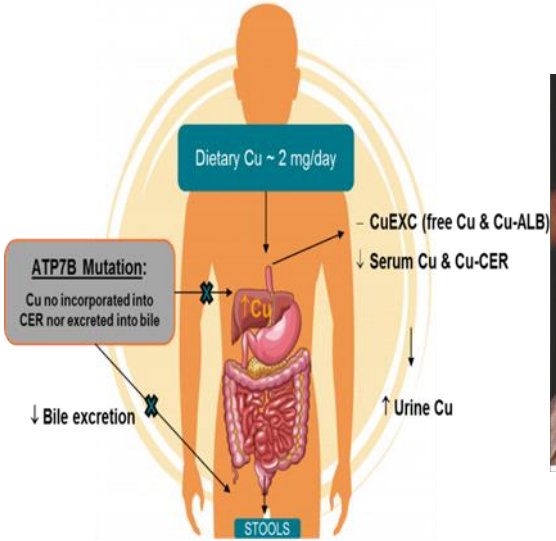
- Some of the physiologically relevant trace elements include iodine, copper, iron, manganese, zinc, selenium, cobalt and molybdenum

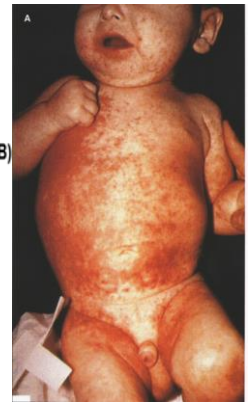
- They are needed in certain amounts for normal physiology but accumulation or deficiency can cause known disorders, e.g.

  Cu and Wilson disease (increased tissue Cu) and, Menkes disease (decreased Cu/Cu-Ceruloplasmin)
  Fe and hemochromatosis (increased body Fe)
  Zn and achrodermatitis enteropathica (decreased Zn, impaired function of Zn enzymes)

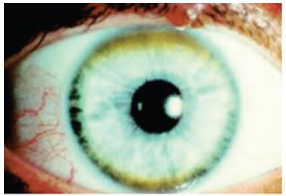
- Diagnosis usually involves gene mutation testing, clinical observations and bio-chemical testing, e.g.

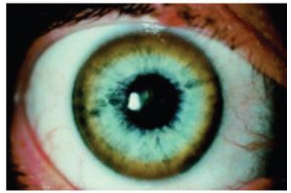
  Wilson disease: Non Ceruloplasmin (CER)-bound Cu
  Hemochromatosis: Total blood Fe, serum ferritin (light chain), liver Fe (MRI)





Achrodermatitis





Wilson disease (Kayser-Fleischer ring)

C. Ferreira, W. Gahl, Translational Science of Rare Diseases, ***DOI: 10.3233/TRD-170015***

Need of metrological traceability for biomarkers of metal disorders: Current challenges of bio-medical analytical methods

- Exchangeable Cu = Total Cu – CuCER. CER by nephelometry: The anti-CER antibody used is not specific to holoCER so the assay can overestimate the concentration of CER due to the presence of the apoCER.
- Off line ultra-filtration based methods based on complexation of exchangeable Cu (Cu mainly bound to albumin) and with EDTA have been found to provide biased results[1]
- WHO recognizes that ferritin is typically assessed in serum or plasma with enzyme immunoassays after blood collection but, there is no specific recommendation on variability among analytical methods and commutability
- WHO International Standard (NIBSC, 94/572) produced for light chain ferritin from E. Coli spiked to cryosupernatant plasma for immunoassays (6.3 µg/ampoule with a variance of the ampoule content: ± 0.345%)
- Reference methodology (IDMS based) published for ferritin from animal tissue extracts[2] but lack of SI traceable methodology for human plasma/serum ferritin
- Need for SI traceable methods and reference materials to underpin/validate bio-chemical tests for diagnostics

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CCQM activities

- K162 (Selenoproteins in human plasma)
- P201 (Total Haemoglobin in human whole blood)

Previous EMPIR projects

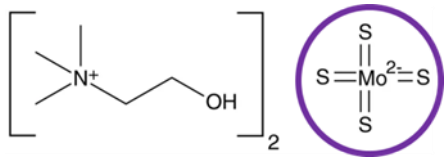
- EMRP HLT05: Metrology for Metalloproteins
- EMPIR 15HLT02 REMIND Role of metals and metal containing biomolecules in neurodegenerative diseases

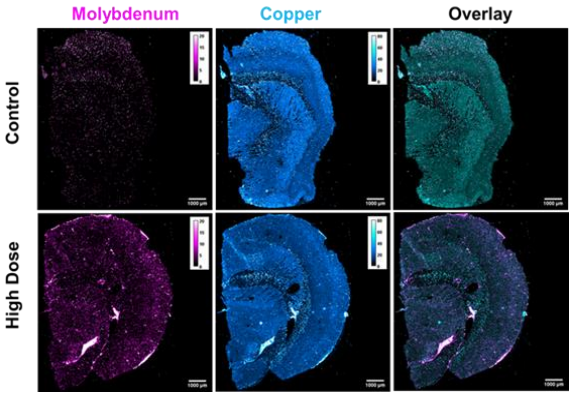
[1] Del Castillo Busto et al., *Anal. Bioanal. Chem.*, 2021; DOI: 10.1007/s00216-021-03517-y
[2] A Tchaikovsky et al., *Metrologia*, 2020; 042101.

Metal Metabolism Disorders (MMD): Other Measurement Needs

- **Quantitative imaging** strategies needed to determine drug distribution down to single cells in pre-clinical samples (help understand drug efficacy and potential toxicity routes)
  - Elemental imaging methods are potential tools to address this need but,
  - Standards and quantitative strategies need development and characterisation
  - Laboratory performance inter-comparison is essential

- **Novel biomarkers of MMD**
  - Isotopic measurements proposed as complementary to other biomarker measurements to help validate diagnosis of MMD (Cu IR in serum and liver disease e.g. Wilson Disease)
  - Methods for bulk IR have been published[1] but further effort needed for validation of determination of isotopic signatures/variation of specific-species





[1]M. Armendia, et al., DOI: 10.1039/C3JA30349G.

Proposed Research Topic shall address:

- Protocols for selection, preparation, fractionation, mounting and preconcentration of samples (e.g. tissues, cells, plasma/serum) with preservation of species integrity
- Strategies for preparation and characterisation of calibrants and labelled materials
- SI traceable methods for key biomarkers of MMD in biological samples (e.g. CuCER in plasma/serum; ferritin light chain in serum). Reference test material production
- Quantitative strategies for elemental spatial distribution in tissues and cells (drug penetration, effect, bio-distribution). Link to histopathology
- Feasibility evaluation of novel biomarkers of MMD (e.g. compound specific IR)
- Engagement with stakeholders (clinical research, hospitals, pharma, PT providers) to support QA schemes, disease diagnosis and the development of improved therapies

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NHS Pathology Solutions
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