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EVALUATION OF THE PERFORMANCE OF ITALIAN LABORATORIES IN THE DETERMINATION OF CADMIUM LEVELS IN BLOOD

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Summary. - *The measurement of the blood cadmium level is necessary for the biological monitoring of workers or of general populations that are thought to be professionally or environmentally exposed to cadmium. However, since the levels of interest are exceedingly low, the analytical determinations involve considerable problems. With the aim of comparing the performances of the Italian laboratories in the blood cadmium levels determination, a working group of the Istituto Superiore di Sanità (Italian National Institute of Health) promoted in 1983 a quality control program including the provision of materials for the internal quality control and the performance of bimonthly or quarterly exercises for the external quality control. The promoting laboratory provided the preparation and distribution of the samples to the laboratories and the processing of the data at the end of each exercise. A global and more thorough evaluation of the performances of each laboratory was carried out at the end of each phase (lasting at least one year), including a graphical evaluation of the results of each laboratory according to a predetermined acceptability criterion and the linear regression analysis. Of the 20 participating laboratories, approximately 50% obtained acceptable results for at least 80% of the examined samples. The mean relative inaccuracy decreased from 36% in the first phase to 20% in the last one. To improve analytical performances, both technologically advanced instrumentations and experienced personnel seem to be necessary.*

Riassunto (Valutazione delle prestazioni dei laboratori italiani nell'analisi del cadmio ematico). - *La misura del livello di cadmio nel sangue è necessaria per il monitoraggio biologico di lavoratori o di popolazioni generali, che si ritengano soggetti ad esposizione ambientale o professionale a cadmio. Tuttavia, poiché i livelli di interesse sono molto bassi, le determinazioni analitiche presentano notevoli difficoltà. Allo scopo di confrontare le prestazioni dei laboratori italiani nella determinazione del cadmio nel sangue, un gruppo di lavoro dell'Istituto Superiore di Sanità ha promosso nel 1983 un programma di sicurezza di qualità, che comprendeva sia la fornitura di materiali per il controllo di qualità interno che esercizi a cadenza bi-o trimestrale per il controllo di qualità esterno. Il laboratorio promotore provvedeva alla preparazione e alla distribuzione dei campioni ai laboratori e alla elaborazione dei risultati al termine di ciascun esercizio. Una valutazione globale più approfondita delle prestazioni di ciascun laboratorio era effettuata alla fine di ogni ciclo o fase del programma della durata di almeno un anno, comprendente una valutazione grafica dei risultati di ciascun laboratorio in base ad un prefissato criterio di accettabilità e l'analisi della regressione lineare. Dei 20 laboratori partecipanti, circa il 50% otteneva risultati accettabili per almeno l'80% dei campioni esaminati. L'inaccuratezza relativa media è diminuita dal 36% nella prima fase al 20% nell'ultima. Per il miglioramento delle prestazioni analitiche sembra necessario disporre sia di strumentazione tecnologicamente avanzata sia di personale esperto.*

Introduction

Cadmium is a nonessential, highly toxic element; its effects on human health are well documented [1-3].

The possibility of exposure to Cd is widespread, and this metal may be a considerable risk for many different groups of population.

The metal and its inorganic compounds have many industrial applications: in electroplating; in pigments for paints, enamel, glass, plastics, fabrics; in low melting-point alloys; as a stabilizer in PVC and other thermoplastics; in photography and litography; in rectifiers; in photoconductors and photoelectric solar cells; in automobile tires and in nuclear reactors [4]. As a consequence, significant occupational hazard (through inhalation or ingestion of CdO fumes and dust, or dust of various Cd compounds) due to exposure to Cd may occur, mainly in metallurgical industry, and production and use of Cd pigments and Cd plastic stabilizers.

The general population may be potentially exposed because of the increasing levels of Cd in the environment. The main sources of Cd environmental pollution are non ferrous metal production; waste incinerators; phosphate fertilizer manufacture; wood, coal and gasoline combu-

stion; and iron and steel industry. Cadmium concentration in the air of industrial areas ranges from 1 to 50 ng/m³ (vs 0.1 to 6 ng/m³ in rural areas). Contaminated dust deposition and phosphate fertilizers use are the main routes of soil pollution. Highly contaminated soils may contain up to 800 µg Cd/g (vs 0.2 to 0.6 µg/g in non polluted soils). Cd is readily absorbed from the soil by plants and thus enters the human food chain via vegetable and animal food production. Fish, crabs and other animals accumulate Cd to a relatively high degree in kidneys and liver.

Daily dietary intake has been evaluated to range from 10 to 85 µg.

Cigarette smoke is a direct source of exposure to Cd, and smokers may absorb 0.1 to 0.2 µg of Cd per cigarette [4].

In order to prevent adverse effects due to occupational and environmental Cd exposure, biological surveillance of workers and of general population groups is necessary, and it can be implemented by monitoring blood or urine Cd levels as exposure indexes.

Analytical determination of Cd still presents relevant problems, mainly because the concentrations of interest are very low (0.1 to 2 µg/l in blood, 0.5 to 3 µg/l in urine for the general population).

Such considerations prompted us to promote, together with the Interlaboratorial Quality Assurance Program for blood lead levels determination, a similar investigation for blood Cd analysis, even if a much smaller number of laboratories was interested in the program [5].

After four years of collaborative activity, we report and discuss the findings of our study.

Materials and methods

The general scheme of the program (procedures for sample processing and distribution, statistical analysis of data and criteria to evaluate laboratory performances) has been described in detail elsewhere [5, 6].

We will only report specific information concerning the materials used and the criteria of evaluation of the results.

Every batch of samples for external quality evaluation was prepared by adding known amounts of $Cd(NO_3)_2$ to at least six portions of bovine blood; the pools were then distributed into plastic test tubes (2 ml aliquots), sterilized by γ-rays, and stored at + 4 °C. Cd concentrations ranged from 0 to 15 µg/l.

Particular attention has been devoted to the lower concentration levels. Cd content was < 2 µg/l in 30%, and < 5 µg/l in 75% of the distributed samples. A new batch of controls was prepared approximately every sixteen months.

Internal quality control samples at two concentration levels were also prepared and assigned to the laboratories in three different occasions. Their Cd content was established according to the results of preliminar analyses carried out by all the participants. Median values were: 1.4 and 4.3 µg/l, respectively, for the two pools of the first batch; 1.1 an 3.5 µg/l for the second, and 1.8 and 6.1 µg/l for the last one.

The graphic criterion adopted for the evaluation of laboratory performance was based on the choice of a maximum allowed bias of 60% to the median at the concentration level of 1 µg/l (0.6 µg/l) and of 10% at 15 µg/l (1.5 µg/l). The acceptable inaccuracy area was delimited, within the space defined by the cartesian axes: x = median, y = bias to the median, by the two lines passing through the points: a) x = 1 µg/l, y = 0.6 µg/l; b) x = 15 µg/l, y = 1.5 µg/l; and a_1) x = 1 µg/l, y = - 0.6 µg/l; b_1) x = 15 µg/l, y = - 1.5 µg/l.

Results

Participating laboratories

During the four years of activity of the program, at least 28 laboratories were interested in assessing their performance in blood Cd levels determination. Almost all of them were from northern Italian regions (Fig. 1), as it was expected since Cd related problems are more relevant in industrial areas.

On the average, 18 laboratories participated in each phase of the program and compliance was within the range 74-83%.

About one third of the participating structures were research laboratories (universities, or other research institutes), while the other two thirds were public or occupational health services. At least eight laboratories performed more than 50 tests/year.

All the participants determined blood Cd by atomic absorption spectrometry with electrothermal atomization

Fig. 1. - Geographical distribution of the laboratories participating in the Cd quality control program during the four years of activity.

(ETAAS). Most of them carried out the analysis without special pretreatments of the sample. Some laboratories, instead, used extraction or mineralization procedures.

Control samples

Homogeinity and long term stability of the samples for internal and external quality assurance were tested in the promoting laboratory by analizing at least 5% of them.

The determinations were performed by atomic absorption spectrometry with electrothermal atomization, L'Vov platform and Zeeman correction.

Accuracy of the Cd additions was verified by evaluating the average recovery for each batch (100.1 ± 1.8, 101.0 ± 1.5, and 99.5 ± 0.8%, respectively).

For each batch, average recoveries - according to the medians of the results of all the laboratories (96.4 ± 6.4, 94.5 ± 4.6 and 97.7 ± 12.9%, respectively) - confirmed within reasonable limits the reliability of the medians as an estimate of the "real" value of the samples. Furthermore, the comparison made by regression analysis between the medians (x) and the values obtained by the promoting laboratory (y) (Fig. 2), showed a good reciprocal correspondence (intercept 0.15 µg/l, slope 1.049, determination coefficient 0.997, standard error of the estimate 0.23 µg/l).

Laboratory performance

At the end of each phase of the program, analytical performances of the participants were evaluated, according to the graphic criterion of acceptability, on the basis of the percentage of the acceptable results obtained.

In Tables 1, 2 and 3, laboratories are classified according to the percentage of the acceptable results (> 90%, 90-80%, 80-70%, 70-50%, and < 50%), and the distribution of the laboratories in each phase is compared with that of the following one.

Even though the number of the participants is too small to point out well defined trends, it is possible to observe that the number of laboratories achieving acceptable results for > 80% of the tested samples was constant over time (approximately 50%); and that the number of laboratories achieving unsatisfactory results for > 50% of the tested samples has decreased (Fig. 3).

Furthermore, it has to be noticed - when considering the situation of each laboratory in later phases of the study - that: a) the laboratories with unsatisfactory analytical performances were more likely to drop out from the program, probably giving up the activity (7 laboratories); b) after entering the program, a marked improvement of analytical results has taken place (in 5 laboratories); c) most of the laboratories with high qualitative standards kept up with their good levels of performance (7 laboratories).

The precision and accuracy of the results have been evaluated: the interlaboratorial precision was determined by computing the pooled standard deviate (PSD) between

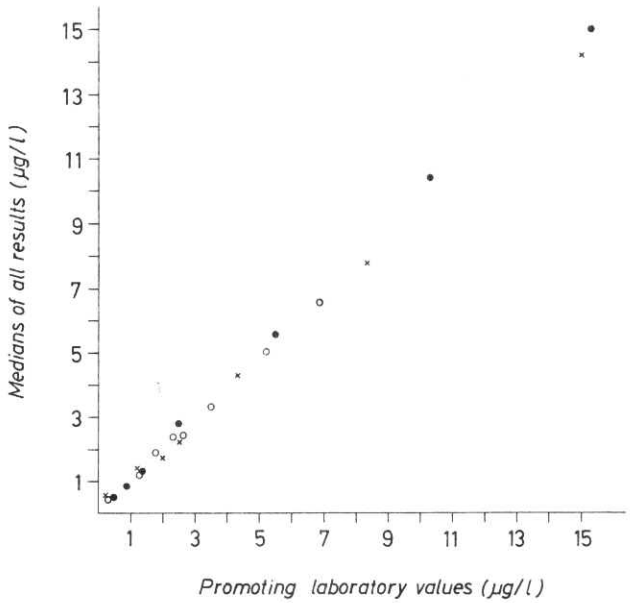

Fig. 2. - Comparison between the medians of the values observed for each sample by all the participating laboratories (y) and the results obtained in Cd determination on the same samples by the promoting laboratory.

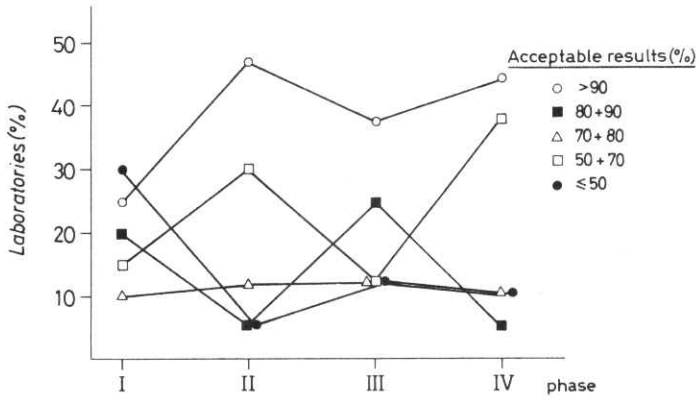

Fig. 3. - Pattern of the distribution of the laboratories by acceptability range in the four phases of the program for the quality control of blood Cd levels determination.

the measurements observed on duplicate analysis of the samples; the relative accuracy was determined by computing the PSD of the cumulative dispersions of the results from their median (Table 4).

The average concentration of the samples distributed during each phase was the same for all the laboratories: 3.1 ± 2.8 µg/l in the first phase; 4.1 ± 4.1 µg/l in the second phase; 4.7 ± 5.2 µg/l and 6.2 ± 5.5 µg/l in the third and fourth phase, respectively.

The average lack of precision, through the four phases, proved to be rather slight: 0.31 ± 0.30, 0.32 ± 0.32, 0.21 ± 0.13, and 0.23 ± 0.14 µg/l, respectively.

The average inaccuracy was approximately 1 µg/l (1.12 ± 1.39, 0.91 ± 0.79, 1.13 ± 0.9, 1.24 ± 1.23 µg/l, in phase I, II, III and IV respectively).

The dispersion of the measurements obtained by all laboratories for the same sample has not significantly

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)	102 104 133 135 140	107 111 113 124 128 133 135 139	107 111 123 124	123	103 136	102 103	113 128 139	131 140 158 162 164	120 121 138 158 160 162	165
Total	5	8	4	1	2	2	3	5	6	1
(%)	25	47	20	5.9	10	11.8	15	29.4	30	5.9

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)	107 111 113 124 128 133 135 139	103 107 113 131 139 164	123	111 124 133 135	102 103	102 128	131 140 158 162 164	140 162	165	158 177
Total	8	6	1	4	2	2	5	2	1	2
(%)	47	37.5	5.9	25	11.8	12.5	29.4	12.5	5.9	12.5

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)	103 107 113 131 139 164	107 111 113 133 139 162 164 177	111 124 133 135	102	102 128	124 135	140 162	103 128 131 161 180	158 177	158 167
Total	6	8	4	1	2	2	2	5	2	2
(%)	37.5	44.4	25	5.6	12.5	11.1	12.5	27.8	12.5	11.1

changed during the program. The variation coefficients, obtained by pooling the measurements performed on the same sample in the same phase, and cutting out the results exceeding three SD, were about 15-30% for samples with concentrations > 2 µg/l, about 35% for concentrations between 1-2 µg/l, and about 50% when the Cd content was < 1 µg/l (Fig. 4).

Since similar results have been obtained by Starkey *et al.* (in the Guilford Trace Element External Quality Assessment Scheme) [7], even if a joint effort to reduce the interlaboratorial variability is certainly to be hoped for, it seems that - besides good laboratory practice - the problem originates from actual limitations of available methods or equipment.

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*

Laboratory (code)	I phase			II phase			III phase			IV phase		
	a	b	c	a	b	c	a	b	c	a	b	c
102	1	0.11	0.50	3	0.13	1.14	3	0.16	1.14	2	0.11	0.88
103	3	-	0.46	3	0.27	0.57	1	0.51	0.23	4	0.51	2.33
104	1	0.05	0.34	-	-	-	-	-	-	-	-	-
107	2	0.05	0.40	1	0.07	0.30	1	0.09	0.28	1	0.37	0.74
111	2	0.23	1.03	1	0.22	0.34	2	0.31	1.16	1	0.11	0.29
113	4	0.51	1.19	1	0.65	0.50	1	0.16	0.43	1	0.13	0.53
120	5	0.77	6.62	-	-	-	-	-	-	-	-	-
121	5	0.18	2.23	-	-	-	-	-	-	-	-	-
123	2	1.36	0.30	2	0.28	0.87	-	-	-	-	-	-
124	2	0.20	0.42	1	0.19	0.44	2	0.16	0.78	3	0.32	0.83
128	4	0.21	0.59	1	0.27	0.34	3	0.00	1.00	4	0.25	1.26
131	-	-	-	4	0.14	0.48	1	0.20	0.32	4	0.21	1.33
133	1	0.11	0.34	1	0.13	0.54	2	0.25	2.52	1	0.15	1.99
135	1	0.10	0.42	1	0.25	0.69	2	-	1.54	3	-	0.62
136	3	0.06	0.58	-	-	-	-	-	-	-	-	-
138	5	0.54	1.32	-	-	-	-	-	-	-	-	-
139	4	0.20	0.83	1	0.14	0.32	1	0.18	0.41	1	0.14	0.21
140	1	0.14	0.52	4	0.19	0.88	4	0.24	1.15	-	-	-
158	5	0.26	2.23	4	1.41	3.45	5	0.34	2.24	5	0.20	3.51
160	4	0.20	1.27	-	-	-	-	-	-	-	-	-
161	-	-	-	-	-	-	-	-	-	4	0.15	1.35
162	5	0.57	1.59	4	0.29	1.74	4	0.24	1.07	1	0.11	0.46
164	-	-	-	4	0.25	1.66	1	0.08	0.48	1	0.09	0.32
165	-	-	-	5	0.52	1.16	-	-	-	-	-	-
167	-	-	-	-	-	-	-	-	-	4	0.56	4.84
177	-	-	-	-	-	-	5	-	3.40	1	0.36	0.44
180	-	-	-	-	-	-	-	-	-	4	0.24	0.43

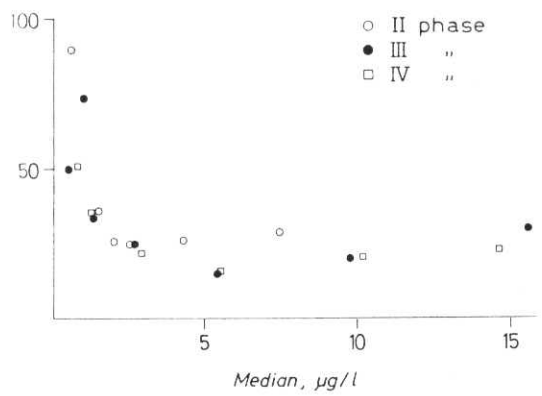

Fig. 4. - Variation coefficients of the results obtained by the laboratories on samples with different Cd concentrations, analyzed during different phases of the program (computed from the average obtained after cutting out the values exceeding by more than three SD the raw average).

The study of the parameters of the regressions between the results obtained by each laboratory (y) and the medians (x) allowed us to add information, concerning systematic and/or random errors in the global performance of each laboratory, to the non-parametric evaluation.

When regression parameters, obtained for each laboratory in the different phases (Table 5), are compared to the already mentioned non-parametric classification, a parallel trend is almost always observed, even if at times a single significant deviation is able to alter such a correspondence.

Certain laboratories have not modified their position: the analysis of their regression parameters at times points out a deterioration, and other times an improvement, of laboratory performance. Such changes have not yet produced relevant modifications on the percentage of acceptable results produced. From a general point of view, the mean values of the regression parameters of all the laboratories, in each single phase, show a global tendency towards the expected values, excepting the standard error of the estimate that in all phases is close to 0.9 µg/l (Table 6).

Conclusions

Our results show that the procedures used in the program (sample preparation, frequency of the distribution, evaluation criteria of the results) were satisfactory.

In particular, the non-parametric criterion used in laboratory classification proved to be adequate to describe real situations, as demonstrated by a more careful statistical analysis of the data.

When program efficacy is considered, at least partly conflicting conclusions are reached. While the relative average inaccuracy shows a decreasing trend, the dispersion of the measurements obtained on the same sample by

Table 5. - *Parameters of the regression lines obtained between laboratory results (y) and median values (x) at the end of each phase, compared with the class attributed to the laboratory on the basis of the percentage of acceptable results. n) number of results; a) intercept, µg/l; b: slope; SE) standard error of the estimate, µg/l; r^2) determination coefficient*

Laboratories (code)	Phase	Class	n	a	b	SE	r^2
102	I	1	40	0.20	1.081	0.44	0.980
	II	3	32	0.44	0.937	0.90	0.955
	III	3	24	0.45	0.883	1.43	0.906
	IV	2	32	0.47	0.889	1.18	0.945
103	I	3	4	1.46	0.228	0.32	0.362
	II	3	24	0.36	1.055	0.64	0.986
	III	1	16	0.11	1.038	0.53	0.992
	IV	3	16	- 0.32	1.304	1.24	0.976
107	I	2	40	- 0.47	1.233	0.48	0.982
	II	1	40	- 0.29	1.105	0.15	0.998
	III	1	32	0.00	1.018	0.16	1.000
	IV	1	32	0.19	1.015	0.39	0.996
111	I	2	40	- 0.40	0.916	1.29	0.808
	II	1	40	0.02	0.994	0.57	0.982
	III	2	32	0.34	0.791	1.04	0.941
	IV	1	32	- 0.01	0.975	0.30	0.996
113	I	4	23	1.16	0.792	1.54	0.748
	II	1	40	- 0.24	1.070	0.66	0.978
	III	1	32	0.12	0.929	0.40	0.994
	IV	1	32	- 0.26	1.100	0.48	0.994
123	I	2	32	- 0.59	1.136	0.86	0.945
	II	2	32	0.62	0.755	0.71	0.939
124	I	2	40	- 0.53	1.052	0.69	0.947
	II	1	40	- 0.40	1.060	0.58	0.982
	III	2	32	- 0.28	1.142	0.40	0.996
	IV	3	32	- 0.53	1.061	1.27	0.955
128	I	4	26	- 0.23	1.223	0.93	0.949
	II	1	16	- 0.19	1.050	0.45	0.992
	III	3	8	0.21	1.039	0.56	0.994
	IV	4	28	- 0.43	1.119	1.37	0.951
131	II	4	8	0.37	1.048	0.28	0.998
	III	1	31	0.15	0.930	0.39	0.994
	IV	4	32	0.28	0.763	0.64	0.976
133	I	1	40	- 0.15	1.063	0.33	0.990
	II	2	40	- 0.23	1.016	0.39	0.992
	III	2	32	- 0.76	1.196	3.58	0.757
	IV	1	32	- 0.28	1.104	1.01	0.972
135	I	1	40	- 0.47	1.257	0.57	0.974
	II	1	16	0.03	0.980	0.39	0.992
	III	2	32	0.23	1.077	2.30	0.859
	IV	3	8	- 0.29	0.947	0.39	0.996
139	I	4	32	0.21	0.896	0.97	0.897
	II	1	40	- 0.26	1.082	0.43	0.990
	III	1	32	- 0.06	1.006	0.44	0.994
	IV	1	32	- 0.13	1.035	0.29	0.998
140	I	1	24	- 0.34	1.004	0.51	0.976
	II	4	40	0.11	0.979	1.37	0.897
	III	4	8	0.93	1.047	1.35	0.922
158	I	5	16	2.94	0.395	1.18	0.658
	II	4	32	1.59	0.602	2.75	0.482
	III	5	24	2.55	0.392	2.11	0.458
	IV	5	16	3.45	0.222	1.38	0.490
162	I	5	8	3.07	- 0.157	0.74	0.588
	II	4	40	1.17	0.669	2.36	0.575
	III	4	24	0.42	1.026	1.61	0.912
	IV	1	32	0.16	1.052	0.45	0.994
164	II	4	40	1.06	0.862	2.51	0.664
	III	1	32	0.00	0.915	0.40	0.994
	IV	1	32	- 0.03	0.976	0.32	0.996
177	III	5	4	- 0.22	1.664	1.07	0.994
	IV	1	32	- 0.18	1.072	0.62	0.988

Table 6. - *Mean values of the regression parameters (laboratory results/medians) in each phase of the program. n) laboratories per phase; r^2) determination coefficient; a) intercept, µg/l; b) slope; SE) standard error of the estimate, µg/l*

Phase	n	a	b	SE	r^2
1	19	0.68 (2.03)	0.964 (0.235)	0.94 (0.68)	0.858 (0.176)
2	17	0.34 (0.65)	0.959 (0.150)	0.93 (0.82)	0.904 (0.163)
3	15	0.29 (0.72)	0.962 (0.188)	1.11 (0.96)	0.914 (0.144)
4	17	0.14 (0.99)	0.982 (0.230)	0.79 (0.47)	0.948 (0.121)

all the laboratories has remained constant. A number of laboratories showed a marked improvement of their performances, while other ones did not show relevant modifications of the quality of the results even after many collaborative activities had taken place. A few laboratories worsened their performance level during the study period.

We believe that a few remarks might try to explain these contradictions: most laboratories carry out very few blood cadmium level measurements (< 50 tests/year), while this analysis can be adequately performed only by experienced laboratory staff and - for blood cadmium levels < 1 µg/l - only when excellent equipment is available; changes in the laboratory staff, that have to be adequately trained, often negatively affect the quality of laboratory performance; in other cases, obsolete equipment yields unsatisfactory results even if analyses are performed by experienced and devoted personnel.

Our work, even if impressive results have not been obtained, proved to be a strong support tool for the laboratories involved in this section of toxicologic clinical chemistry; it has made possible an evaluation of the reliability of data concerning blood cadmium levels presently provided by the Italian laboratories; finally, it points out sources of error, and shows a way to further studies on possible remedial measures.

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