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The German external quality assessment scheme in occupational and environmental medicine

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Summary. - According to a technical guideline for dangerous substances (TRGS 410) issued in 1979 by the Ministry of Labour of the Federal Republic of Germany, toxicological analyses in biological materials must be performed under conditions of "statistical quality control". The German Society for Occupational and Environmental Medicine is entrusted with the organization of the German external quality assessment scheme (EQAS). Since 1982 about 100 laboratories regularly take part in each run. Blood and urine samples spiked with two different concentrations (A, B) are distributed to the laboratories. Since 1991 additional samples with environmental exposure levels are also included in the EQAS. A laboratory is certified as successful if both its results (A, B) fall within the tolerance range given by the reference laboratories. The thirteenth (1994) external quality assessment exercise included blood and urine samples containing 21 inorganic and 29 organic substances, besides 8 inorganic and 14 organic analytes within the environmental concentration range.

Key words: Germany, accreditation, external quality assessment scheme, metals, organic solvents, pesticides.

Riassunto *(Il programma tedesco per la valutazione esterna di qualità in medicina occupazionale ed ambientale)*. - Le linee guida per la manipolazione di sostanze pericolose (TRGS 410) promulgate nel 1979 dal Ministero del Lavoro dell'allora Repubblica Federale di Germania, stabiliscono che le analisi di sostanze tossiche in materiali biologici devono essere effettuate in condizioni di "controllo di qualità statistico". Il compito di organizzare schemi di valutazione esterna della qualità è affidato alla German Society for Occupational and Environmental Medicine. Dal 1982 circa 100 laboratori partecipano regolarmente agli esercizi. I materiali di controllo sono costituiti da campioni di sangue e di urine addizionati degli analiti da misurare in due diverse concentrazioni (A e B). Dal 1991, lo schema include anche campioni con concentrazioni di analita paragonabili a quelle dovute ad esposizione ambientale. Ciascun partecipante ottiene la certificazione se i risultati ottenuti per entrambi i campioni (A e B) cadono dentro i limiti di tolleranza stabiliti dai laboratori di riferimento. Il tredicesimo esercizio di valutazione esterna della qualità (1994) comprendeva 21 sostanze inorganiche e 29 organiche in matrici di sangue e urine. Livelli di concentrazione relativi ad esposizione ambientale erano disponibili per 8 sostanze inorganiche e 14 organiche.

Parole chiave: valutazione esterna di qualità, medicina occupazionale, medicina ambientale, Germania.

Introduction

In Germany, an external quality assessment scheme (EQAS) for toxicological analyses in occupational medicine started in 1982. The legal basis of this programme has been outlined in a technical guideline for quality control of toxicological analyses, as part of the code governing the handling of dangerous substances in the Federal Republic of Germany, issued in 1979 ("Technische Regel für Gefahrstoffe - Statistische Qualitätssicherung - TRGS 410 der Gefahrstoffverordnung") [1]. According to this Directive, each laboratory analysing biological specimens for occupational medicine has to apply certain measures for internal and external quality control. The latter is being accomplished by taking part in intercomparison programmes.

The technical guideline sets the framework for:

- organization of round-robins;
- evaluation of the participants' results;
- establishment of so-called "assigned values" (Sollwerte) for the test samples by several well experienced laboratories.

This framework has originally been set up by the German Bundesärztekammer (Federal Chamber of Physicians) for clinical analyses and it has been successfully applied for many years [2].

In occupational medicine, EQAS are organized by the German Society of Occupational and Environmental Medicine. The first round robin was performed in 1982, followed by at least one every year thereafter. The 13th run was performed in Autumn 1994.

The following topics of the German EQAS will be discussed in detail:

- biological materials and analytes within the German EQAS;
- assessment of the assigned values for specimens sent to the participants in the round robin;
- criteria for evaluation of results and for certification;
- features of the German EQAS: number of participating laboratories and frequency of accurate results.

Table 1. - Analytes and biological materials within the 14th exercise of the German EQAS: concentration range relevant for occupational medicine

Biological materials	Analytes	
Whole blood	Cadmium	Manganese
	Chromium	Mercury
	Cobalt	Nickel
	Lead	
	Benzene	Trichloroethene
	Toluene	Tetrachloroethene
	Xylenes	
Plasma	p,p'-DDE	PCB-101
	HCB	PCB-138
	α-HCH	PCB-153
	β-HCH	PCB-180
	γ-HCH	PCB-Sum
	PCB-28	PCP
	PCB-52	
Urine	Aluminium	Fluoride
	Antimony	Lead
	Arsenic	Manganese
	Cadmium	Mercury
	Chromium	Nickel
	Cobalt	Thallium
	Copper	Zinc
	δ-Aminolevulinic acid	
	Butoxyacetic acid	
	Ethoxyacetic acid	
	o-Cresol	
	Hippuric acid	
	1-Hydroxypyrene	
	Mandelic acid	
	Methylene dianiline	
	Methylhippuric (Toluric) acids	
	trans-,trans-Muconic acid	
	PCP	
	Phenol	
	Phenylglyoxylic acid	
	Trichloroacetic acid	

Table 2. - Analytes and biological materials within the 14th exercise of the German EQAS: concentration range relevant for environmental medicine

Biological materials	Analytes	
Whole blood		Cadmium
		Lead
		Mercury
Plasma	p,p'-DDE	PCB-101
	HCB	PCB-138
	α-HCH	PCB-153
	β-HCH	PCB-180
	γ-HCH	PCB-Sum
	PCB-28	PCP
	PCB-52	
Urine	Arsenic	Palladium
	Cadmium	PCP
	Chromium	
	Nickel	

Biological materials and analytes within the German EQAS

Samples of the following body fluids were available for the most recent run of the German EQAS:

- defribrinated animal whole blood, with the addition of EDTA and azide for stabilisation and Triton X-100 for erythrocyte lysis;
- animal plasma, stabilized by addition of azide and centrifuged before spiking;
- acidified, pooled human urine, deep-frozen to increase sedimentation and then centrifuged to obtain a homogenous fluid.

Four main classes of analytes can be determined in the test materials prepared for occupational exposure (Table 1) and two in test samples prepared for environmental exposure (Table 2):

- inorganic compounds (metals and fluoride) in whole blood and urine;
- volatile organic compounds (aromatic and chlorinated hydrocarbons) in whole blood;
- less volatile organochlorine compounds as dichlorodiphenyldichloroethane (DDE), hexachlorocyclohexane (HCH), polychlorinated biphenyls (PCB) and pentachlorophenol (PCP) in plasma;
- urinary metabolites of organic compounds, e.g. hydroxypyrene, muconic acid, hippuric, mandelic and phenylglyoxylic acid, toluric acids, phenol, o-cresol, trichloroacetic acid, ethoxy- and butoxyacetic acid.

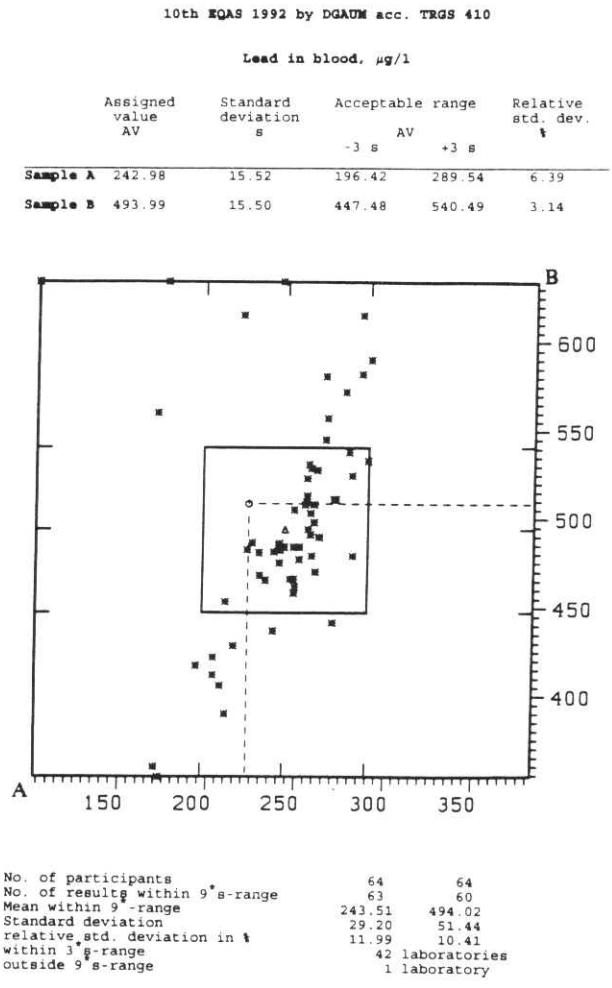

Fig. 1. - Example of an evaluation diagram (Youden-plot) sent to each participant in the German EQAS.

Specimens with concentration levels compatible with environmental exposure are offered to participating laboratories since the 11th run of the German EQAS, due to a proposal of a Joint Commission for Biological Monitoring of the German Umweltbundesamt and Bundesgesundheitsamt (Federal Departments for Environment and Health) (Table 2). The concentration ranges for selected analytes in biological materials are reported in Table 3.

Table 3. - Concentration ranges for selected analytes and biological materials within the 12th to 14th exercises of the German EQAS; concentrations for additional samples with environmentally relevant analyte contents are given in brackets

Biological material	Analyte	Concentration range
Whole blood	Cadmium	7.0 - 17.0 µg/l (1.0 - 3.6 µg/l)
	Cobalt	9.2 - 12.1 µg/l
	Lead	374.0 - 1064.0 µg/l (34.9 - 182.3 µg/l)
	Nickel	7.2 - 32.6 µg/l
	Benzene	8.6 - 15.1 µg/l
	Trichloroethene	116.1 - 534.3 µg/l
Plasma	HCB	12.2 - 21.1 µg/l (1.8 - 10.1 µg/l)
	γ-HCH	3.5 - 11.1 µg/l (1.0 - 4.5 µg/l)
Urine	Aluminium	49.5 - 245.6 µg/l
	Antimony	3.6 - 32.7 µg/l
	Arsenic	39.3 - 144.9 µg/l (8.5 - 28.5 µg/l)
	Manganese	4.0 - 43.0 µg/l
	o-Cresol	2.8 - 11.0 mg/l
	Ethoxyacetic acid	13.0 - 34.0 mg/l
	Muconic acid	2.7 - 6.5 mg/l
	Pentachlorophenol	1.9 - 9.2 µg/l (2.4 - 7.8 µg/l)
	Toluric acids	211.5 - 546.4 mg/l

Establishment of the assigned values

For each analyte and material "assigned values" have to be established. To this aim, several well experienced and well equipped laboratories in Germany and other European countries analyze each analyte in multiple independent runs applying their methods of choice. The spiked amount is unknown to these reference laboratories. After exclusion of outliers, i.e. data lying outside the 95% range, the remaining data pool is taken for the statistical calculation of the assigned value (mean).

This method of experimental assignment of the target values allows the detection of errors in the specimen preparation (e.g. random or systematic deviations from the nominal spiked amount) as well as contamination or losses during storage and shipping.

For the majority of the analytes, the arithmetic mean of the participants' results is very close to the assigned value indicating a good approach to the "true" value.

Table 4. - Number of participants and analytes in the 13 German intercomparison exercises

Year	Run no.	Labs no.	No. of analytes in				
			Blood/Plasma			Urine	
			Metals	Solvents	Pesticides	Inorganic	Organic
1982	1	35	-	-	-	10	2
1983	2	51	3	-	-	10	5
1985	3	74	4	-	-	10	8
1986	4	82	6	-	-	11	8
1987	5	87	6	-	-	11	8
1988	6	90	6	-	-	11	8
1989	7	85	6	-	-	14	7
1990	8	96	6	4	13	15	7
1991	9	95	6	4	13	15	7
1992	10	85	6	-	-	13	7
1992	11	101	6	4	13	13	7
			3	-	*13*	*4*	
1993	12	108	7	-	-	14	10
			3	-	-	*4*	*1*
1994	13	120	7	5	13	14	11
			3	-	*13*	*4*	*1*

In italics analytes available at concentrations comparable to those derived from environmental exposure.

Criteria for evaluating the participants' results

Each participant receives an evaluation diagram (a Youden-plot) and a certification report comparing his own results with the assigned values and the acceptable ranges. If both sample results (A, B) lay within the acceptable range the participant will receive a certification for the analyte.

In the Youden-plot (Fig. 1) the concentrations of a single analyte in both specimens (A, B) are reported as abscissa and ordinate with the assigned values as the centre of the diagram (marked as a triangle). The inner square represents the acceptable range of results (assigned value ± 3 SD). The results from all participants are plotted in this diagram and individual or collective tendencies with respect to systematic or random deviations become obvious. In addition, the participants' results can be compared with the assigned value. In Fig. 1, the marked lab (circle) fulfils the requirements of the German EQAS and thus will receive certification.

Features of the German EQAS

During the thirteen years of activity, of the German EQAS the number of participating laboratories increased about threefold from 35 in the first run to about 110 during the recent runs. This enlargement is interpreted as a consequence of the validity of the intercomparison programme (Table 4).

Over the years the number of materials and analytes also increased from one material (urine) containing ten inorganic and two organic analytes in 1982, to the broad range of materials and analytes available in the latest run (Table 4).

The number of sample pairs analysed per run increased even more (by a factor of ten) than the number of laboratories. About 10 parameters were analyzed by each laboratory on an average in the recent runs. The mean success rate (that is the ratio between the number of correctly analyzed sample pairs and the total number of analyzed pairs) is approximately 60% and shows a positive tendency during subsequent runs. The type of biological fluid or the analyte seems to have only a minor influence on the success rate. Obviously, experience and skill of the laboratory is of greater importance.

In conclusion, we may state that the German EQAS is a well performing and renowned system accepted by numerous analysts in the field of occupational and environmental medicine.

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Appendix. - Summary of the scheme

Country	Federal Republic of Germany.
Status of scheme	National, but open to participants from other countries. Compulsory for German laboratories performing toxicological analyses in occupational medicine. Run by the German Society of Occupational and Environmental Medicine. *Aims:* to fulfil the legal demands set by the technical guideline for quality control of toxicological analyses, as part of the code governing the handling of dangerous substances (TRGS 410 GefStoffV); in addition to offer an intercomparison programme in the field of toxicological analyses in occupational and environmental medicine for research laboratories on a voluntary basis. *Participants:* about 120 laboratories of all types performing toxicological analyses in occupational and environmental medicine.
Scheme description	*Control materials:* in-house preparations; human (urine) and animal matrix (whole blood, plasma); spiked concentrations: multielemental samples; liquid materials; glass vials for plasma and solvents in whole blood, plastic vials for metals in whole blood and urine; assigned values are established in multiple analyses by several national and European reference laboratories. *Internal quality control samples/calibrators:* no provision of this type of materials; calibration and internal quality control has to be organised by each participating laboratory. *Organization of EQAS exercises:* frequency of exercises: at least one run per year; number of samples: two samples for each analyte and matrix; strategy of distribution: shipping by surface mail after registration of the laboratories for the current run; time schedule for returning results: within approximatively five weeks after deadline of the EQAS run; methods of transmission of results: by surface mail. *Elaboration of results*: preparation of a Youden-plot for each analyte and matrix and a certification report for each laboratory. *Criteria for evaluation of laboratory performance*: both results of a participating laboratory for a given parameter must lay within the acceptable range evaluated by the reference laboratories in order to obtain a certification. *Measures taken against poor performers*: no certification. *Provision of advice and training*: carried out frequently on the basis of personal communications and contacts. *Financial support*: registration fee of participants.
Organization	German Society of Occupational and Environmental Medicine Professor Dr. Jürgen Angerer Institut für Arbeits- u. Sozialmedizin und Poliklinik für Berufskrankheiten der Universität, Schillerstraße 25-29 D-91054 Erlangen, Germany Tel + 49 9131-852374. Fax + 49 9131-852317
Analytes and matrices covered	Metals in whole blood and urine, fluoride in urine. Aromatic and chlorinated hydrocarbons in whole blood. Organochlorine compounds (e.g. DDE and HCH), polychlorinated biphenyls and pentachlorophenol in plasma. Metabolites of organic compounds in urine.