Clinical Chemistry 43:8
1342–1347 (1997)

Laboratory Management

Creatinine measurement proficiency testing: assignment of matrix-adjusted ID GC-MS target values

Anna Carobene,[1] Carlo Ferrero,[1] Ferruccio Ceriotti,[1]* Annalisa Modenese,[1] Marco Besozzi,[2] Elena De Giorgi,[1] Michela Franzin,[1] Carlo Franzini,[3] Marzia Galli Kienle,[4] and Fulvio Magni[1]

The results of an external quality-assessment experiment for serum creatinine measurement are described. Fifty-one laboratories performed quintuplicate analyses during three different analytical runs on six lyophilized sera and two frozen human serum pools. Isotope dilution gas chromatography–mass spectrometry (ID GC-MS) target values were assigned to all the materials. Intralaboratory within- and between-run imprecision results were very similar for all the materials tested (CV ≤2.20% and ≤4.70%, respectively). The overall imprecision obtained was high (CV 6.5–20.0%) because of increased interlaboratory–intermethod variability. A significant positive bias (+9.2–+43.7%) was found for all the materials at lower creatinine concentration. By using two human sera at different concentrations, we could calculate the constant and the proportional calibration bias displayed by each peer group. The majority of the lyophilized materials showed a behavior divergent from the frozen pools, indicating matrix-related problems. We propose a new algorithm for calculating matrix bias correction factor instrument–reagent specific for each material.

INDEXING TERMS: quality control • reference method • control materials

The analytical goals for creatinine on the basis of biological variability are very demanding (CV ≤2.2% for precision and ≤2.8% for accuracy *[1]*). Imprecision is strictly dependent on analyzer characteristics, and can be easily verified. On the contrary, variables affecting inaccuracy (method specificity, type of calibration, calibrator matrix, and value assignment) are more difficult to identify and control. These variables lead to a wide dispersion of results among different laboratories. As a result, the measurement appears far from the desirable performances.

Currently, there is more room for improvement in accuracy than for precision in creatinine determination. Through the use of reference methods and appropriate materials, it is possible to come closer to the "trueness" of the results. The availability of a definitive method is certainly a problem, but for accuracy of routine methods the real difficulty is the material used. The case of creatinine is particularly critical because the lack of commutability *[2]* is emphasized by the poor specificity and weakness of the majority of the routinely used picrate reaction-based methods *[3–5].*

This fact forces almost all the proficiency testing programs to use peer group target values without any means to verify the real accuracy of any single laboratory, and without progress toward improvement of the agreement between the different laboratories.

Here we describe the results of an external quality-assessment scheme (EQAS) from 51 laboratories of Lombardy region (Italy).[5] We tried to focus on several aspects related to the accuracy of creatinine measurement. First, with a peculiar experimental design of replicate analyses, we could estimate components of variability. Second,

[1] Istituto Scientifico H S Raffaele, Laboratorio Analisi, Via Olgettina 60, 20132 Milano, Italy.
[2] IRCCS Centro Auxologico Italiano, Laboratorio Analisi, Milano, Italy.
[3] Università di Milano Istituto Scienze Biomediche, Ospedale L.Sacco, Milano, Italy.
[4] Dipartimento di Chimica e Biochimica Medica, Via Saldini 50, Università di Milano, Italy.
*Author for correspondence. Fax +39-2-2643-2640; e-mail ceriotf@hsr.it.
Received December 3, 1996; revised April 21, 1997; accepted April 29, 1997.

[5] Nonstandard abbreviations: EQAS, external quality-assessment scheme; ID GC-MS, isotope dilution gas chromatography–mass spectrometry; SRM, Standard Reference Material; and MTBSTFA, *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-trifluoroacetamide.

through the use of frozen sera and the ultimate accuracy reference, an isotope dilution gas chromatography–mass spectrometry (ID GC-MS) method, we calculated constant and proportional components of the calibration error. Third, we verified the presence of matrix effects in most lyophilized sera and, with a modification of the algorithm proposed by Ross et al. *[6]*, we calculated a matrix bias correction factor.

Materials and Methods

ID GC-MS CREATININE METHOD

A Finnigan MAT95 mass spectrometer (Finnigan MAT, Bremen, Germany) was used for GC-MS analysis. HPLC purification was carried out with a Jasco HPLC pump (model PU880, Tokyo, Japan) and with a variable-wavelength ultraviolet detector (model 875-UV, Jasco). The HPLC column was a Lichrosphere 100 RP-18 (250 × 4 mm, 5-μm particles) from Merck (Darmstadt, Germany).

Creatinine [Standard Reference Material (SRM) 914a, 99.8% purity] and lyophilized reference sera SRM 909a1 (certified value = 84 ± 1 μmol/L) and 909a2 (463 ± 6 μmol/L) were from NIST (October 13, 1993; revision of certificate dated February 24, 1993). Sera were reconstituted according to the NIST insert. [$^2H_3$]Creatinine (98 atom % excess) was from Isotec (Miamisburg, OH). *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-trifluoroacetamide (MTBSTFA) was purchased from Fluka (Buchs, Switzerland). All solvents and general chemicals used were of analytical grade.

All solutions and sera were dispensed with known accuracy and imprecision as already reported *[7]*. Calibrators were prepared by mixing various amounts of SRM 914a creatinine with [$^2H_3$]creatinine to provide a series of mixtures with known ratios of the two isotopomers between 0.8–1.2.

Weighed amounts of each serum were supplemented with a weighed aliquot of the [$^2H_3$]creatinine solution to get about a 1:1 ratio of [^{1}H]creatinine:[^{2}H]creatinine. After stirring, supplemented sera were kept at room temperature for 2 h to allow equilibration before protein precipitation obtained with acetone. The aqueous phase was separated and evaporated to dryness under reduced pressure. An isocratic separation of creatine from creatinine was achieved by HPLC with H_2O containing 0.1% HCOOH (pH 5.5–5.7 with NH_4OH) as mobile phase at 1 mL/min flow rate. Creatinine was monitored at 235 nm and the collected fraction was dried under vacuum at 40 °C. Creatinine was converted into its *tert*-butyldimethylsilyl derivative with 70 μL of CH_3CN:MTBSTFA (2:1 by vol) at 70 °C for 30 min. Gas chromatographic separation was achieved with a 30-m SPB-35 column (Supelchem, Milan, Italy). The injector temperature was at 250 °C, the initial GC oven temperature was set at 170 °C for 1 min and subsequently increased to 180 °C at 2.5 °C/min, and to 270 °C at 30 °C/min. Injections of samples were alternated with duplicate analysis of calibrators having ^{1}H:^{2}H ratios of 0.8, 1.0, 1.2, 1.0, 0.8, etc. The isotopic ratio was determined by monitoring ions at *m/z* 298 and 301 for unlabeled and labeled creatinine, respectively.

Concentration of serum creatinine (μmol/L) was then computed from the measured isotopic ratio on the basis of the weight of each serum aliquot, the density, and the internal calibrator added, as already described *[7]*.

EXPERIMENTAL DESIGN

Eight different materials were sent to 51 clinical laboratories of the Lombardy region: two fresh-frozen human serum pools (CON1 and CON2) and six lyophilized materials (LYO1–LYO6). The frozen pools were delivered in solid CO_2, stored at −20 °C, thawed on the day of analysis, and analyzed within 1 h. Lyophilized sera were stored at 4 °C and reconstituted 1 h before analysis. In each material, creatinine was measured in quintuplicate in three consecutive days with the automated analyzers routinely used (15 results per laboratory, per control material). The study participants were asked to classify their analytical method according to the chemical principle, the instrumentation, the source of reagents, and the type of calibrator. According to this classification we identified three homogeneous groups [Boehringer–Hitachi, Johnson & Johnson (J&J), Beckman] and two miscellaneous groups.

CONTROL MATERIALS

CON1 and CON2 were prepared from sera obtained with Serum Separator Tubes (SST Vacutainer; Becton Dickinson, Milan, Italy). Concentration was adjusted by adding appropriate amounts of creatinine (SRM 914a). LYO1–LYO6 were lyophilized commercial materials: LYO1 (Roche N, lot no. A 1136); LYO2 (Roche A, lot no. S 1135 2); LYO3 (Boehringer, Precinorm U, lot no. 177111 61); LYO4 (Boehringer, Precipath A, lot no. 177481 71); LYO5 (Bio-Rad, Lyphochek 1, lot no. 15011); and LYO6 (Bio-Rad, Lyphochek 2, lot no. 15012).

INSTRUMENTATION

Analytical instruments used in this experiment were: Boehringer Hitachi analyzers 704 (2), 717 (7), 747 (6), 911 (3), (Boehringer Mannheim, Milan, Italy); Beckman CX7 (4), CX3 (1), CX5 (1) (Beckman Analytical, Cassina de Pecchi, Italy); Dax 24 (1) (Bayer, Cavenago, Italy); Olympus AU 5000 (3), Au 510 (1) (Kontron Instruments, Milan, Italy); Shimadzu CL 7000 (1), 7200 (1) (Shimadzu Italia, Milan, Italy); IL 900 (4), ILAB 1800 (2), Monarch (1) and Phoenix (1) (Instrumentation Laboratory, Milan, Italy); Ektachem analyzers 700 XR (8), 500 (3), 250 (1), (J&J, Cinisello Balsamo, Italy).

SOFTWARE

EQAS data were collected via an ad hoc computer program compiled in CA-Clipper Version 5.2 (Computer Associates, Milan, Italy) and distributed on floppy disk together with the samples. Data were automatically transferred in a Lotus 1-2-3 spreadsheet (release 3.1; Lotus Italia, Milan, Italy).

STATISTICAL ANALYSIS

The mean of each analytical run, the laboratory mean (mean of three analytical runs), the group mean, and the grand mean (mean of laboratory means) were calculated. SD and within-run CV (CV_w), between-run CV (CV_b, containing only the across-day component of variability), between-laboratories CV (CV_{inter}), and overall CV (CV_{ovr}) were calculated with analysis of variance performed on a Lotus 1-2-3 spreadsheet.

Calibration bias line. For each peer group we calculated the equation of the line defined by the two frozen pools (CON1 and CON2):

$$y = a_p + b_p x$$

where y is peer group mean and x is the IDMS value; fixed constant calibration bias (a_p) and fixed proportional calibration bias ($b_p - 1$) of each peer group were obtained from the parameters of the line.

Statistical verification of matrix effect occurrence. Each laboratory mean, obtained for every lyophilized material, was corrected for the calibration bias of the laboratory itself according to the following formula:

$$[(Y_{iL} - a_i)/b_i]$$

where Y_{iL} is the mean of lyophilized sera L of the laboratory i and a_i, b_i are parameters of the laboratory calibration bias line.

The statistical significance of the difference between corrected results, grouped according to the peer groups, and ID GC-MS value of each material was calculated (Student's *t*-test). A statistically significant difference indicates the presence of a matrix bias (i.e., noncommutability of the material).

Matrix bias correction factor. A factor to correct bias introduced by the matrix of the lyophilized control materials has been obtained by modifying the formula proposed by Ross et al. *[6]* to take into account the problem of the constant component of the calibration bias, very common in creatinine measurement with routine methods. The algorithm proposed by Ross et al. *[6]* for the calculation of the matrix bias correction factor of lyophilized sera is:

$$\{1 + [(Y_{pF} - C_F)/C_F]\}(C_L/Y_{pL})$$

where $Y_{p\,F}$ is the peer group mean of fresh frozen human pool.

$Y_{p\,L}$ is the peer group mean of lyophilized sera, C_F is the GC-IDMS value of fresh frozen human pool, and C_L is the GC-IDMS value of lyophilized sera.

Modified algorithm:

$$[(b_p C_L) + a_p]/Y_{pL}$$

where b_p and a_p are the parameters of the calibration bias line of a peer group method p.

Results

The reliability of our ID GC-MS method is demonstrated by the results obtained on NIST reference materials SRM 909a1: 84.3 μmol/L, CV 1.05% and 909a2: 470.0 μmol/L, CV 0.41%.

An overview of all results obtained on the six lyophilized materials and the two frozen pools is shown in Table 1. We report ID GC-MS target values and overall and peer group means. Results obtained by the clinical laboratories (including overall means and ANOVA) are also summarized. In some cases, such as LYO5, very large discrepancies among method means are evident.

The results obtained on the two frozen human serum pools were used to calculate constant calibration bias and proportional calibration bias of three homogeneous groups of analytical systems (we considered homogeneous the groups constituted by instruments, reagents, and calibrators from the same manufacturer). Table 2 shows the biases from the ID GC-MS values and the parameters of the lines obtained.

The results of the statistical verification of the occur-

Table 1. Results of creatinine proficiency testing (μmol/L).

Reference data		All laboratories (n = 51)						Method groups, mean ± SD									
				CV, %				Enzymatic J & J (n = 12)		Picrate Beckman (n = 6)		Picrate Boehringer (n = 15)		Enzymatic (n = 12)		Other (n = 16)	
	ID GC-MS, value ± SD	Grand mean	Bias, %	Within day	Between days	Between labs.	Overall										
LYO1	106.9 ± 0.6	126.4	18.0	2.2	2.1	7.7	8.3	124.5	1.4	118.8	2.1	130.7	1.4	106.2	0.8	128.1	3.3
LYO2	499.1 ± 3.2	509.2	2.0	1.3	2.3	7.5	8.0	559.2	6.4	513.4	6.1	481.9	3.3	484.3	4.8	497.9	9.7
LYO3	164.3 ± 1.1	175.0	6.6	1.6	2.5	8.8	9.3	195.4	1.7	168.4	2.2	171.4	1.2	157.8	8.6	168.1	4.3
LYO4	348.4 ± 3.6	346.5	−0.4	1.3	2.2	9.7	10.0	395.7	4.6	347.1	3.8	329.4	2.3	318.5	14.7	330.1	7.5
LYO5	105.6 ± 1.5	152.0	43.7	2.2	4.7	19.3	20.0	111.9	1.2	170.6	6.6	161.9	1.2	101.4	0.1	171.7	5.7
LYO6	531.5 ± 4.4	532.2	0.1	1.3	2.4	6.5	7.1	526.3	4.2	578.1	10.0	518.5	3.0	478.9	6.5	538.8	11.9
CON1	114.7 ± 1.5	125.5	9.2	2.2	2.3	6.3	7.1	125.5	1.4	127.1	1.9	126.4	1.3	114.8	6.4	124.9	3.1
CON2	343.8 ± 1.0	344.8	0.2	1.3	2.2	6.0	6.5	362.2	2.8	354.6	2.7	335.6	2.1	346.8	24.4	335.6	7.1

Table 2. Data of calibration bias lines for three homogeneous groups of analytical systems.

	J & J		Beckman		Boehringer–Hitachi	
	CON1	CON2	CON1	CON2	CON1	CON2
y = Group mean, μmol/L	125.5	362.2	127.1	354.6	126.4	335.6
x = ID GC-MS value, μmol/L	114.7	343.8	114.7	343.8	114.7	343.8
b_p	1.033		0.994		0.914	
a_p, μmol/L	6.9		13.1		21.5	
Total percent bias	+9.3%	+5.4%	+10.8%	+3.2%	+10.1%	−2.4%

rence of matrix effect are presented in Table 3. Only three of 18 material/analytical system combinations exhibit commutable behavior.

By using the formula illustrated in ***Materials and Methods***, one can calculate a "matrix bias correction factor" taking into account the different components of the calibration bias. Table 4 shows the matrix bias correction factor of each lyophilized material for the different method groups. By multiplying the peer group means by these factors, one can remove the component of inter-method variability due to matrix effects from the results obtained on lyophilized materials. Fig. 1 shows the peer group means obtained, for each material, before and after results modification according to the matrix bias correction factors. In Fig. 2 comparability of data achievable on fresh frozen sera and lyophilized sera after correction is shown (J&J method group).

Discussion

We developed an ID GC-MS method similar to the one proposed by Stöckl and Reinauer *[8]* that combines a sufficient practicability with good precision (CVs from 0.41% to 1.42%) (Table 1) and accuracy (bias of 0.36% and 1.51% from NIST target values on 909a1 and 909a2, respectively).

Our experiments (see Table 1 and Fig. 1a) emphasize that: (*a*) there are very discordant percent biases from the ID GC-MS target values—very high for control materials with lower creatinine concentrations, very small for sera with higher concentrations; (*b*) the major component of variability is the between-laboratories variability that is always very high; (*c*) the intralaboratory variability can be considered acceptable but, especially at the lower concentrations, it is far from the analytical goal calculated on the basis of biological intraindividual variability *[1]*; and (*d*) the frozen pools (CON1 and CON2), although showing very similar intralaboratory variability, exhibit a lower interlaboratory imprecision. The results are comparable (in terms of imprecision and inaccuracy) with those obtained in a previous experiment *[9]*. Large differences among the method means were present (Table 1). In particular, LYO5 shows bias of >50% between enzymatic and picrate methods, suggesting the presence of some noncreatinine substance reacting with picrate. Unfortunately, 16 laboratories were working with miscellaneous conditions [calibrators and (or) reagents from manufacturers different from those of the instrumentation] or with unique systems, and it was not possible to classify and treat those data. Also, the enzymatic group is not homogeneous, with one laboratory using the UV creatinine reaction and another using the Trinder coupled reaction. For these reasons we performed further calculations only for the three homogenous groups of analytical systems: J&J analyzers, Beckman CX family, and Boehringer–Hitachi family.

Assuming the frozen pools as not affected by any matrix effect, we used them to calculate calibration bias (e.g., method bias observed relative to ID GC-MS method) according to Ross et al. *[6]*. Percent biases obtained on CON1 were completely different from those on CON2, thus suggesting the occurrence of a significant constant calibration bias (Tables 1 and 2). We decided to take into account constant calibration bias by calculating the equation of the line defined by the two pools. The data of slope and intercept (Table 2) clearly individuate a different behavior of the three peer groups. Note the similarity of

Table 3. Results (μmol/L) obtained on lyophilized materials corrected for calibration bias and significance of difference (μmol/L) between corrected values and definitive method values.

		J&J (n = 12)		Beckman (n = 6)		Boehringer (n = 15)	
Material	Target values	Corrected means	Difference	Corrected means	Difference	Corrected means	Difference
LYO1	106.9	113.8	6.9*	106.4	−0.5 NS	119.5	12.6*
LYO2	499.1	534.5	35.4*	503.5	4.4 NS	503.9	4.8*
LYO3	164.3	182.5	18.1*	156.3	−8.0*	164.0	−0.3 NS
LYO4	348.4	376.2	27.8*	336.2	−12.2*	336.9	−11.5*
LYO5	105.6	101.6	−4.0*	158.5	52.9*	153.6	47.9*
LYO6	531.5	502.6	−28.9*	568.7	37.3*	544.0	12.5*

* $P < 0.05$; NS, not significant.

Table 4. Matrix bias correction factors of each material for the different method groups.

Control material	J&J	Beckman	Boehringer
LYO1	0.943	1.004	0.912
LYO2	0.935	0.991	0.991
LYO3	0.904	1.047	1.002
LYO4	0.927	1.035	1.032
LYO5	1.037	0.692	0.729
LYO6	1.057	0.936	0.978

the parameters of our regression line for Hitachi systems with the equation of the correlation between an HPLC reference method and the Hitachi 911 results presented by Blijenberg et al. *[5]*. Clearly the methods based on the Jaffe reaction are affected by an important positive constant calibration bias (Table 2) caused probably by an aspecific signal. This is particularly evident at low creatinine concentrations or with some type of artificial material such as LYO5. This positive bias, in the case of the Boehringer–Hitachi group, can be almost completely attributed to the

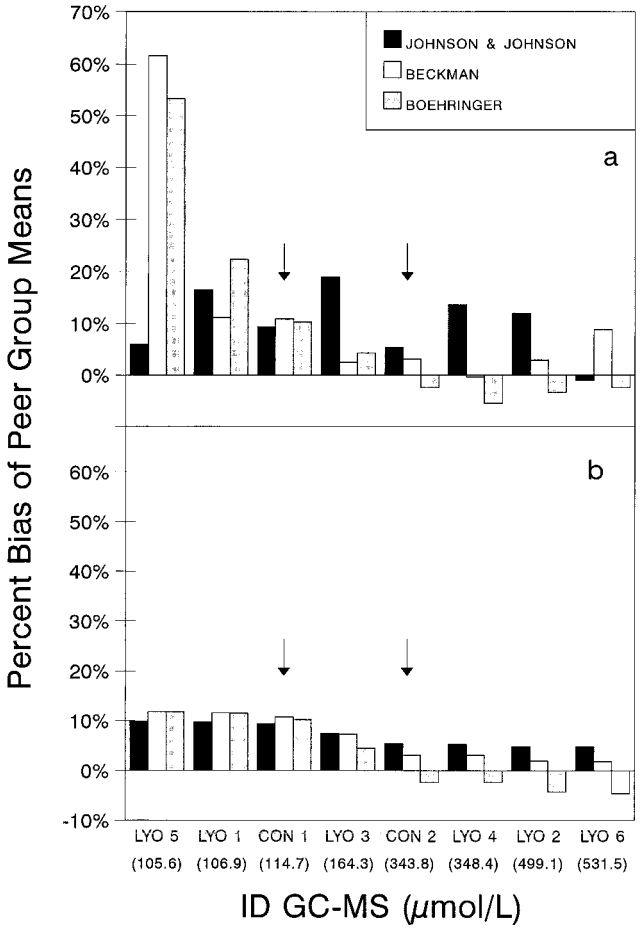

Fig. 1. Effects of the application of matrix bias correction factor.

Each *bar* represents the mean percent bias of every peer group mean from ID GC-MS value, before (*a*) and after (*b*) the application of the matrix bias correction factor. Plot (*b*) is representative of the calibration bias. *Arrows* indicate the frozen pools.

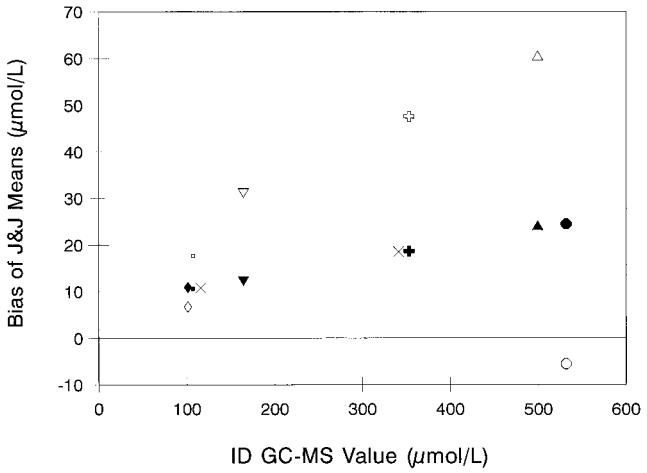

Fig. 2. Bias/concentration profile of J&J peer group.

Mean values before (*open symbols*) and after (*closed symbols*) correction are compared with mean values of fresh frozen sera (*x*-axis). (◆, ◇, LYO5; ■, □, LYO1; ▼, ▽, LYO3; ✚, ✙, LYO4; ▲, △, LYO2; ●, ○, LYO6; ×, CON1 and CON2).

picrate reactivity with proteins. The reading window of the Boehringer method is quite long (~90 s), with a prolonged delay from the starter addition (~90 s). This favors the interference from slow-reacting interferents such as proteins *[10]*. In fact, an extensively dialyzed albumin solution (50 g/L) gives (on an Hitachi 747) an apparent creatinine value of 21 ± 0.9 μmol/L. The apparent accuracy displayed for samples with intermediate concentration is due to a concomitant negative proportional bias. Better performances were obtained with enzymatic methods, both for dry and wet chemistry (Table 1). In particular, laboratories using wet chemistry enzymatic methods provided very promising results. This finding is in agreement with Blijenberg et al. *[3, 4]*, but the very limited number of participants using these methods (two) does not allow any generalization.

Table 3 shows clearly that lyophilized sera behave differently from the frozen pools. Only in three of 18 material/method combinations was the difference between the two types of materials not significant. These results imply that the use of target values on these types of materials is useless and can lead to faulty considerations. The bias introduced by the matrix is typical for a defined analytical system. Fig. 1a shows how different this effect is for the various materials and analytical systems. With the application of the algorithm proposed, it is possible to calculate factors (shown in Table 4) that are able to correct for the error introduced by the matrix. Fig. 1b, in which the matrix effect is corrected, shows almost identical behavior for the different materials with similar creatinine content, whether frozen or lyophilized. Indeed the bias/concentration profile of results obtained on lyophilized sera after correction closely resembles behavior of fresh frozen sera (Fig. 2). The proposed algorithm has a more general applicability than the previous one *[6]* and can give reliable results even when a constant calibration bias is present.

All matrix bias correction factors were calculated with the peer group means, but we tried also to calculate the factors by using single laboratory data of the same peer group. The results obtained showed a noteworthy concordance among laboratories of the same group. The variability of the obtained factors, measured as CV, ranged between 0.80% and 3.75% according to the material and the group of methods. This homogeneity of data allows us to hypothesize the possibility of the use of a relatively small number of pilot laboratories to calculate the matrix bias correction factor for a defined lot of control material to be used in an EQAS.

The major problem of EQAS, when artificially manipulated control materials are involved, is the bias introduced by the materials themselves for the different types of methods. This fact forces the use of peer group means, but without any guarantee, apart from the producer declaration, of the real accuracy of the analytical system. However, it is not possible to verify whether the difference among the various analytical systems are caused by the characteristics of the material only or by real accuracy problems with a risk "of an implicit endorsement of methodologies that fail to satisfy fundamental accuracy goals" *[11]*. Obviously the more straightforward approach to this problem should be the use of fully commutable material such as fresh or frozen sera, but the costs of distributing this type of material prevent its use, at least on a regular basis. The matrix-adjusted target values can be an acceptable compromise that allows the utilization of the lyophilized sera provided that two important limitations are adequately considered: (*a*) the matrix bias correction factor can be calculated only for well-defined analytical systems; (*b*) the serum pools used in generating the algebraic correction are the same as normal fresh serum specimens. The last one can be an important drawback; the probability that a minimally manipulated serum pool could exhibit a noncommutable behavior is low, but a check of the commutability, e.g., according to the College of American Pathologists' protocol *[12]*, is advisable. Moreover, this approach is not intended to substitute the direct comparison with a Reference Method on fresh sera *[13]*, but only to minimize the matrix effect, thus allowing the use of Reference Method target values for lyophilized materials.

This work was supported by grant no. 869, funded by Lombardy Region, Italy. The assays performed in this study were made possible through the efforts of: L. Guerrini, M. Cavalleri, C. Petrini, A. Bianchi Bosisio, E. Solbiati, P. Cueroni, A. Nespolo, E. Scarazzatti, R. Vigoni, S. Bossini, A. Petrella, P. Maestrini, F. Tirelli, A. Cespa, L. Ferrari, G. Casiraghi, C. Okely, R. Antinozzi, F. Mariani, M.L. Carati, A. Ferrari, T. Baratto, G. De Leo, C. Ottomano, E. Guagnellini, G. Gallina, G. Giocoli, M. Musmeci, V. Malacrida, M. Iannone, A. Marocchi, M. Panteghini, M. Mancosu, A. Marelli, R. Trotti, F. Aguzzi, P. Mocarelli, A. Pagano, P.A. Bonini, and M. Murone.

References

1. Fraser CG, Hyltoft Petersen P, Ricos C, Haeckel R. Proposed quality specifications for the imprecision and inaccuracy of analytical systems for clinical chemistry. Eur J Clin Chem Clin Biochem 1992;30:311–7.
2. Rej R, Jenny RW, Bretaudiere JP. Quality control in clinical chemistry: characterization of reference materials. Talanta 1984;31: 851–61.
3. Blijenberg BG, Brouwer HJ, Kuller TJ, Leeneman R, van Leeuwen CJM. Improvements in creatinine methodology: a critical assessment. Eur J Clin Chem Clin Biochem 1994;32:529–37.
4. Blijenberg BG, Brouwer HJ. The accuracy of creatinine methods based on the Jaffe reaction: a questionable matter. Eur J Clin Chem Clin Biochem 1994;32:909–13.
5. Blijenberg BG, Brouwer RJ, Baadenhuijsen H, Boerma GJM. Creatinine and surveys: an assessment. Eur J Clin Chem Clin Biochem 1995;33:855–8.
6. Ross JW, Myers GL, Gilmore BF, Cooper GR, Naito HR, Eckfeldt J. Matrix effects and the accuracy of cholesterol analysis. Arch Pathol Lab Med 1993;117:393–400.
7. Magni F, Paroni R, Bonini PA, Galli Kienle M. Determination of serum glucose by isotope dilution mass spectrometry: candidate definitive method. Clin Chem 1992;38:381–5.
8. Stöckl D, Reinauer H. Candidate reference methods for determination of target values for cholesterol, creatinine, uric acid and glucose in external quality assessment and internal accuracy control. I. Method setup. Clin Chem 1993;39:993–1000.
9. Ferrero C, Carobene A, Ceriotti F, Modenese A, Arcelloni C. Behavior of frozen serum pools and lyophilized sera in an external quality-assessment scheme. Clin Chem 1995;41:575–80.
10. Spencer K. Analytical reviews in clinical biochemistry: the estimation of creatinine [Review]. Ann Clin Biochem 1986;23:1–25.
11. Tietz NW, Rodgerson DO, Laessig RH. Are clinical laboratory proficiency tests as good as they can be? [Opinion]. Clin Chem 1992;38:473–5.
12. Eckfeldt JH, Copeland KR. Accuracy verification and identification of matrix effects. The College of American Pathologists' protocol. Arch Pathol Lab Med 1993;117:381–6.
13. Tietz NW. Accuracy in clinical chemistry—does anybody care? [Opinion] Clin Chem 1994;40:859–61.