Ann. Ist. Super. Sanità
Vol. 25, N. 3 (1989), pp. 405-416

THE INTERLABORATORIAL QUALITY ASSURANCE PROGRAM FOR BLOOD LEAD DETERMINATION. AN EVALUATION OF METHODS AND RESULTS

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Summary. - *For over five years a national program, promoted by a working group of the Istituto Superiore di Sanità (Italian National Institute of Health), has been active in Italy for the quality control of the blood lead levels determination. The program is based on the adoption, by the laboratories, of the same known-titre materials, for the internal quality control, and on the participation in periodical collaborative exercises for the external quality evaluation. The promoting laboratory prepared the control samples, verified their homogeneity and stability and distributed them to the laboratories following a randomized procedure; then, it provided a preliminary elaboration of the results (precision, difference from the median, distribution) after each exercise, and carried out the global evaluation of the performances of each laboratory after at least one year of activity in the program using parametric (regression analysis) and non-parametric (evaluation of the results according to pre-determined acceptability criteria) statistical methods. After four years of activity, the results obtained show that the adopted scheme and the procedures used turned out to be adequate. The study of the regression parameters between the results of each laboratory and the medians of the results of all the laboratories has confirmed the validity of the graphic criterion adopted, also yielding specific information on the relative contribution of the different kinds of error (systematic, constant and/or proportional and casual) to the global error. Furthermore, the proportion of the laboratories with "good level" performances (i.e., acceptable results in at least 80% of the examined samples) has increased from approximately 30% in the first phase to approximately 50% in the fourth phase.*

Riassunto (Programma di controllo di qualità interlaboratoriale per la determinazione del piombo nel sangue. Valutazione delle metodologie impiegate e dei risultati). - *Da oltre cinque anni è attivo in Italia, promosso da un gruppo di lavoro dell'Istituto Superiore di Sanità, un programma nazionale per il controllo di qualità nella determinazione del piombo nel sangue, basato sull'adozione, da parte dei laboratori, degli stessi materiali a titolo noto, per il controllo di qualità interno e sulla partecipazione ad esercizi collaborativi periodici per la valutazione esterna della qualità. Il laboratorio promotore provvedeva alla preparazione dei campioni di controllo, alla verifica della loro omogeneità e stabilità, alla loro distribuzione ai laboratori, secondo una procedura randomizzata, ad una preliminare elaborazione dei risultati (precisione, scarto dalla mediana, distribuzione) al termine di ciascun esercizio e alla valutazione globale delle prestazioni di ciascun laboratorio al termine di almeno un anno di attività del programma, con metodologie statistiche parametriche (analisi della regressione) e non parametriche (valutazione dei risultati in base a prefissati criteri di accettabilità). Al termine di quattro anni di attività, i risultati ottenuti indicano che lo schema adottato e le procedure utilizzate si sono rivelate adeguate. Lo studio dei parametri della regressione tra i risultati di ciascun laboratorio e le mediane dei risultati di tutti i laboratori ha confermato la validità del criterio grafico adottato, fornendo anche specifiche informazioni sul contributo dei diversi tipi di errore (sistematici - costanti e/o proporzionali - e casuali) all'errore globale. Inoltre, la percentuale di laboratori, le cui prestazioni possono essere definite di buon livello (risultati accettabili per almeno l'80% dei campioni esaminati) è cresciuta da circa il 30% nella prima fase a circa il 50% nella quarta.*

Introduction

In Italy, potentially intense exposure to environmental lead pollution is possible, mainly because of three factors:

- lead concentration in gasoline is still 0.45 g/l, while lower limits have already been adopted in the United States of America and in the majority of European countries; the distribution of "clean" gasoline is still in an experimental phase;

- in broad regional areas (i.e. in Emilia-Romagna, Tuscany, Umbria, Abruzzi and Apulia), a widespread industrial and artisan production of earthenware with lead-containing enamels exists;
- many industrial settlements exist to mine and to purify this metal, with relevant problems of professional exposure and of environmental pollution in the surrounding areas.

Therefore, it is particularly important to monitor the level of exposure in the general population, and expecially in the groups at higher risk, by determining the blood lead levels: blood lead is the most commonly used dose-indicator and many laboratories include this analytical determination in their activities.

The validity of a program of biological monitoring is determined, for the most part, by the reliability of the analytical data produced by the program itself. Concerning this, the adoption of well designed quality control programs has shown to be an effective tool both to improve the analytical performances of the involved laboratories and to allow an evaluation of the reliability of the data [1, 2].

These general considerations, and particular provisions of the law [3], have prompted - since 1983 - the implementation of an interlaboratorial quality assurance program for blood lead determination as a part of the activities of the Istituto Superiore di Sanità [4]. The program is still active, and the most part of the public Italian laboratories involved in environmental toxicology and hygiene activities participate in it.

The results reported in this paper, derived from a global analysis of the bulk of data produced during four years of collaborative activity, allow to reach general conclusions concerning the structure of the program, its efficacy and the present level of the analytical performances in the Italian laboratories.

Materials and methods

Quality assurance procedures and schemes

The general scheme of the program, briefly summarized below, is described in detail elsewhere [4].

The promoting center provided for samples preparation, samples distibution, statistical analysis of the data and evaluation of the results.

Samples preparation

Cow blood, sonicated and centrifuged in order to obtain a homogeneous material, was used for the preparation of the samples. Different pools at various concentration levels were obtained by adding known amounts of lead to aliquots of the treated material. The different concentration levels were chosen to cover the whole expected range of samples from the general population; unusually high or low concentration levels were also taken into account.

Two pools, at medium-low and medium-high concentration levels (approximately 150 and 350 µg/l, respectively), were prepared for internal quality control (IQC). Consensus values were assigned to IQC samples, as the median of the overall results obtained by the participating laboratories, after having analyzed four samples for each concentration level.

Samples distribution

Samples for IQC were distributed to the participants once a year.

For external quality control (EQC), four samples were sent in duplicate to each laboratory; bimonthly during the first two years of activity, and quarterly afterwards. An electronic randomized procedure was used to assign the different samples to the laboratories, in order to prevent sample identification from anyone else other than the promoting center.

Statistical analysis and evaluation of the results

At the end of each trial electronic data processing was carried out, and suitable information was sent to each laboratory. In particular, for each analyzed sample, the following data were reported: results obtained by the other laboratories; mean; standard deviation; median; bias to the median, and comparison of each result of the laboratory with a previously established acceptability criterion.

The adopted graphic criterion is briefly outlined: at two concentration levels (100 and 800 µg/l, respectively) a maximum allowed bias to the median was established (± 20 and ± 80 µg/l, respectively), considering the current analytical and clinical requirements. In the space defined by the two cartesian axes: y = bias to the median, x = median, an acceptable inaccuracy zone was delimited by the two straight lines for which equations are calculated on the basis of the established limits. Laboratory results were considered acceptable when their bias to the median fell inside the acceptable inaccuracy zone.

At the end of each year of activity, a deeper analysis of the analytical results was carried out, and the global performance of each laboratory was evaluated by means of both parametric and non-parametric criteria.

Regression analysis, carried out for each laboratory between its results (y) and the median of the results obtained by all the laboratories for the same sample (x), pointed out the presence of constant or proportional errors.

On the other hand, by plotting the bias to the median obtained by a laboratory in various trials on the previously defined acceptable inaccuracy area (besides allowing to point out imprecision, inaccuracy and trends towards under- or overestimates), the following operative criterion of acceptability of the global laboratory performance was established. On the basis of the percentage of points falling outside the inaccuracy area, laboratories were subdivided into classes. Global laboratory performance could be

considered acceptable when at least 80% of the bias to the median of the provided results was found inside the established limits.

Results

Participating laboratories

During five years of activity, a total of 77 laboratories were involved in the program: their geographical distribution is shown in Fig. 1.

On the average, approximately 60 laboratories have participated - on an exclusively voluntary basis - in each phase of the program; the average respondence was between 80 and 90%. The interested laboratories were mainly laboratories of hygiene and prophylaxis, or multiarea preventive structures; nevertheless, also university institutes and other research centers participated in the program.

Many of these laboratories were involved in a permanent monitoring activity (i.e., periodical check-up of workers exposed to lead), performing several hundreds blood lead determinations per year.

Control samples

The samples distributed to the laboratories during this period have been prepared in three different occasions. Each preparation has been used for approximately a year.

Fig. 1. - Geographical distribution of the laboratories participating in the interlaboratorial quality assurance program for blood lead determination during the five years of activity.

The promoting laboratory has analyzed in different occasions a proportion of about 5% of the total samples, to verify the homogeneity and the stability of each batch. The mean per cent recovery of the amount of added lead in each batch was, respectively, 100.8 ± 2.6, 100.4 ± 3.4, and 101.2 ± 2.0.

The choice of the median of the results obtained by all the laboratories as an estimate of the "real" value of the lead content of the examined samples has proved to be sufficiently valid, because the mean per cent recovery of the amount of added lead, computed from the medians for each batch was, respectively, 96.7 ± 5.5, 96.9 ± 1.9 and 95.5 ± 3.0 per cent.

However, the results obtained show, in accordance with data reported by other Authors for similar programs [1], a slight underestimate (approx. 4%) when compared to the expected value. This could be due to the widespread tendency to overestimate lead content in blood samples with very low concentration levels, such as those measured when bovine blood is used as a basis for sample preparation, and *vice versa* to a tendency to underestimate high lead concentration levels.

Similar conclusions have been reached by Boone *et al.* [5], in comparing the results obtained, on the same blood samples, by the laboratories participating in the CDC Proficiency Testing Program and by the NBS with an absolute method (isotopic dilution mass spectrometry).

Therefore, it would seem appropriate and advisable to devote more attention to the analytical problems concerning blood lead determinations at unusually high and/or low concentration levels.

Laboratory performances

The analytical performances of each laboratory, evaluated according to the acceptability criterion of the results described above, are summarized in Tables 1-3, showing the distribution in classes of the laboratories, according to the percentage of acceptable results obtained at the end of each phase of the program.

In particular, the lst, 2nd, 3rd, 4th and 5th class correspond to > 90%, 89-80%, 79-70%, 69-50% and < 50% of acceptable results, respectively.

In each table, the distribution of the laboratories in the various classes at the end of each phase is compared to that obtained in the following phase. It can be observed that the number of laboratories in the first class steadily increases from the I to the III phase, while, in parallel, the numerosity of the fifth class decreases. The numerosity of the intermediate classes is almost constant. In the IV phase, instead, while the numerosity of the fifth class is still decreasing, the numerosity of the third class increases and is constant that of the other classes. These patterns are pointed out by the diagram shown in Fig. 2.

The laboratory performance has also been evaluated through the characteristics of analytical reliability (Table 4).

Table 1. - *Classification of the laboratories according to the percentage of acceptable results. I and II phase*

Classes	1		2		3		4		5	
Acceptable results (%)	>90%		90-80%		80-70%		70-50%		< 50%	
Phase	I	II	I	II	I	II	I	II	I	II
Laboratories (codes)	103 104 107 111 127 129 134 153 159	103 104 106 107 113 130 134 136 139 140 150 165 171	102 106 125 130 135 137	111 115 121 125 129 131 133 152 159 164	113 115 117 121 131 133 136 139 163	102 108 114 120 126 135 137 141 142 153	110 116 123 124 128 132 138 140 141 145 146	110 117 119 122 123 127 128 138 161 162 163 169	108 112 114 118 218 119 120 122 126 142 143 148 150 152 154 157 158 160 161	112 116 118 124 132 146 148 151 154 155 157 158 160 166 168 170
Total	9	13	6	10	9	10	11	12	19	16
%	16.7	21.3	11.1	16.4	16.7	16.4	20.4	19.7	35.2	26.2

Table 2. - *Classification of the laboratories according to the percentage of acceptable results. II and III phase*

Classes	1		2		3		4		5	
Acceptable results (%)	>90%		90-80%		80-70%		70-50%		<50%	
Phase	II	III	II	III	II	III	II	III	II	III
Laboratories (codes)	103 104 106 107 113 130 134 136 139 140 150 165 171	103 104 107 111 113 117 129 133 134 136 138 139 142 152 160 161 164 165 177	111 115 121 125 129 131 133 152 159 164	106 132 137 141 166 171 172	102 108 114 120 126 135 137 141 142 153	110 125 127 128 130 163 169	110 117 119 122 123 127 128 138 161 162 163 169	102 115 120 124 131 135 140 162 175 176	112 116 118 124 132 146 148 151 154 155 157 158 160 166 168 170	112 114 116 119 121 122 126 148 153 155 157 158 168 170
Total	13	19	10	7	10	7	12	10	16	14
%	21.3	33.3	16.4	12.3	16.4	12.3	19.7	17.5	26.2	24.6

Table 3. - *Classification of the laboratories according to the percentage of acceptable results. III and IV phase*

Classes	1		2		3		4		5	
Acceptable results (%)	>90%		90-80%		80-70%		70-50%		<50%	
Phase	III	IV	III	IV	III	IV	III	IV	III	IV
Laboratories (codes)	103	102	106	117	110	110	102	108	112	103
	104	104	132	128	125	122	115	112	114	116
	107	106	137	140	127	124	120	114	116	119
	111	107	141	141	128	125	124	115	119	131
	113	111	166	160	130	126	131	120	121	148
	117	113	171	175	163	127	135	121	122	155
	129	129	172	176	169	130	140	132	126	158
	133	133				135	162	138	148	182
	134	134				153	175	170	153	
	136	136				163	176	178	155	
	138	139				167		179	157	
	139	142				168		180	158	
	142	152				169			168	
	152	161				177			170	
	160	162				181				
	161	164				184				
	164	165								
	165	166								
	177	171								
		172								
Total	19	20	7	7	7	16	10	12	14	8
%	33.3	31.7	12.3	11.1	12.3	25.4	17.5	19	24.6	12.7

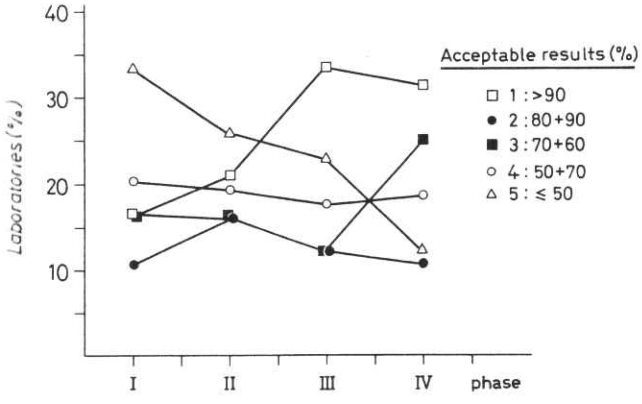

Fig. 2. - Pattern of the distribution of the laboratories by acceptability range in the four phases of the interlaboratorial quality assurance program for blood lead determination.

The precision of each laboratory in each phase has been computed with the pool standard deviation formula, by cumulating the dispersions of the duplicate.

Similarly, the accuracy has been computed with the same formula, by cumulating the dispersions from the medians of the results of the laboratory.

Since the samples had been allocated according to a strictly randomized procedure, the mean concentration of the samples analyzed by each laboratory in each phase was practically the same for all the laboratories, i.e. approximately 400 µg/l.

Besides this information, in Table 4 is reported the classification of the laboratories according to the percentage of acceptable results and, for the laboratories that have not used the direct method in atomic absorption with graphite furnace, the analytical method adopted.

While the imprecision of the laboratories does not appreciably change in the different phases of the program, and is dispersed around global mean values of 10 µg/l, the relative inaccuracy is characterized by markedly higher mean values in the I phase (50 ± 33.8 µg/l) when compared to those observed in the II (38 ± 29 µg/l), and is steady around these last values in the two following phases (34 ± 21, and 35 ± 21 µg/l, respectively).

The mean inaccuracy for the laboratories that in the different phases have obtained at least 80% of acceptable results for the analyzed samples, proved to be remarkably low: 21 ± 11, 15.8 ± 9, 17 ± 7 and 17 ± 6.5 µg/l respectively, in the different phases.

Finally, it has to be noted that the AAS methods requiring sample pretreatment and anodic stripping voltammetry, that for various reasons are more prone to errors, have progressively decreased from 26% in the first phase to 18% in the second, 12% in the third, to go up again to 18%

Table 4. - *Laboratory performance during each phase of the program in terms of: a) percentage of acceptable results (1 = > 90%; 2 = 90-80%; 3 = 80-70%; 4 = 70-50%; 5 = < 50%); b) precision (pooled standard deviation between replicate measurements), µg/l; c) accuracy (pooled standard deviation between laboratory values and medians), µg/l; d) analytical methods other than direct GFAAS (1 = FAAS; 3 = GFAAS after extraction; 4 = Delves Cup; 5 = ASV; 6 = GFAAS after mineralization)*

Lab.	I phase				II phase				III phase				IV phase			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
102	2	6.3	36.8		3	3.9	25.7		4	48	22		1	5.1	16.9	
103	1	5.8	21.5		1	13.6	14.9		1	13.6	23.1		5	20.6	55.6	
104	1	2.3	19.3		1	2.7	12.6		1	2.4	17.3		1	2.6	15.1	
106	2	4.5	16.1		1	3.9	11.2		2	8.3	18.3		1	10	15.1	
107	1	6.5	21.3		1	3.8	10.6		1	11.4	25.9		1	3.4	11.1	
108	5	22.3	81.5	(3)	3	9.2	29.9		-	-	-		4	-	39.4	
110	4	12.8	50.8	(4)	4	12.7	34.7	(4)	3	13.9	34.5	(4)	3	20.6	37.9	(4)
111	1	9.1	17		2	6.1	18.2		1	9.5	9.5		1	3.8	19.6	
112	5	25	84		5	8.8	81.9		5	30	31.5		4	14.7	64.5	
113	3	10.9	49.9		1	6.4	22.1		1	11	22.7		1	8.1	18.1	
114	5	-	44.3	(3)	3	-	19.7	(3)	5	-	41.2	(3)	4	-	57.3	(3)
115	3	17.8	20	(3)	2	17.7	18.8	(3)	4	14.3	37.4	(3)	4	19.8	88.3	(3)
116	4	6	48	(5)	5	7.8	77.8	(5)	5	6.4	78.6	(5)	5	9.9	84.8	(5)
117	3	13.8	36	(3)	4	11.7	49.8	(3)	1	12.7	20.8		2	11	24.4	
118	5	9.4	127	(5)	5	7.7	145	(3)	-	-	-		-	-	-	
119	5	15.7	66	(3)	4	10.4	27.4	(3)	5	11.1	48.8		5	12.2	41.1	
120	5	20.9	41	(5)	3	15.8	12.4	(5)	4	16.9	27.4	(5)	4	16.8	32.9	(5)
121	3	3.1	40.6		2	2.7	22.7		5	4.9	90.6		4	9.8	45.1	
122	5	23.4	74.8		4	12.7	57.7		5	8.7	77.6		3	2.2	17.3	
123	4	9.8	37	(3)	4	12.3	43.2	(3)	-	-	-		-	-	-	
124	4	28.1	62	(1)	5	8.8	70.9		3	9.4	74.8		3	9	37	
125	2	4.8	20.6		2	5.5	21.1		3	5.9	25.1		3	11.2	31	
126	5	19.1	96	(5)	3	15	23.9	(5)	5	13	65.6		3	14.2	26.5	(5)
127	1	3.1	22.8		4	7.5	32.7		3	4.8	34.4		3	5.2	35.9	
128	4	9.1	27.4		4	9.3	27.3		3	-	21.6		2	-	26.2	
129	1	8.1	11.4		2	10	11		1	5.2	11.8		1	10.9	10.6	
130	2	10.9	27.7		1	10	22.4		3	17.7	30.5		3	11.2	37.9	
131	3	12.2	26.5		2	6.5	22.9		4	11.9	35		5	7.9	41.4	(6)
132	4	26.4	66.9	(1)	5	-	57.1	(1)	2	-	38.6	(1)	4	-	48.1	(1)
133	3	3.4	34.2		2	4.2	27.1		1	6.8	16.6		1	14.2	15.7	
134	1	4.4	13.5		1	5.8	13.4		1	7.3	18.6		1	8.0	14.4	
135	1	8.6	51.6		3	4.2	38.5		4	7.3	34.6		3	3.5	42.4	
136	3	1.3	33.4		1	0.9	8.2		1	1.3	15.4		1	1.7	13.5	
137	2	16.2	31.1		3	15	20.9		2	8.9	25.8		-	-	-	
138	4	8.6	64		4	4.6	45.2		1	7.1	17		4	7.3	46.2	
139	3	7	24.2		1	4	8.2		1	6.2	15.9		1	6.2	17.4	
140	4	8.6	19.7		1	6.9	17.8		4	10.7	35.3		2	9.2	23.5	
141	4	11.3	36	(4)	3	16.9	28.5	(4)	2	24	24.5	(4)	2	20.4	41.6	(4)
142	5	6.2	91.5		3	12.8	17.8		1	10.6	10.8		1	5.8	13.1	
143	5	25.3	49		-	-	-		-	-	-		-	-	-	
145	4	5.5	25		-	-	-		-	-	-		-	-	-	
146	4	20.7	91		5	11.9	35.1		-	-	-		-	-	-	
148	5	21.3	92.9		5	28.9	74		5	42	81.4		5	63	97.5	
150	5	12.5	32.5		1	-	10.1		-	-	-		-	-	-	
152	5	9.4	81		2	12.8	20.1		1	17.5	17.1		1	13.1	15.8	
153	1	2	13.7		3	3	30.7		4	4.9	28.5		3	2.9	15	
154	5	54	73.8		5	18.8	55.2		-	-	-		-	-	-	
155	-	-	-		5	19.9	63		5	14.1	78.3		5	21.6	68	
157	5	7.1	182		5	31.7	74		5	4	47.5		-	-	-	
158	5	8	74		5	21.1	60		5	26.8	61.9		5	18.8	58.9	
159	1	19	25		2	5.6	19		-	-	-		-	-	-	
160	5	10.5	66		5	12.2	33.6		1	9.7	35.1		2	13.8	16.6	
161	5	5.1	95		4	8.1	30.8		1	8.6	21.6		1	5.3	20.9	
162	5	6.2	78		4	6.1	19.3		4	10.1	27.6		1	4.9	40.3	
163	3	8.8	18.3		4	8.7	30.9		3	7.5	15.7		3	6.7	31.1	
164	-	-	-		2	9.2	29.9		1	4.2	9.7		1	3.3	12.2	
165	-	-	-		1	9.8	13		1	8.4	14		1	8.3	17	
166	-	-	-		5	7.2	103		2	7.6	19.2		1	2.4	10.5	
167	-	-	-		-	-	-		-	-	-		3	14.2	43	
168	-	-	-		5	10.2	126		5	24.8	35.7		3	16.7	32.8	
169	-	-	-		4	11.6	29.9		3	6.2	29.4		3	7.2	35.2	

Table 4. - *(continued)*

Lab.	I phase				II phase				III phase				IV phase			
	a	b	c	d	a	b	c	d	a	b	c	d	a	b	c	d
170	-	-	-		5	8.8	113.5		5	11.2	78.8		4	6.2	65.1	(3)
171	-	-	-		1	2.5	41.8		2	3.5	22.6		1	4.4	15.8	
172	-	-	-		-	-	-		2	9.4	31.6		1	8.8	24.8	
175	-	-	-		-	-	-		4	7.3	44		2	9.9	21.1	
176	-	-	-		-	-	-		2	18.8	17.4		2	17.6	25.6	
177	-	-	-		-	-	-		1	11	30.2		3	21	45.8	
178	-	-	-		-	-	-		-	-	-		4	73	44.9	
179	-	-	-		-	-	-		-	-	-		4	19.9	56.1	
180	-	-	-		-	-	-		-	-	-		4	12.3	42.5	
181	-	-	-		-	-	-		-	-	-		3	12	35.8	(1)
182	-	-	-		-	-	-		-	-	-		5	8.7	72.8	
184	-	-	-		-	-	-		-	-	-		3	2.7	73.5	
Mean		11.9	49.8			9.8	37.8			11.8	33.8			12.1	35.6	
SD		9.2	33.3			6.1	29.1			8.8	20.9			12	20.8	

in the fourth phase. Negligible improvements have been observed in the analytical performances of the laboratories that continued to use such methods.

A deeper evaluation of the laboratory performances in the different phases can be inferred from the results of the analysis of the regression carried out at the end of each phase between the results of each single laboratory (y) and the values of the overall medians, obtained by cumulating all the values obtained for each sample in the different pools (x).

To verify the correspondence between the indications yielded by the non-parametric criterion used for the classification of the laboratories and the information obtained from the parametric criteria, we have grouped in Table 5 the laboratories that, according to the evaluation of the number of results falling within the acceptability limits, had improved their performances in the second phase in comparison with the first phase.

The values of the regression parameters, shown in the table, for each of these laboratories in the two considered phases, confirm this correspondence and point out specific reasons for the improvement of the performances (reduction of systematic errors - constant and/or proportional - and of the dispersion of the measurements).

Table 6 shows the laboratories that have not changed their classification in the second phase (all the laboratories, but one, were classified in the first group). The comparison between the parameters of the obtained regressions still point out a certain amount of improvement, generally a reduced dispersion of the values around the medians.

Finally, Table 7 shows the laboratories that worsened their performances in the second phase. The data reported here substantially confirm such an evaluation, but they also point out, however, that - even if the final outcome is negative - a few parameters have been improved.

In Table 8 the means of a few regression parameters, computed for the four phases, are compared: only the 42 laboratories that took part to all the four phases of the program are considered here. The values reported here point out a significant improvement of all the parameters from the first to the second phase; then in the following phases a substantially stable condition is observed.

A similar trend can be observed in Table 9, in which the means of the same parameters obtained in the following phases are compared, considering all the laboratories that had participated in both phases.

Conclusions

The results described above allow us to reach the following conclusions concerning the efficiency of the adopted quality control program and on the present level of the analytical performances of the Italian laboratories:

a) the elementary, non-parametric, statistical procedure, based on the percentage of results included between fixed acceptability levels and used to evaluate the quality of the analytical performance, proved to be effective and adequate to describe real situations;

b) the scheme of the interlaboratorial quality assurance program adopted (number of samples in each pool, frequency of distribution, procedures adopted to prevent sample identification) and the technical solutions used to prepare and to store the samples, also proved to be appropriate;

c) the participation in the program has been an effective incentive towards an improvement of the quality of the laboratory data. In fact, the laboratories whose analytical performances - according to the results obtained - can be defined of good level (i.e: with at least 80% of the results within the fixed acceptability limits) increased from the

Table 5. - *Comparison between the regression parameters (laboratory values = y; overall medians = x), obtained in the I and II phase, respectively, by the laboratories that, according to the non-parametric criterion, had improved their performances. n: number of examined samples; r^2: determination coefficient; a: intercept, µg/l; b: slope; SE: standard error of the estimate, µg/l*

Lab.	Phase	n	r^2	a	b	SE	Class
106	I	43	0.973	5.58	0.986	31.00	(2)
	II	40	0.996	10.55	0.963	15.74	(1)
108	I	47	0.588	47.63	0.675	90.05	(5)
	II	40	0.981	- 29.28	1.003	31.28	(3)
113	I	40	0.985	- 47.73	1.234	30.63	(3)
	II	48	0.990	- 11.04	1.040	29.10	(1)
114	I	20	0.921	45.69	0.884	63.18	(5)
	II	24	0.937	22.20	1.024	65.48	(3)
115	I	48	0.974	0.89	0.992	31.10	(3)
	II	48	0.993	- 7.18	1.048	23.38	(2)
119	I	44	0.739	82.91	0.679	79.07	(5)
	II	39	0.980	23.17	0.969	34.95	(4)
120	I	48	0.957	- 67.10	1.119	46.56	(5)
	II	48	0.990	- 12.96	0.980	23.52	(3)
121	I	40	0.969	- 1.21	1.097	41.22	(3)
	II	40	0.992	- 9.02	1.067	24.05	(2)
122	I	48	0.789	- 36.26	0.913	93.17	(5)
	II	24	0.871	- 5.22	1.074	84.06	(4)
126	I	40	0.703	- 43.45	1.137	171,66	(5)
	II	48	0.990	1.36	0.968	34.95	(3)
130	I	44	0.981	- 17.32	1.062	35.97	(2)
	II	48	0.993	9.73	0.951	30.07	(1)
131	I	48	0.982	- 16.13	1.087	34.95	(3)
	II	48	0.995	- 12.65	1.122	14.49	(2)
133	I	48	0.967	- 24.21	1.013	41.52	(3)
	II	47	0.991	- 5.34	1.061	27.36	(2)
136	I	48	0.978	- 2.83	0.916	31.27	(3)
	II	48	0.999	- 2.05	1.004	8.44	(1)
139	I	48	0.993	- 18.64	1.110	20.02	(3)
	II	48	0.998	- 0.30	1.012	12.63	(1)
140	I	48	0.941	12.46	1.000	46.38	(4)
	II	48	0.992	9.26	0.959	21.07	(1)
141	I	48	0.967	23.38	0.850	30.79	(4)
	II	48	0.974	3.52	0.992	44.11	(3)
142	I	36	0.740	98.34	0.824	108.39	(5)
	II	40	0.990	8.85	1.003	28.16	(3)
150	I	40	0.947	14.95	1.067	37.57	(5)
	II	8	0.999	- 5.94	1.062	5.64	(1)
152	I	48	0.832	54.02	1.063	92.51	(5)
	II	48	0.990	- 7.92	1.053	25.24	(2)
161	I	8	0.997	- 20.63	1.478	23.10	(5)
	II	48	0.970	- 2.79	1.039	44.80	(4)

Table 6. - *Comparison between the regression parameters (laboratory values = y; overall medians = x), obtained in the I and II phase, respectively, by the laboratories that, according to the non-parametric criterion, had not improved their performances. n: number of examined samples; r^2: determination coefficient; a: intercept, µg/l; b: slope; SE: standard error of the estimate, µg/l*

Lab.	Phase	n	r^2	a	b	SE	Class
103	I	36	0.956	- 12.85	0.983	41.97	(1)
	II	40	0.993	- 12.63	1.060	20.93	(1)
104	I	48	0.993	- 8.55	1.066	19.36	(1)
	II	48	0.998	5.10	0.936	9.03	(1)
107	I	40	0.995	- 14.36	1.105	16.04	(1)
	II	48	0.999	- 14.97	1.023	7.53	(1)
125	I	47	0.983	- 3.64	1.053	29.63	(2)
	II	48	0.988	4.44	1.034	29.48	(2)
134	I	48	0.990	13.41	0.938	18.51	(1)
	II	24	0.998	7.67	0.952	13.23	(1)

Table 7. - *Comparison between the regression parameters (laboratory values = y; overall medians = x), obtained in the I and II phase, respectively, by the laboratories that, according to the non-parametric criterion, had worsened their performances. n: number of examined samples; r^2: determination coefficient; a: intercept, µg/l; b: slope; SE: standard error of the estimate, µg/l*

Lab.	Phase	n	r^2	a	b	SE	Class
102	I	44	0.974	- 6.67	0.986	36.17	(2)
	II	48	0.978	24.85	0.895	28.65	(3)
111	I	40	0.983	- 11.64	1.011	25.78	(1)
	II	48	0.993	- 4.06	0.983	23.87	(2)
116	I	48	0.559	- 8.58	1.141	151.4	(4)
	II	24	0.809	23.72	0.774	91.67	(5)
117	I	48	0.928	15.68	0.865	42.90	(3)
	II	48	0.952	4.94	1.066	64.12	(4)
124	I	48	0.930	16.59	1.125	60.41	(4)
	II	48	0.974	21.83	0.916	35.57	(5)
127	I	48	0.966	9.21	0.988	34.47	(1)
	II	48	0.968	3.59	0.918	42.83	(4)
129	I	48	0.989	4.24	0.994	18.67	(1)
	II	48	0.996	10.85	0.975	16.78	(2)
132	I	28	0.793	26.39	0.996	100.68	(4)
	II	24	0.934	8.42	1.109	70.24	(5)
135	I	48	0.975	- 49.89	1.205	43.64	(1)
	II	24	0.968	- 29.93	1.055	39.09	(3)
137	I	48	0.954	21.74	0.902	39.91	(2)
	II	48	0.982	14.69	0.959	31.27	(3)
146	I	32	0.762	- 61.95	1.123	137.64	(4)
	II	32	0.962	5.83	0.891	39.65	(5)
153	I	32	0.997	23.98	0.974	12.36	(1)
	II	48	0.961	2.11	0.939	42.49	(3)
159	I	8	0.990	22.83	0.900	18.64	(1)
	II	28	0.995	26.22	1.080	20.97	(2)
163	I	8	0.998	- 49.14	1.085	12.20	(3)
	II	48	0.967	28.70	0.920	43.64	(4)

Table 8. - *Variation of the means of the regression parameters (laboratory values = y; overall medians = x): only the 42 laboratories participating in all the four phases of the program are taken into consideration. r^2: mean of the determination coefficients; SD: standard deviation; a: mean of the absolute values of the intercept, µg/l; Δb: mean of the absolute values of the difference of the slopes from 1.0000; SE: mean of the standard error of the estimate, µg/l*

Phase	r^2	SD	a	SD	Δb	SD	SE	SD
I	0.9098	0.1197	32.58	35.52	0.1211	0.1225	52.15	36.19
II	0.9573	0.0764	15.19	16.37	0.0689	0.0629	40.75	29.75
III	0.9518	0.0788	19.70	22.30	0.0747	0.0654	34.44	24.52
IV	0.9580	0.0731	17.32	15.09	0.0644	0.0603	39.42	28.99

Table 9. - *Variation, in two consecutive phases, of the means of the regression parameters: laboratory values (y) vs. overall medians (x). Only the laboratories participating in two consecutive phases of the program are taken into consideration. n: number of participating laboratories; r^2: mean of the determination coefficients; SD: standard deviation; a: mean of the absolute values of the intercepts, µg/l; Δb: mean of the absolute values of the difference of the slopes from 1.0000; SE: mean of the standard errors of the estimate, µg/l*

Phase	n	r^2	SD	a	SD	Δb	SD	SE	SD
I	51	0.8920	0.1320	38.12	51.00	0.122	0.118	56.58	39.61
II	51	0.9480	0.1100	17.51	19.20	0.070	0.060	39.33	27.88
II	53	0.9429	0.1036	20.57	22.77	0.083	0.100	42.51	31.00
III	53	0.9561	0.0721	22.66	27.60	0.077	0.070	35.57	22.00
III	55	0.9572	0.0711	22.85	27.22	0.078	0.068	36.91	25.65
IV	55	0.9586	0.0681	18.39	15.56	0.063	0.048	40.10	28.98

first to the fourth phase from 30% to about 50%: this represents a 66% increase of "good level" laboratories induced by our study;

d) at the same time, also the laboratories that already from the start had good level performances, during the program have improved, as it is shown by the progressive decrease of the casual component of the error (standard error of the estimate);

e) methods other than the direct one in atomic absorption with graphite furnace in general present greater practical problems and are more prone to error;

f) the reasons for a worsening of the quality of the analytical performances have to be imputed to:

- substitution of the technician
- a decrease of interest in the specific analytical activity;

g) lack of improvement, most of the time, has to be ascribed to the usage of inadequate equipment and to outdated technology;

h) the results of the cooperative activity can be considered as positive, even if they outline a still unsatisfactory global situation.

In conclusion, this first nationwide interlaboratorial quality assurance experience finally offers an *in vivo* quantification of the benefits induced by a properly planned approach to the problems of the chemical-clinical laboratory for analyses of toxicologic interest. This result, together with the many suggestions rising from this experience, shows how it is convenient and of general interest (and also what a pressing need it is, if we only think to the implications in problems concerning the safety of the workplace) to develop adequately and, above all, systematically this quality control activity, to confront in a well organized way the problem of quality assurance in the analytical field concerning the bioelements.

Review submitted on invitation by the Editorial Board of the *Annali*.
Accepted for publication: 26 April 1989.

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