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GENERAL PAPER

Criteria to define the standard deviation for proficiency assessment for the determination of essential trace elements in serum: comparison of *Z*-scores based on the Horwitz function or on biological variability

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Abstract A critical issue in the organisation of Proficiency Testing/External Quality Assessment Schemes is the definition of the criteria against which the performance of individual laboratories should be evaluated. Organisers of *EQAS* in Occupational and Environmental Laboratory Medicine (http://www.occupational-environmental-laboratory.com) collaborate to define common acceptable levels of performance. The aim of this study was to compare the Horwitz function to the Fraser's approach. Sets of results obtained from the distribution of test materials in the Network schemes (for the measurands: copper, selenium or zinc in serum) were used to calculate *Z*-scores according to both approaches. Quality specifications derived from both approaches were also compared to the standard deviations obtained. Except for selenium, Horwitz criteria suggests a more stringent evaluation than Fraser criteria, the latter being very stringent as regard the participant analytical variability.

Keywords Quality specifications · Trace elements · Human serum · Human plasma · Proficiency testing · Horwitz · Fraser

Introduction

A critical issue in the organisation of Proficiency Testing/External Quality Assessment Schemes (*PTs/EQAS*) is the definition of the criteria against which the performance of

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individual laboratories should be assessed. Previous work by this group (Network of Organisers of *EQAS* for Occupational and Environmental Laboratory Medicine, http://www.occupational-environmental-laboratory.com) and within the European Project CoEPT has shown that different criteria are used even in the same field of application by different scheme organisers and therefore the performance of the same laboratory could be considered acceptable in one scheme but questionable or unacceptable in another. For this reason, the Network members collaborate to define common acceptable levels of performance, taking into account both clinical and analytical issues, and have already published limits for some measurands [1, 2].

However, regarding copper (Cu), selenium (Se) and zinc (Zn) in serum, desirable performance, defined using the quality specifications (QS) for total allowable error based on the biological variability approach [3], is unattainable by more than 20% of the participants [4], especially for selenium. Consequently, these QS are too stringent, particularly in sectors where acceptable performance is required for laboratory licensing. As an alternative, the possibility of applying the Horwitz function [5] to the field of occupational and environmental laboratory medicine is discussed and compared with previous published limits [1, 2] derived from the Fraser's approach [3] based on biological variability.

Materials and methods

Desirable QS for Cu, Se and Zn in serum were defined, according to Fraser [3] (Eq. 1), using the average data from the few studies in which human biological intra- and inter-individual variabilities of serum or plasma Cu, Se and Zn were reported [6–9]

$$\mathrm{QS} = \frac{\sqrt{\mathrm{CV}_{\mathrm{intra}}^2 + \mathrm{CV}_{\mathrm{inter}}^2}}{4} + z\frac{\mathrm{CV}_{\mathrm{intra}}}{2} \quad (1)$$

where $\mathrm{CV}_{\mathrm{intra}}$ and $\mathrm{CV}_{\mathrm{inter}}$ are the intra- and inter-individual biological variation, respectively, expressed as coefficients of variation and z is equal to 1.65 for a 95% probability level.

However, because relative analytical imprecision increases rapidly at low concentrations, QS were set at fixed values for concentrations below 7 µmol/l, for Cu, 8 µmol/l, for Zn and 0.6 µmol/l, for Se, as previously reported [2].

The QS are (see also Fig. 1):

Cu ±0.56 µmol/l or ±8%, whichever is greater
Se ± 0.048 µmol/l or ±8%, whichever is greater
Zn ±0.80 µmol/l or ±10%, whichever is greater

QS based on the Horwitz's equation [5] were calculated according to Eq. 2 and 3, where C is the assigned value expressed as mass fraction.

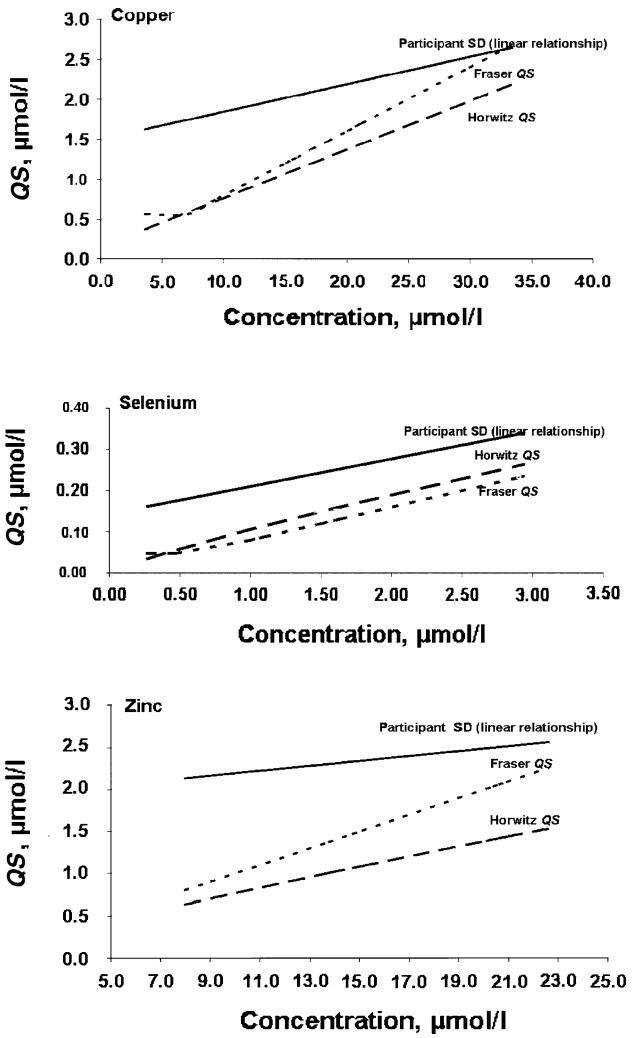

Fig. 1 Comparison of participant's analytical variability to desirable values calculated according to Horwitz function [5] or Fraser approach [3]

$$\sigma_H = 0.02\ C^{0.8495} \quad (2)$$

$$QS = 2\sigma_H \quad (3)$$

The QS values were converted to µmol/l (Fig. 1).

Data used for this comparison were taken from the sets of results reported by participants in *EQAS* for samples with very low (around 3.5 µmol/l for Cu and 0.25 µmol/l for Se), low (9 µmol/l for Cu, 8 µmol/l for Zn and 0.50 µmol/l for Se), medium (15 and 20 µmol/l for Cu and Zn, respectively, and 1.00 and 1.50 µmol/l for Se) and high (30 µmol/l for Cu and 3.00 µmol/l for Se) concentrations. These concentrations were chosen to cover physiological and pathological ranges of values [10–12]. For each set of results, means and standard deviations were calculated after simple elimination of outliers at ±3 standard deviation. Grubb's test was not used. These means were used as target concentration to evaluate performance assessments.

Table 1 Distribution of Cu, Zn and Se *Z*-scores, expressed as median and confidence interval according to quality specifications (QS) whatever the sample target concentrations

	Cu		Zn		Se	
	Median	Confidence interval	Median	Confidence interval	Median	Confidence interval
Fraser QS	0.00	−2.54 to 2.50	0.00	−2.81 to 3.28	0.17	−3.75 to 4.17
Horwitz QS	0.00	−3.19 to 2.88	0.00	−3.65 to 4.48	0.15	−3.30 to 3.97

Table 2 Percentage of questionable and unsatisfactory *Z*-scores according to Fraser [2, 3] or Horwitz [5] quality specifications (QS), at different concentrations of Cu, Se and Zn

Element	Sample concentration (µmol/l)	Fraser *QS* Percentage of questionable and unsatisfactory *Z*-scores	Horwitz *QS*
Cu	3.5	40.2	57.3
	9.0	32.0	33.6
	15.0	22.8	27.2
	20.0	32.6	35.6
	30.0	20.2	31.5
Se	0.25	49.3	56.5
	0.50	63.4	55.4
	1.00	45.3	33.7
	1.50	35.7	30.1
	3.00	34.0	27.8
Zn	8.0	34.6	57.5
	15.0	23.7	42.9
	20.0	47.2	49.1

Z-scores were calculated according to:

$$Z - score = \frac{x_i - X}{\mathrm{QS}/2} \quad (4)$$

where x_i refers to the participant's result, X the target value and QS the quality specifications. Performance is considered satisfactory for $|Z\text{-score}| \leq 2$, questionable for $2 < |Z\text{-score}| \leq 3$ and unsatisfactory for $|Z\text{-score}| \geq 3$ [13].

Results and discussion

The performances of participants applying either the Horwitz or the Fraser criteria are indicated in Tables 1 and 2. Figure 1 presents the *Z*-score values obtained by participants for a single sample in the range of reference values. Neither the Horwitz nor the Fraser criteria were fulfilled by the majority of the participants (Table 2; Fig. 2). Except for selenium, Horwitz criteria suggest a more stringent evaluation than Fraser criteria, the latter being very stringent as regard the participant analytical variability (Figs. 1, 2; Tables 1, 2).

Participation in external quality assessment schemes or proficiency testing schemes allows laboratories to evaluate the quality of their results. It is also necessary to fulfil the requirement for accreditation [14, 15] and, in some jurisdictions, it may be mandated by law [16, 17]. For clinical purposes, the method proposed by Fraser [3] for the calculation of QS may represent a useful and objective way to assess laboratory performance. However, it suffers from two limitations. First, biological variability is rarely reported in pathological states and as performance depends on concentration, QS derived exclusively from the healthy population could be insufficient. Second, reports dealing with intra- and inter-individual variabilities show discrepant results and therefore the QS may vary according to data used [6–9]. The Horwitz function was developed using data from inter-laboratory method performance studies for food analysis but the distribution of standard deviation for biological tests may not follow the same proposed law as in

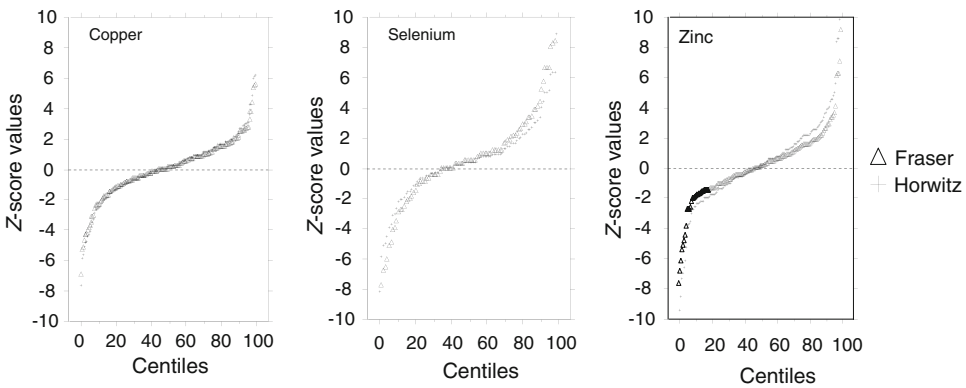

Fig. 2 Distribution of Cu, Zn and Se *Z*-scores for samples concentration within normal range (Cu and Zn: 15 µmol/l, Se: 1.00 µmol/l), expressed as centiles, according to Fraser [2, 3] and Horwitz [5] quality specifications. *Z*-score scale has been limited to the range −10, +10

food analysis. Therefore, care should be taken before applying criteria derived from other sources to the clinical field. Collaboration among scheme organisers in the same field allows opportunities to highlight and discuss potential problems, based on the on-going experience, and hence to propose performance goals compatible with the state-of-the-art.

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