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## Interlaboratory comparison investigations (ICI) and external quality assurance schemes (EQUAS) for cadmium in urine and blood: Results from the HBM4EU project

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## ABSTRACT

Human biomonitoring (HBM) of cadmium is essential to assess and prevent toxic exposure. Generally, low cadmium levels in urine and blood of the general population place particularly high demands on quality assurance and control measures (QA/QC) for cadmium determination. One of the aims of the HBM4EU project is to harmonize and advance HBM in Europe. Cadmium is one of the chemicals selected as a priority substance for HBM implementation in the 30 European countries under HBM4EU. For this purpose, analytical comparability and accuracy of the analytical laboratories of participating countries was investigated in a QA/QC programme comprising interlaboratory comparison investigations (ICI) and external quality assurance schemes (EQUAS). This paper presents the evaluation process and discusses the results of four ICI/EQUAS rounds for the determination of cadmium in urine and blood. The majority of the 43 participating laboratories achieved satisfactory results, although low limits of quantification were required to quantify Cd concentrations at general population exposure levels. The relative standard deviation of the participants' results obtained from all ICI and EQUAS runs ranged from 8 to 36% for cadmium in urine and 8–28% for cadmium in blood. Applying inductively-coupled plasma mass spectrometry (ICP-MS), using an internal standard, and eliminating molybdenum oxide interferences was favourable for the accurate determination of cadmium in urine and blood. Furthermore, the analysis of cadmium in urine was found to have a critical point at approximately 0.05 µg/l, below which variability increased and laboratory proficiency decreased. This QA/QC programme succeeded in establishing a network of laboratories with high analytical comparability and accuracy for the analysis of cadmium across 20 European countries.

**Abbreviations:** Interlaboratory Comparison Investigation, (ICI); External Quality Assurance Scheme, (EQUAS); control material, (CM); consensus value, (C); assigned value, (A); relative standard deviation, (RSD); robust RSD for the CM of each round, (study RSDR); RSD of the mean values from the expert laboratories, (RSDmean-of-means); geometric mean, (GM).

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## 1. Introduction

Cadmium is a heavy metal which has been used in many industrial products and processes, such as in the production of pigments and more recently in the manufacture of cadmium telluride solar panels (Hetherington et al., 2008; IARC, 2012; Nordberg et al., 2015). Industrial emissions, massive use of fertilizers, leaching processes and inadequate recycling strategies, but also geological sources have led to a ubiquitous presence of cadmium in the environment (Thornton, 1992; İşikli et al., 2006; Akram et al., 2019; Hou et al., 2019). Dietary intake and smoking are the main determinants of cadmium exposure of the general population in industrialised countries (Mezynska and Brzóska, 2018; EFSA, 2009), whereas in developing countries other additional relevant exposure routes exist, for example from electronic waste recycling (Motawei and Gouda, 2016; Kim et al., 2019; Adam et al., 2021). Cadmium can be stored and accumulated in various organs, especially in the liver and kidneys (Järup and Akesson, 2009). Biochemical, morphological and functional disorders of renal function are the primary toxic effects of chronic cadmium exposure (Järup, 2003; Satarug et al., 2010). In addition, cadmium and cadmium compounds are classified as carcinogenic to humans (IARC, 2012). Due to the low but prevalent exposure of the general population and the toxic effects following chronic low dose exposure, the assessment and prevention of cadmium exposure is a major public health issue (Järup and Akesson, 2009; Satarug et al., 2003).

For human biomonitoring (HBM) of cadmium exposure, primarily the determination of cadmium in urine, but also of cadmium in blood is applied (Vacchi-Suzzi et al., 2016; Klotz et al., 2013; Fransson et al., 2014; Aoki et al., 2017; Garner et al., 2017). The available HBM data have revealed generally low cadmium levels in both matrices in the general population of industrialised countries (Ruiz et al., 2010; Berglund et al., 2015; Bonberg et al., 2017; Nisse et al., 2017; Saravanabhavan et al., 2017), requiring limits of quantification (LOQ) of 0.1 µg/l or below. This LOQ was met in almost all recent HBM studies by using inductively-coupled plasma mass spectrometry (ICP-MS). However, this technique involves the challenge of controlling the impact of interfering element clusters, particularly of molybdenum oxide, which is generated in the ICP from background molybdenum content (Jarrett et al., 2008; Akerstrom et al., 2013; Schindler et al., 2014; Cañas et al., 2013). Thus, a high level of quality assurance is crucial for the determination of cadmium in biological matrices of the general population.

HBM4EU is a European project which represents a joint effort of 30 countries and European Commission authorities, co-funded under Horizon 2020 (<https://www.hbm4eu.eu>). The main aim of this initiative is the harmonization and advancement of HBM in Europe. HBM4EU targets the exposure of EU citizens to a variety of chemicals and their possible health effects to support policy making (Ganzleben et al., 2017). Cadmium was included in the first priority substance list of HBM4EU and in the first joint HBM studies of the project (Louro et al., 2019; Vorkamp et al., 2021).

One of the objectives within the HBM4EU project is the establishment of a network of analytical laboratories across Europe (Esteban López et al., 2021) for the HBM of environmental pollutants, generating high-quality and comparable HBM data for the prioritized substances. Thus, HBM4EU has implemented a quality assurance/quality control (QA/QC) scheme to verify analytical comparability between candidate laboratories for the analysis of samples within HBM4EU. An essential component of this QA/QC scheme is the design and implementation of interlaboratory comparison investigations (ICI) and external quality assurance schemes (EQUAS). The ICIs included candidate laboratories from the HBM4EU consortium and investigated the results with a view to comparability between these laboratories, whereas the EQUAS involved additional external expert laboratories that have experience with HBM population studies in other regions of the world and that applied comprehensively validated analytical procedures (Esteban López et al., 2021).

This paper presents the ICI/EQUAS programme for cadmium developed in HBM4EU, including the evaluation process, difficulties encountered and the results obtained.

## 2. Materials and methods

### 2.1. Design of the HBM4EU ICI/EQUAS programme for cadmium in urine and blood

In the QA/QC programme, four rounds of tailor-made ICI and EQUAS exercises were conducted from February 2018 to November 2019 to assess the proficiency of laboratories for cadmium in urine (Cd (U)) and cadmium in blood (Cd (B)). The organisational processes and conditions of ICI and EQUAS exercises for all substance groups in the HBM4EU project are described in detail in Esteban López et al. (2021).

Successful participation in the ICI/EQUAS for Cd (U) and Cd (B) was mandatory for laboratories to analyse the respective HBM4EU project samples. Candidate laboratories were requested to apply the same procedure in the ICI/EQUAS as they would use for analysis of samples in the frame of the HBM4EU project. A total of four ICI/EQUAS rounds for Cd (U) and Cd (B) were organized. The first round was conducted as an ICI and the following three rounds were conducted as EQUAS to be consistent with the overall HBM4EU QA/QC programme (Esteban López et al., 2021). Each round comprised the analysis of control materials (CMs) with two concentrations of Cd (U) and Cd (B), respectively. The results were reported to the laboratories before the next round. After the 1st round, a web conference was held for the participants to solve possible difficulties and improve future results. A web conference was also offered after each of the following rounds, but was not deemed necessary by the participants as no major difficulties had been encountered.

### 2.2. Invitation of participants

The process for selecting the candidate laboratories that participated in the Cd ICI/EQUAS has been described elsewhere (Esteban López et al., 2021; short description in the Supplemental Material). In brief, two calls to identify candidate laboratories to perform Cd analysis in HBM4EU were carried out, resulting in a list of 38 candidate laboratories from 22 countries after the first call. This number increased to 58 laboratories from 25 countries after the second call.

All laboratories that had previously registered as candidate laboratories for the analysis of cadmium in HBM4EU samples were invited to the ICI/EQUAS programme for Cd (U) and Cd (B). Candidate laboratories could participate in the ICI/EQUAS for either Cd (U) or Cd (B) or both. The 38 candidate laboratories established after the first call were invited to participate in the 1st round of the programme. The participants were asked to report LOQs of the analysis and the details of the applied methods in addition to the measured concentrations. The candidate laboratories were also informed that LOQs of 0.05 µg/l for Cd (U) and 0.15 µg/l for Cd (B) were advisable for successful participation. The setting of these LOQ target values was aligned according to the existing HBM data on cadmium in population studies (Castaño et al., 2012; Järup and Åkesson, 2009).

After the 1st round, the revised candidate list was used to invite 58 laboratories to participate in the 2nd, 3rd and 4th round for Cd (U) and/or Cd (B).

### 2.3. Selection of expert laboratories

For the rounds organized as EQUAS (2nd, 3rd and 4th), six expert laboratories for Cd (U) and Cd (B) were selected by the HBM4EU Quality Assurance Unit (QAU). Experts were laboratories with experience in the analysis of Cd (U) and Cd (B), having documented their expertise in peer-reviewed publications. In addition, the following selection criteria were considered, although none of them was mandatory: number of

years of experience in the analysis of Cd (U) and Cd (B), application of highly sensitive and selective analytical techniques with sufficiently low limit of detection (LOD) and LOQ, application of isotope-labelled standards for quantification, availability of in-house validation reports, data on on-going intra-laboratory performance (e.g. control charts), ISO 17025 accreditation for the biomarker of interest and success rate in ICI/EQUAS or comparative results in HBM studies. For Cd (U) and Cd (B), two expert laboratories were from outside Europe. Four expert laboratories were from Europe and three of them also participated as candidates in the ICI/EQUAS.

#### 2.4. Preparation and testing of control materials

The control materials were freshly prepared and tested for homogeneity before each round of the ICI/EQUAS programme. The native control material consisted of human urine (Cd (U)<sub>native</sub>) or bovine blood (Fiebig-Nährstofftechnik, Idstein-Niederauff, Germany) in EDTA solution (Cd (B)<sub>native</sub>), both with the addition of sodium azide. For the animal materials, health conditions were certified. Stock solutions (Cadmium ICP standard, Cd(NO<sub>3</sub>)<sub>2</sub> in HNO<sub>3</sub> 2–3%, 1000 mg/l, Merck) were diluted to two different concentrations to obtain the spiking solutions. The addition of these spiking solutions to Cd (U)<sub>native</sub> and Cd (B)<sub>native</sub> yielded the target concentrations for the CM (Cd (U)<sub>low</sub>, Cd (U)<sub>high</sub>, Cd (B)<sub>low</sub>, Cd (B)<sub>high</sub>) (Suppl. Table 1).

Five millilitres of the CMs for Cd (U) were filled into tubes with caps (82 × 13 mm, polypropylene, Sarstedt). Three millilitres of the CMs for Cd (B) were filled into tubes with caps (57 × 15.3 mm, polypropylene, Sarstedt). Previous investigations did not show any Cd contamination of the tubes used in the programme. CMs were prepared for each round, stored at ≤ -18 °C until shipment and then shipped under ambient conditions (Suppl. Fig. 1).

Details of the analytical method for the determination of homogeneity and stability of Cd (U) and Cd (B) are given in Table 1. A more detailed method description can be found in the Supplementary material. For the determination of homogeneity, ten randomly selected tubes of each CM of each round were taken from storage, thawed, re-homogenised by vortex shaking and simultaneously analysed in duplicate.

**Homogeneity testing:** Homogeneity was evaluated according to ISO 13528:2015 (Fearn and Thompson, 2001; Thompson, 2000) using ICP-MS (see Supplementary material).

**Stability testing:** The stability of the CM was tested in accordance with ISO 13528 (Statistical methods for use in proficiency testing by inter-laboratory comparison, 2015) and the International Harmonised Protocol for the Proficiency Testing of Analytical Laboratories (Thompson et al., 2006). For stability assessment, samples were stored under conditions representative of storage at the participants' laboratories (-18 °C) and at -80 °C (considered the maximum stability). Stability was determined by simultaneous ICP-MS analysis of six randomly selected samples from each concentration and after storage at both -18 °C and -80 °C for a time interval covering the time between shipment and the deadline for result submission. Stability was assessed by comparing the means of the six samples at -18 °C and -80 °C using the T-test.

#### 2.5. Distribution of control materials

The control materials were dispatched to the participants under ambient conditions (Suppl. Fig. 1). Each participant received samples for Cd (U)<sub>low</sub>, Cd (U)<sub>high</sub> and/or Cd (B)<sub>low</sub>, Cd (B)<sub>high</sub>, according to their registration. In the 1st ICI/EQUAS round, three samples of Cd<sub>low</sub> and three samples of Cd<sub>high</sub> were sent to the participants. Additionally, the participants received three samples of Cd<sub>native</sub>, with the purpose of determining potential background levels. As no background was found, no further Cd<sub>native</sub> samples were sent to the participants in subsequent rounds. From the 3rd round onwards, the participants received only one sample of each concentration (Cd<sub>low</sub>, Cd<sub>high</sub>) in order to mimic best the real analysis situation of the HBM4EU project samples.

At the time of shipment, a letter with instructions on sample handling, a sample receipt form, a result submission form and a method information form were sent to the participants. Participants were asked to perform a single analysis of each sample using the same procedure as used for analysis of samples in the frame of HMB4EU and to submit their results within four weeks after sample shipment.

In the 2nd, 3rd and 4th round, the selected expert laboratories received three samples of each CM (Cd<sub>low</sub> and Cd<sub>high</sub>) and were asked to provide a single or duplicate analysis so that they should submit at least six results per material (Cd<sub>low</sub> and Cd<sub>high</sub>, both for Cd(U) and Cd(B)).

#### 2.6. Assessment of laboratory performance

In brief, for an ICI, a minimum of seven quantitative results from participating candidate laboratories was required for regular evaluation. For Cd (U)<sub>low</sub>, Cd (U)<sub>high</sub>, Cd (B)<sub>low</sub> and Cd (B)<sub>high</sub>, the following values were calculated using robust statistics so that outliers were not excluded, but only had a minor impact on the performance parameters (Thompson et al., 2006; Analytical Methods Committee, 1989a, b; ISO 13528:2015): robust mean of the participants' results taken as consensus value (C), uncertainty of the consensus value (u<sub>ICI</sub>), robust ICI standard deviation of the consensus value (σ<sub>ICI</sub>) and the Z-scores for each participant.

The uncertainty of the consensus value was calculated as follows:

$$u_{ICI} = 1.25 \frac{\sigma_{ICI}}{\sqrt{n}} \quad (1)$$

with: n = number of results used for calculation of the consensus value with n ≥ 7.

In the EQUAS, the evaluation of the candidate results was based on the data generated by a minimum of three and a maximum of six designated expert laboratories. The mean-of-means of the individual expert laboratories was used as the assigned value. The uncertainty (u<sub>EQUAS</sub>) was defined as the relative standard deviation of the expert means (RSD<sub>mean-of-means</sub>) divided by the square root of the number of expert laboratories:

$$u_{EQUAS} = \frac{RSD_{\text{mean-of-means}}}{\sqrt{n}} \quad (2)$$

The mean-of-means was considered suitable for use as assigned value (A) in EQUAS studies if u<sub>EQUAS</sub> did not exceed a value of 17.5% derived from the following equation:

$$u_{EQUAS} \leq 0.7 \times \sigma_T \quad (3)$$

**Table 1**

Analytical method parameters for determination of homogeneity and stability of Cd (U), Cd (B) and Mo background levels.

Quantitated ion and matrix	Instrument	Reagent gas	Sample volume	Dilution	Internal standard	Calibration	LOD Cd/Mo (µg/l)	LOQ Cd/Mo (µg/l)
<sup>114</sup> Cd or <sup>98</sup> Mo in urine	ICP-triple quadrupole-MS	Argon	0.4 ml	1:10	Rhodium	external, matrix-based, multi-level	0.023/0.040	0.050/0.127
<sup>114</sup> Cd or <sup>98</sup> Mo in blood	ICP-triple quadrupole-MS	Argon	0.2 ml	1:20	Rhodium	external, matrix-based, multi-level	0.040/0.050	0.050/0.270

with  $\sigma_T$  = a pre-set relative target standard deviation for proficiency of 25%

This target relative standard deviation ( $\sigma_T$ ) reflected the maximum variability that was considered acceptable for the candidate results and was also used for the Z-score calculation in the ICI/EQUAS. The value of  $\sigma_T$  (25%) was set based on expert opinion, taking into account what was technically feasible and realistic in current routine practice.

As measure of proficiency, Z-scores were calculated using the consensus value derived from the participants' results (ICI) or the mean of the expert laboratories (EQUAS) as the assigned value, and the  $\sigma_T$  of 25% (Equation (4)).

In the first round, conducted as an ICI, the value of  $u_{ICI}$  was negligible for Cd (U)<sub>low</sub>, Cd (U)<sub>high</sub>, Cd (B)<sub>low</sub> and Cd (B)<sub>high</sub> so that the Z-scores (Z) of the results submitted by the participants (x) were calculated according to the equation:

$$Z = \frac{x - C}{\sigma_T * C} \quad (4)$$

In the 2nd, 3rd and 4th round, conducted as EQUAS, the Z-scores of the participants' results were calculated according to:

$$Z = \frac{x - A}{\sigma_T * A} \quad (5)$$

In ICI/EQUAS, Z-scores were classified in three categories:

- $|Z| \leq 2 \Rightarrow$  satisfactory
- $2 < |Z| < 3 \Rightarrow$  questionable
- $|Z| \geq 3 \Rightarrow$  unsatisfactory

The results of the participating laboratories were evaluated on an individual biomarker/matrix/concentration basis.

If no numerical value for a CM was reported by a participant, the specified LOQ that was reported by the participant was used for the Z-score calculation according to equation (5). These LOQ-Z-scores (LOQ-Z) were not included in the final evaluation, but were only used to assess the laboratory's performance with respect to its reported LOQ.

Statistical analyses were conducted using IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

### 3. Results and discussion

#### 3.1. Spiking concentrations, homogeneity and stability testing

Spiking concentrations in the CM (Cd (U)<sub>low</sub>, Cd (U)<sub>high</sub>, Cd (B)<sub>low</sub>, Cd (B)<sub>high</sub>), as shown in Suppl. Table 1, were selected in accordance with the expected exposure levels of the general population, which was the target population in HBM4EU aligned studies. DEMOCOPHES, a previous pan-European HBM project in mother-child pairs, used urinary CM with ranges of 0.2–1.0 µg/l for Cd on the basis of data from the German Environmental Survey 1998 and the German Environmental Survey for Children (Schindler et al., 2014). A more recent study that analysed Cd (U) in the general population of northern France reported a geometric mean (GM) of 0.39 µg/l and 0.37 µg/l Cd (U) for women and men, respectively (Nisse et al., 2017). For Cd (B), low levels starting from 0.02 µg/l, high levels up to 4.4 µg/l and mean values ranging from 0.3 µg/l to 1.53 µg/l have been documented for smoking and non-smoking men and women in the general population of several European countries (Mezynska and Brzóška, 2018). Nisse et al. (2017) reported a GM of 0.375 µg/l for Cd (B). The spiking concentrations chosen for the ICI/EQUAS of 0.000 (native urine unspiked) to 0.350 µg/l Cd (U) and 0.120–0.720 µg/l Cd (B) were therefore considered adequate to test the accuracy of the participating laboratories for quantitative determinations within the environmental exposure range.

Homogeneity and stability testing of the CMs was conducted separately for each of the four ICI/EQUAS rounds by the same laboratory

(IPASUM). The results of the homogeneity testing for Cd (U) and Cd (B) in the four ICI/EQUAS rounds are shown in Table 2. No outliers were detected in any ICI/EQUAS round for Cd (U) and Cd (B), the homogeneity was adequate and the method was considered suitable. The Mo background levels determined by single analysis for each CM were below 10 µg/l and below 5 µg/l in urine and blood, respectively (Table 2).

The results of the stability testing for Cd (U) and Cd (B) in the four ICI/EQUAS rounds are shown in Suppl. Table 2. No statistically significant instability was detected in any ICI/EQUAS round, minor deviations were caused by the day-to-day imprecision of the applied method.

#### 3.2. Participation and range of reported LOQs

In the first round of the ICI/EQUAS programme, 21 and 19 laboratories (55% and 50%) out of 38 candidate laboratories participated (Table 3) for urine and blood, respectively. 58 laboratories were invited to the following ICI/EQUAS rounds.

The range of LOQs reported by the participants in the four ICI/EQUAS rounds is shown in Suppl. Table 6. The recommended LOQs were  $\leq 0.05$  µg/l for Cd (U) and  $\leq 0.15$  µg/l for Cd (B). Two candidates did not provide their LOQs. In the 1st round, 14 candidates met the LOQ requirements for Cd (U) and Cd (B), representing 67% and 74% of all reported LOQs, respectively. In the following ICI/EQUAS rounds, the proportion of candidates meeting the required LOQs increased for Cd (U) and remained fairly constant for Cd (B). The expert laboratories also reported their LOQs and met the respective requirements except for one laboratory in the 2nd round for Cd (B) (Suppl. Table 6).

#### 3.3. Establishment of assigned values derived from expert laboratories (EQUAS)

Each expert laboratory analysed either three samples of each CM (Cd<sub>low</sub> and Cd<sub>high</sub>) in duplicate (round 2) or six samples of each CM in single or duplicate analysis (round 3 and 4). In the 2nd and 3rd round, all six selected expert laboratories submitted results, while in the fourth round one expert (Exp4) was missing. The details of the expert analyses for Cd (U) and Cd (B) are shown in Suppl. Fig. 2 and Suppl. Fig. 3, the corresponding assigned values and uncertainties can be found in Table 4 and Table 5. The RSD of the assigned values derived from the expert laboratories (RSD<sub>expert labs</sub>) decreased from the 2nd to the 4th round for all CMs except for Cd (B)<sub>high</sub>. Overall, the RSD<sub>expert labs</sub> for the high CM was lower than for the low CM in each round. The precision of the mean values ( $\pm 2 * SD$ ) varied considerably among the expert laboratories from round to round and for the different CMs.

#### 3.4. Method characteristics

Details of the methods used by candidates and experts to analyse Cd (U) and/or Cd (B) are shown in Suppl. Table 3 and Suppl. Table 4. All experts and most candidates applied ICP-MS to analyse Cd in urine and blood. The use of atomic absorption spectrometry (AAS) was very

**Table 2**

Results of the homogeneity testing for Cd (n = 10) and Mo (n = 1) background levels in urine (U<sub>low</sub> and U<sub>high</sub>) and blood materials (B<sub>low</sub> and B<sub>high</sub>) of the four ICI/EQUAS rounds (mean  $\pm$  SD in µg/l).

	Round 1	Round 2	Round 3	Round 4
Cd (U) <sub>low</sub>	0.198 $\pm$ 0.010	0.063 $\pm$ 0.007	0.055 $\pm$ 0.007	0.076 $\pm$ 0.005
Mo (U) <sub>low</sub>	9.47	8.61	9.59	7.38
Cd (U) <sub>high</sub>	0.451 $\pm$ 0.013	0.213 $\pm$ 0.022	0.156 $\pm$ 0.009	0.156 $\pm$ 0.008
Mo (U) <sub>high</sub>	9.51	8.50	9.61	7.31
Cd (B) <sub>low</sub>	0.238 $\pm$ 0.016	0.105 $\pm$ 0.013	0.168 $\pm$ 0.017	0.174 $\pm$ 0.023
Mo (B) <sub>low</sub>	4.51	1.19	1.29	3.56
Cd (B) <sub>high</sub>	0.508 $\pm$ 0.017	0.749 $\pm$ 0.083	0.300 $\pm$ 0.025	0.407 $\pm$ 0.051
Mo (B) <sub>high</sub>	4.56	1.18	1.35	3.58

**Table 3**

Number of registered laboratories and of laboratories submitting results for Cd (U) and Cd (B).

	Round 1	Round 2	Round 3	Round 4
Cd candidate laboratories	38	58	58	58
Cd (U) Registration	21	39	42	22
Participation	21	37	42	20
Cd (B) Registration	19	35	37	21
Participation	19	33	36	20

limited among the participants of the ICI/EQUAS and ranged between 5% and 11% over all rounds.

For Cd (U), an internal standard and the respective normalisation were used by 71% of all participants in the first ICI/EQUAS round. In the following rounds, the percentage of laboratories using the response normalised to an internal standard increased to 89% in the 4th round. The percentage of candidates using an internal standard without normalising the response declined from 10% in the first round to 3%–5% in the following rounds. In the first round, 19% of the participants did not use an internal standard, while this percentage decreased to 5% in the last round. Measures to suppress molybdenum oxide interferences were applied by around half of the participants. More details on the suppression measures are given in [Suppl. Table 8](#).

For the analysis of Cd (B), around 80% of the participants used an internal standard with normalised response in the first three ICI/EQUAS rounds ([Suppl. Table 4](#)). In the last round, the proportion of laboratories that normalised their response to an internal standard was highest, reaching 94%. Molybdenum interferences were eliminated by a variable percentage of candidates across the four ICI/EQUAS rounds. While in the 1st round only 27% of the participants reported the elimination of molybdenum oxides by effective reaction/collision cell application, half of all laboratories applied such a procedure in the last round for Cd (B).

Among the six experts, the methods to determine Cd in urine and blood were quite uniform as all of them used ICP-MS and normalised their results to an internal standard ([Suppl. Table 3](#); [Suppl. Table 4](#)). The percentage of expert laboratories that eliminated molybdenum oxide interferences was 60% for Cd (U) and 40% for Cd (B) in the 2nd and in the 3rd round. In the last round, one expert could no longer participate so that 50% of the experts applied elimination of molybdenum oxides.

### 3.5. Assessment of laboratory performance

When comparing the overall performance of all participating laboratories in the different rounds, various aspects of the test design, such as organisation as ICI or EQUAS, target concentrations of the CMs and applied methods, should be taken into account.

One interesting aspect of the EQUAS exercises is the comparison of the assigned values for Cd calculated from the results of five to six selected expert laboratories with the consensus values achieved by the

**Table 4**

Comparison of assigned values and consensus values for Cd (U) and Cd (B) in rounds 2-4.

Round	CM	Results from 5 to 6 experts		Results from all participants			
		Assigned value (A) ( $\mu\text{g/l}$ )	SD ( $\mu\text{g/l}$ )	Consensus value (C) ( $\mu\text{g/l}$ )	SD ( $\mu\text{g/l}$ )	difference of C from A ( $\mu\text{g/l}$ )	
Cd (U)	2	low	0.041	0.012	0.053	0.019	0.012
		high	0.215	0.046	0.236	0.032	0.021
	3	low	0.087	0.007	0.091	0.011	0.004
		high	0.190	0.010	0.186	0.024	-0.004
4	low	0.060	0.004	0.064	0.011	0.004	
	high	0.146	0.007	0.150	0.012	0.004	
Cd (B)	2	low	0.133	0.042	0.163	0.046	0.030
		high	0.767	0.036	0.759	0.079	-0.008
	3	low	0.210	0.116	0.214	0.048	0.004
		high	0.354	0.048	0.362	0.056	0.008
	4	low	0.135	0.008	0.148	0.026	0.013
		high	0.405	0.019	0.422	0.038	0.017

participating candidates in the three EQUAS rounds. The switch from ICI to EQUAS in the 2nd round was not due to problems with the ICI evaluation, but aimed to harmonize the exercises for all substance groups in the HBM4EU QA/QC programme targeting information on the accuracy ([Esteban López et al., 2021](#)). For all CMs of Cd (U) and Cd (B), the difference between the assigned and the subsequently calculated consensus values was within the range of the standard deviation of the assigned value (except for Cd(B)<sub>low</sub> in 4th round) and of the consensus value ([Table 4](#)). This indicates that the different evaluation schemes of ICI and EQUAS generated comparable Z-score results for the participating laboratories.

For the appraisal of the participant results, Z-score values were determined based on a pre-set relative target standard deviation for proficiency ( $\sigma_T$ ) of 25%, which was extracted from previous experience for these parameters ([Esteban López et al., 2021](#)). The Z-scores of the participants who submitted quantitative results in the ICI/EQUAS rounds are shown in [Suppl. Fig. 4](#). The performance of the participants who did not provide quantitative data but indicated '<LOQ' as a result was assessed using LOQ-Z-scores, but was not included in the final evaluation of the candidates. The respective interpretations of the LOQ-Z-scores are shown in [Suppl. Table 5](#). The LOQ-Z-scores achieved by the candidates are shown in [Suppl. Table 6](#).

The effect of the Cd target concentrations on candidate performance is reflected in [Table 5](#), which shows details of the outcome of the four ICI/EQUAS rounds for Cd (U) and Cd (B). The number of participating laboratories that were unable to detect the biomarker in the CM and thus indicated '<LOQ' in their report was highest for Cd (U)<sub>low</sub> in the 2nd round, where the sample was not spiked and the expert-assigned value was the lowest (0.041  $\mu\text{g/l}$ ). Accordingly, the lowest number of satisfactory results for this CM was recorded in the 2nd round, as satisfactory Z-scores were only obtained by 22 participants (69%) for Cd (U)<sub>low</sub>. The best performance of all rounds was obtained for Cd (U)<sub>high</sub> in the 3rd round with 40 candidates (98%) achieving a satisfactory evaluation. The Z-scores of the participants who submitted quantitative results for the respective CMs in the respective rounds are shown in [Suppl. Fig. 5](#).

The effect of Cd concentration on study RSDR and Z-scores was also apparent for the blood samples. For Cd (B)<sub>low</sub>, the average study RSDR over all rounds was 19.5%, while it was 11.0% for Cd (B)<sub>high</sub>. The interlaboratory variability of the results was highest for the 2nd round of Cd (B)<sub>low</sub>. This CM contained the lowest cadmium concentration detected in the homogeneity testing (0.105  $\mu\text{g/l}$ ; [Table 2](#)) and eight of the 33 participants could not detect it. Furthermore, the analysis of Cd (B)<sub>low</sub> in the 2nd round resulted in the lowest percentage of satisfactory results (i.e. 76%) of all blood samples. The best performance of all rounds was achieved for Cd (B)<sub>high</sub> in the 4th round, where all participants obtained a satisfactory evaluation.

The analysis of CMs with higher concentrations generally resulted in lower study RSDR values compared to CMs with lower concentrations, not only for all laboratories reporting results ([Table 5](#)), but also for the

**Table 5**  
ICI/EQUAS results obtained for Cd (U) and Cd (B).

round	CM	Consensus (ICI)/Assigned value (EQUAS) in µg/l	RSDexpert labs	Uncertainty of ICI (uICI)/EQUAS (uEQUAS)	Study RSDR	No. of labs reporting results	Performance (Classified by Z-score results)		
							% satis	% quest	% unsat
Cd (U)	1	low	0.238	n.a.	5%	20 (1 <sup>a</sup> )	90%	5%	5%
	1	high	0.448	n.a.	3%	20 (1 <sup>a</sup> )	90%	5%	5%
	2	low	0.041	30%	1.2%	32 (5 <sup>b</sup> )	69%	3%	28%
	3	high	0.215	21%	9%	37	92%	0%	8%
Cd (B)	1	low	0.087	8%	3%	40 (2 <sup>b</sup> )	95%	0%	5%
	1	high	0.190	5%	2%	41 (1 <sup>b</sup> )	98%	0%	2%
	2	low	0.060	7%	3%	19 (1 <sup>b</sup> )	90%	5%	5%
	2	high	0.146	4%	2%	20	95%	0%	5%
Cd (B)	1	low	0.251	n.a.	3%	18 (1 <sup>b</sup> )	89%	0%	11%
	1	high	0.536	n.a.	2%	18 (1 <sup>b</sup> )	89%	0%	11%
	2	low	0.133	31%	1.3%	25 (8 <sup>b</sup> )	76%	16%	8%
	2	high	0.767	5%	2%	32 (1 <sup>b</sup> )	91%	6%	3%
Cd (B)	3	low	0.210	28%	1.1%	31 (5 <sup>b</sup> )	87%	6%	6%
	3	high	0.354	14%	6%	34 (2 <sup>b</sup> )	91%	3%	6%
	4	low	0.135	6%	3%	16 (2 <sup>b</sup> )	88%	13%	0%
	4	high	0.405	5%	2%	17 (1 <sup>b</sup> )	100%	0%	0%

<sup>a</sup> Number of laboratories reporting, <LOQ<sup>c</sup>; n.a: not applicable; satis: satisfactory results; quest: questionable results; unsat: unsatisfactory results.

successful laboratories (Suppl. Table 7). The study RSDR values were comparable to the participant RSD found in the DEMOCOPHES ICI/EQUAS programme (Schindler et al., 2014). In the former study, the participant RSD ranged between 6.2% and 32% for concentrations between 0.21 and 0.99 µg/l.

The average performance of the candidates over all ICI/EQUAS rounds for Cd (U) and Cd (B) regarding all low and all high CMs was quite similar. The best results were obtained for Cd (U)<sub>high</sub> and Cd (B)<sub>high</sub> with an average of 94% and 93% satisfactory Z-scores, while only 86% of the participants achieved satisfactory Z-scores for Cd (U)<sub>low</sub> and 85% for Cd (B)<sub>low</sub>.

A comparison of the Z-scores obtained for CM<sub>low</sub> over all rounds with Z-scores achieved for CM<sub>high</sub> showed a statistically significant difference only among the results of the candidates for Cd (U). The mean Z-score for Cd (U)<sub>low</sub> was significantly (p < 0.01) higher than the mean Z-score for Cd (U)<sub>high</sub> (Suppl. Fig. 6 A). No significant differences were found between the Z-scores of the candidates for Cd(B)<sub>low</sub> and Cd (B)<sub>high</sub> (Suppl. Fig. 6 C) and for Cd analyses performed by the expert laboratories (Suppl. Fig. 6 B,D). Overall, the mean Z-scores for candidates were slightly higher than the Z-scores for experts, but there were no statistically significant differences between these groups (Suppl. Fig. 7). The Z-scores obtained for all analyses of Cd (U) compared to all analyses of Cd (B) did not differ significantly either (Suppl. Fig. 8).

Regarding the rounds with similar target concentrations, a decreasing study RSD<sub>R</sub> for Cd(U)<sub>low</sub> from round 2 to round 4 combined with an improved candidate laboratory performance could be observed. The percentage of satisfactory results increased from round 2 to round 4. These tendencies may be due to a training effect, which however was not observed when comparing the study RSD<sub>R</sub> and the Z-scores between the similarly spiked rounds 3 and 4 for Cd (U)<sub>low</sub>. Another possibility could be that the determination of Cd (U) has a critical point between the low CM of round 2 (A = 0.041 µg/l) and round 4 (A = 0.060 µg/l). This assumption is supported by the fact that the reported LOQ of several laboratories was 0.050 µg/l, which was also the recommended LOQ for Cd (U). Furthermore, the mean LOQ of all participants was 0.053 µg/l in round 2, i.e. above this hypothetical critical point of approximately 0.050 µg/l, while the mean LOQ of round 4 (0.049 µg/l) was just below 0.050 µg/l.

For Cd (U)<sub>high</sub>, however, a training effect might become visible when comparing the study RSD<sub>R</sub> values and the performance of the candidates between all rounds (Table 5). Although the highest concentration was applied in the 1st round, the percentage of satisfactory results was higher in the following rounds, while the interlaboratory variability remained constant and even decreased in the 4th round, which could be indicative of a training effect. In addition, performance improved from rounds 2 and 3, which were both conducted as EQUAS with a similar number of participants. A further reduction of the concentration in round 4 only led to an increase in unsatisfactory Z-scores, which would be consistent with a tipping point near the LOQ.

For Cd (B), the participants' results for CMs with low consensus/assigned values showed a higher study RSDR than the results for CMs with higher consensus/assigned values (Fig. 1 B). This hyperbolic dependency is consistent with the known association between precision and concentration. However, such a clear reciprocal effect could not be confirmed for Cd (U) (Fig. 1 A).

The dependency of the study RSD<sub>R</sub> in blood on the Cd concentrations (Fig. 1 B) is consistent with the general association between precision and concentration (Thompson, 1988). An exponential increase in the coefficient of variation with decreasing Cd concentration in urine has also been shown for urine in the German External Quality Assessment Scheme (G-EQUAS) (Göen et al., 2012). In the present study, such clear dependency was not found for urine. However, the examined concentration range in the ICI/EQUASs for Cd (U) was limited to very low levels from 0.041 µg/l to 0.448 µg/l (Fig. 1 A) compared to the observed Cd concentrations between about 0.1 and 3.5 µg/l in G-EQUAS (Göen et al., 2012).

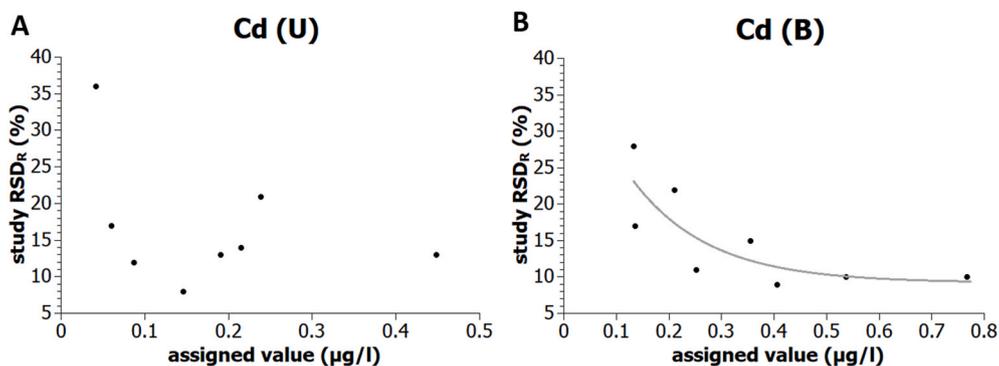


Fig. 1. Relationship between the study RSD<sub>R</sub> and consensus/assigned value for Cd (U) and Cd (B).

Although many European laboratories can provide high-quality data for Cd (U) and Cd (B), challenges remain with regard to method sensitivity, in particular for blood samples. LOQs for Cd (B) were generally higher than for Cd (U), resulting in a higher number of results reported as '< LOQ' (Suppl. Table 6). The biological matrix can have a strong impact on the analysis, especially for the determination of Cd (B) (Trzcinka-Ochocka et al., 2016). However, the obtained Z-scores

showed no significant differences between Cd (U) and Cd (B) over all rounds at either level (Suppl. Fig. 8).

With regard to Cd (B)<sub>low</sub>, the comparison of rounds 2 and 4 with the same spiking concentrations also pointed to a training effect of the participating laboratories in terms of a higher percentage of satisfactory Z-scores and a lower interlaboratory variability. The highest percentage of unsatisfactory Z-scores was observed in the 1st round, which also

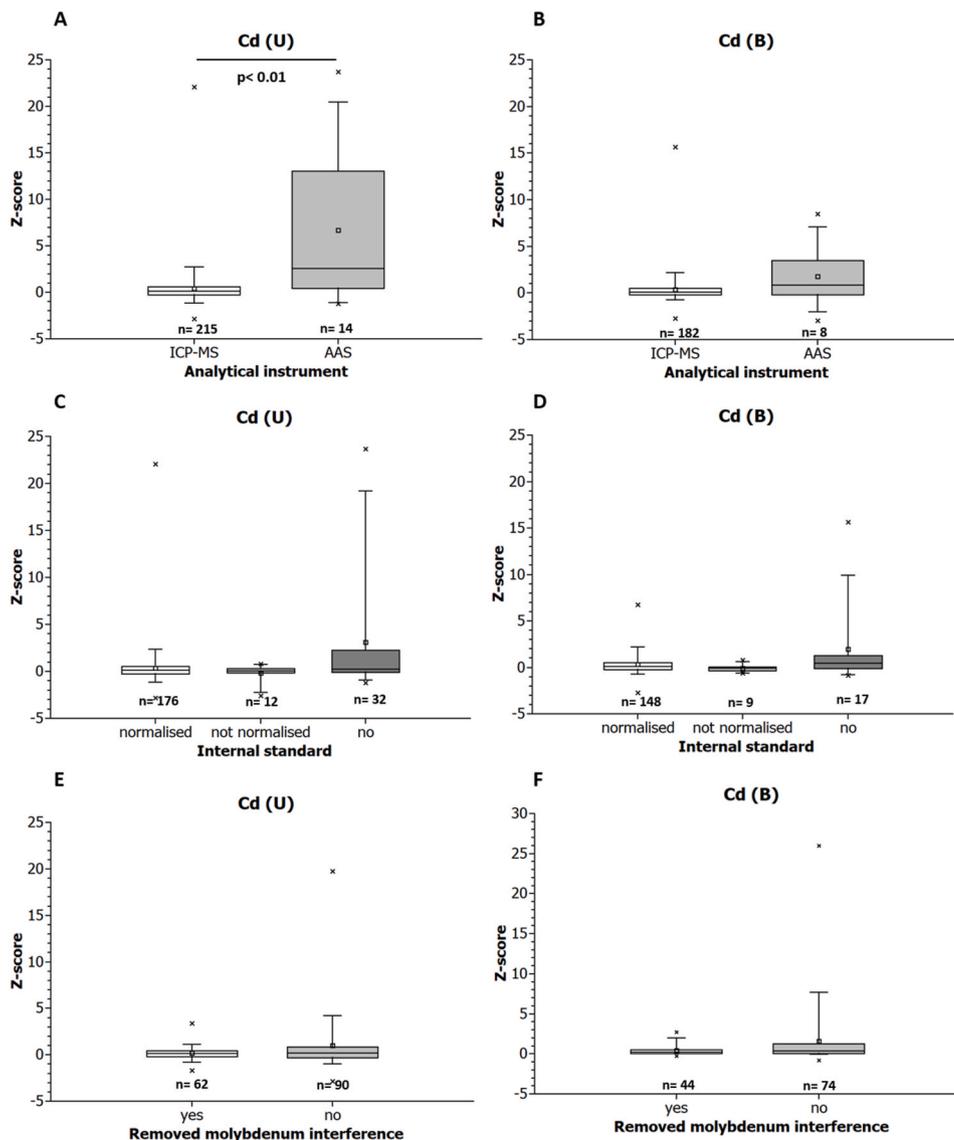


Fig. 2. Boxplots of the unsigned Z-scores obtained with different methods for the analysis of Cd (U) and Cd (B) by all participants in rounds 1–4. The box of the boxplots ranged from the 25th to the 75th percentile with the horizontal line showing the mean, the whiskers showing the 5–95th percentiles and the crosses the minimum and maximum values. Groups of Z-scores for all CMs over all rounds were compared using Mann–Whitney U tests: Z-scores obtained by using ICP-MS and AAS for determination of Cd (U) and Cd (B) (A, B), Z-scores obtained by using or not using an internal standard for the measurement of Cd (U) and Cd (B) (C, D), Z-scores achieved when molybdenum interferences were eliminated during the analysis of Cd (U) and Cd (B) (E, F).

accounts for a certain training effect of the participating laboratories; however, no clear improvement was observed for Cd (B)<sub>low</sub> between rounds 1 and 3.

The Z-scores obtained for the analysis of Cd were also compared with regard to the different methods used by the participants. Quantitative data of all rounds for both CM<sub>low</sub> and CM<sub>high</sub> were combined and divided into two to three groups according to methodological differences. Each group is presented in Fig. 2. The unsigned Z-scores were lower when the results were obtained by ICP-MS rather than by AAS (Fig. 2 A, B). Statistical analysis using the non-parametric Mann–Whitney *U* test showed significant differences ( $p < 0.01$ ) between the application of different instruments only for the determination of Cd (U), but not for Cd (B). Furthermore, there was a tendency for participants who used an internal standard to quantify Cd (U) or Cd (B) to achieve better Z-scores than participants who did not use an internal standard (Fig. 2 C, D). In tendency, lower Z-scores were also achieved when molybdenum interferences were eliminated during the analysis of Cd (U) or Cd (B) (Fig. 2 E, F). However, these differences were not statistically significant.

The possible influences of the different analytical methods were investigated mainly with regard to the instrument used (ICP-MS or AAS), the use of an internal standard and the elimination of molybdenum oxide interferences. In general, the AAS technique as a mono-elemental method of metal determination has a high sensitivity and selectivity for specific elements such as Cd (Trzcinka-Ochocka et al., 2016). Nevertheless, the most powerful technique presently applied for Cd measurements in biological matrices is ICP-MS as it shows less spectral interference, a wider dynamic range and a lower LOD than AAS (Trzcinka-Ochocka et al., 2016; Vorkamp et al., 2021). The better outcome associated with the use of ICP-MS instead of AAS to determine Cd (U) and Cd (B) in the four ICI/EQUAS rounds might, however, also be influenced by the fact that laboratories using AAS mainly did not use an internal standard (IS) or did not communicate it if they used one. Furthermore, the number of candidates working with AAS represented only 6% of all participants for Cd (U) and 4% for Cd (B), so that deductions from this comparison have to be interpreted with caution.

Brodzka et al. (2013) investigated the effectiveness of internal standardization of ICP-MS for trace element determination in urine and came to the conclusion that this method requires the use of internal standards. Thus, it is not surprising that the Z-scores obtained by Cd analyses without application of an IS (15% for urine, 10% for blood) were higher compared to data generated with an IS. Interestingly, the lack of a subsequent normalisation to the IS showed no clear change in the Z-scores. However, the statistical power was poor due to the low number of non-normalised values.

The present background levels of Mo in the CMs for Cd were on average 8.75 µg/l in urine and 2.65 µg/l in blood (Table 2). These Mo concentrations were only at a moderate level considering a biological reference value (BAR) of 150 µg/l Mo in urine, which represents the background exposure in a reference population without occupational exposure to Mo (Michalke et al., 2020). Despite these relatively low Mo concentrations in the analysed CMs, the achieved Z-scores for the Cd determination without compensation for Mo tended to be higher than the Z-scores of laboratories that eliminated Mo interferences (Fig. 2 E, F) (Schindler et al., 2014). This effect was not yet statistically significant, but it was stronger for Cd (U) than for Cd (B), which might be mainly due to the higher Mo concentrations in the urinary materials. Comparing the Z-scores of all participants over all rounds showed that the best results were obtained when using ICP-MS, an internal standard and a method that excludes interfering molybdenum clusters (see Fig. 2).

Finally, laboratories from 20 European countries were approved for the analyses of Cd in the HBM4EU project according to the criterion of having to achieve satisfactory Z-scores in both CMs from at least two rounds. For Cd (U), 37 of the 43 participants (86%) and for Cd (B) 29 of the 37 participants (78%) successfully participated in the ICI/EQUAS programme of the HBM4EU project. The study RSD<sub>R</sub> for the laboratories

with satisfactory results ranged from 35% (CM<sub>low</sub> in round 2) to 8% (CM<sub>high</sub> in round 4) for Cd (U) and from 21% (CM<sub>low</sub> in round 2) to 7% (CM<sub>high</sub> in round 2) for Cd (B) (see Suppl. Table 7). This demonstrated not only a good existing capacity for the analysis of Cd (U) and Cd (B) across Europe, but also a high analytical comparability and accuracy of the generated data among the successful participants of the ICI/EQUAS programme. Hereby, a quality-assured network of laboratories meeting the requirements of the HBM4EU programme has been established.

#### 4. Conclusions

The QA/QC programme of the HBM4EU project for Cd (U) and Cd (B) provided insights into the European interlaboratory comparability of these parameters at the concentration level of the general population. The results of the quality assurance programme demonstrated that high interlaboratory comparability could be achieved at this exposure level, if the laboratories used state-of-the-art techniques, e.g. ICP-MS with collision/reaction cell, effective procedures for interference suppression/elimination and compensation measures against imprecision (e.g. by using an internal standard). Moreover, trends of increasing comparability during the programme for both parameters indicated a training effect of recurrent proficiency tests and encourage the implementation of continuous interlaboratory comparison investigations at international level. Altogether, 37 and 29 European laboratories achieved satisfactory results in the determination of Cd (U) and Cd (B), respectively, in at least two rounds, indicating a high capacity of high-quality Cd analysis in Europe, although not all EU countries were represented. The data indicated that a high interlaboratory comparability with a mean study RSD<sub>R</sub> of 17% for Cd (U) and 15% for Cd (B) among the participating laboratories could be ensured for joint population studies within this pan-European human biomonitoring project. The current network for cadmium analysis within 20 European countries should be maintained and, if possible, extended in follow-up projects aiming to support public authorities in risk assessment.

#### Declaration of competing interest

The authors declare no conflict of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijheh.2021.113711>.

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