Success Story: Medical Lab Achieves Certification for ICP-MS Method for Trace Elements in Urine

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The Institution

The Laboratory of Industrial and Environmental Toxicology, Cliniques Universitaires Saint Luc, Brussels, is specialized in biological monitoring of occupational and environmental exposure to chemical substances. In relation to its service activities, the laboratory carries out over 20,000 analyses of metals every year in several biological media including whole blood, plasma, urine and alternative matrices (e.g. water, intraarticular fluid). In this context, in June 2010, the laboratory was awarded ISO 15189 accreditation (specific accreditation for Medical Laboratories) for the analysis of twenty metals in urine and alternative matrices by ICP-MS. At the same time, analytical methods are developed and validated for research activities, clinical and environmental studies in close collaboration with the Louvain Centre for Toxicology and Applied Pharmacology.

Instrumentation for Metal Analysis

Prior to 2005, metals analyses were carried out using six graphite furnace atomic absorption spectrometers (GFAAS) and one flame atomic absorption spectrometer (FAAS). In order to increase analytical sensitivity and sample throughput, a first Agilent 7500ce ICP-MS was installed in the laboratory and was dedicated to metal analyses in urine and alternative matrices. Twenty two elements (beryllium, aluminum, vanadium, chromium, manganese, cobalt, nickel, copper, zinc, arsenic, selenium, molybdenum, cadmium, tin, antimony, tellurium, barium, platinum, thallium, lead, bismuth and uranium) are routinely monitored using the 7500ce fitted with a Micro Mist nebulizer, following a 1:10 dilution in 0.5% HCl / 1% HNO_3 in no-gas or helium mode (ISO 15189 accredited method). All elements are analyzed in a single run. In 2008, a second Agilent 7500cx ICP-MS was purchased and dedicated to whole blood and plasma analyses. Typically we analyze Mn, Co, Cd, Hg, Tl and Pb in a single run in whole blood and Al, Cu, Zn, Se, B in plasma samples using a Babington and a Micro Mist nebulizer, respectively, following a 1:10 dilution in a basic diluent: 1-butanol (2%w/v), EDTA (0.05%w/v), Triton X-100 (0.05%w/v), NH_4OH (1%w/v), internal standards (Sc, Ge, Rh and Ir) and MilliQ water.

Occupational Exposure to Hardly Soluble Indium Compounds

Indium (In) is a rare soft, silvery-white metal found primarily in ores of zinc, copper, and tin. Demand for indium has increased dramatically over the past 15 years, due largely to the growth of the electronics market. Production of indium tin oxide (ITO) constitutes the leading end-use of indium and accounts for most global indium consumption. ITO thin-film coatings are used primarily for electrical conductive purposes in a variety of flat-panel devices – most commonly liquid crystal displays (LCDs). Other end-uses include low-melting point solders and alloys, compounds, electrical components and semiconductors, and research. One of the most important indium refineries in the world is located in Belgium.

With reports of interstitial pneumonia cases in several indium-processing workers worldwide, occupational exposure to these compounds needed to be investigated further. The first step was to validate a method for the determination of indium levels in urine and plasma using our 7500cx ICP-MS. The final goal of the pilot study was to assess whether the indium concentrations in urine and plasma could be used as exposure biomarkers in a group of workers manufacturing indium ingots and mainly exposed to hardly soluble indium compounds such as indium trioxide (In_2O_3) and indium hydroxide ($In(OH)_3$). Twenty non-exposed controls were also included in this pilot study.

Analytical Protocol

Indium stock solution at 1000 ppm was used to prepare six pre-calibration levels from 10 ppb to 5 ppm. Then, a 1:100 dilution of those pre-calibrators was realized in a basic diluent solution. The basic diluent solution was prepared in a low-density polyethylene bottle by mixing 1-butanol (2%w/v), EDTA (0.05%w/v), Triton X-100 (0.05%w/v), NH_4OH (1%w/v), internal standards and MilliQ water. Samples (urine and plasma) were prepared by a simple 1:10 dilution in this basic diluent solution and quantification of In was realized at m/z 115 in no gas mode (In is free of spectral overlaps) using Rh m/z103 as the internal standard.

Great care was taken to avoid external contamination of the samples. All biological samples were collected in a room separate from the indium-contaminated areas. Blood samples were collected by venipuncture using 85.1160 needles and trace element

free tubes (S-Monovette® Trace Element K_2EDTA, Sarstedt, D-51588, Nümbrecht). Blood was centrifuged at 1800 g for 10 minutes and plasma was transferred to polyethylene tubes by means of disposable polyethylene pipettes. Spot urine samples were collected into clean polypropylene cups. All samples were kept frozen at -20°C prior to analysis.

Results

The linear range covered an equivalent sample concentration range from 1 ppb to 500 ppb (Figure 1). The limits of quantification (LOQ) of In were calculated to be 0.05 and 0.08 ppb in urine and plasma, respectively.

Indium was found to be present in the urine and plasma of all of the workers exposed to the metal in their workplace while no indium was determined above the LOQ in the biological samples taken from the control group. Results obtained in control plasma (n=20/ all <LOQ) show a significant difference when compared with the mean level observed for workers' samples (n=60/ mean= 4.91 µg/L). Results in urine show a similar pattern with a mean of 1.22 µg/g of creatinine for exposed workers versus <LOQ for the controls (Figure 2).

Conclusions

The Laboratory of Industrial and Environmental Toxicology undertakes routine monitoring of elements in biological samples as well as research projects in collaboration with the Louvain Centre for Toxicology and Applied Pharmacology.

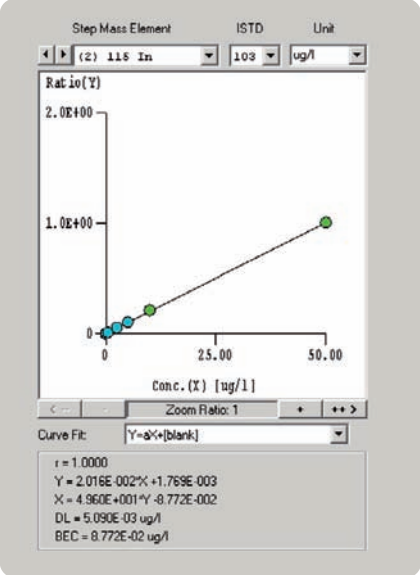

Figure 1: Calibration curve for indium quantification from 0.1 to 50.0 ppb (corresponding to a sample concentration range of 1 to 500 ppb given the 1:10 dilution factor).

Its work to standardize processes and procedures and ensure the reliability and accuracy of test results has been recognized by the award of the internationally recognized ISO 15189 accreditation for the analysis of twenty metals in urine and alternative matrices by ICP-MS. This was achieved in part by dedicating an Agilent 7500ce ICP-MS to the routine monitoring of 22 elements in urine samples and an Agilent 7700cx to whole blood and plasma analyses.

The example outlined in this article of one of the research projects undertaken by the labstudy showed that the 7500cx ICP-MS has sufficient sensitivity to determine indium in the urine and/or plasma of workers exposed to hardly soluble indium compounds (In_2O_3 or $In(OH)_3$). Further investigation is needed to set a biological limit value for indium in relation to the occupational health implications of indium and its compounds.

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Further Information

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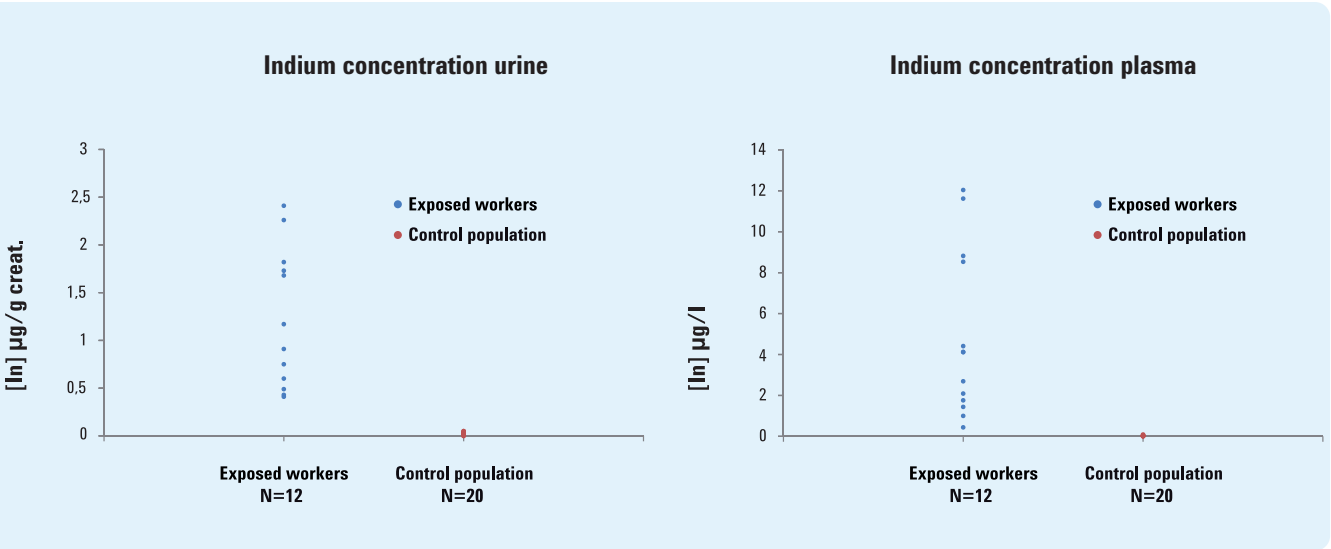

Figure 2: Indium concentration in urine (µg/g creatinine) and plasma (µg/liter) in 12 workers exposed to hardly soluble indium compounds (In_2O_3 or $In(OH)_3$) (mean of 5 different sampling times for each worker) and in 20 controls.