REPORT

Thematic Network	European organisers of external quality assessment/ proficiency testing schemes related to occupational and environmental medicine
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SUMMARY

Background:
Biological monitoring is essential for measuring undue exposure to harmful agents and is undertaken in many laboratories throughout the EU. As the determination of accurate results is crucial it is important that properly validated methods are used and that independent assessments of performance (external quality assessment, EQA) are undertaken. EQA organisers have identified topics for closer collaboration within a Thematic Network to resolve disparities among schemes and to promote improvements in analytical performance for biological monitoring.

Objectives:
The objectives of this Thematic Network were:
- to harmonise the goals of individual schemes with respect to setting common standards for laboratory performance, and the provision of mutual support;
- to undertake programmes of education and training for laboratories involved in occupational and/or environmental medicine.

Work Programmes:
1. Develop standards of performance for the measurement of lead and aluminium to meet national and EU requirements.
2. Co-ordinate national activities in gathering information from participants, such as workload, methodologies, etc. and prepare reports on best practice etc.
3. Initiate collaborative work and avoid duplication of effort among different schemes.
4. Education and training.

Results and Achievements:
The Network Participants have
- Proposed quality specifications for measurement of lead in blood and aluminium in serum and will be applying these to a comparison of analytical performance by laboratories throughout the EU.
- Identified variations in the implementation of EU legislation and considered the implications of these on analytical quality specifications and the organisation of EQA schemes.
- Documented the repertoires and other management information of laboratories participating in the EQA schemes.
- Prepared an audit of the organisational and managerial practices within the EQA schemes to identify those areas of common practice and those where mutual recognition would be possible.
- Proposed a mechanism to facilitate harmonisation among schemes and to enable the establishment of new cross-national EQA activities.
- Developed a culture that is now able to embrace metrological concepts and is seeking to (i) similarly educate scheme participants (ii) apply these to the organisation of EQA schemes.
- Submitted one paper for publication, prepared two others that are almost ready for submission and presented one paper at a scientific conference.

CONTENTS

ABBREVIATIONS

BE	Belgium
DE	Germany
DK	Denmark
EEC	European Economic Community
EQA	External quality assessment
EQAS	External quality assessment scheme(s)
ES	Spain
EU	European Union
FI	Finland
FR	France
ISO	International Standards Organisation
IT	Italy
NHS	National Health Service
NL	The Netherlands
UK	United Kingdom
WP	Work package

1. BACKGROUND

Undue exposure to agents such as metals, pesticides, organic solvents etc. can be harmful to health and some are also carcinogenic. The most likely sources of exposure are within industrial and occupational settings but environmental sources can be responsible for severe clinical problems. Typical exposures to toxic and/or carcinogenic agents may occur:-

At work: Harmful materials, such as carcinogens and toxic metals, are widely used at work and considerable national and European legislation exists to minimise occupational exposure and to protect the health of workers.

From natural exposures: For example, chemicals that have an agricultural use can run off or soak through land and contaminate drinking water. In some regions this has become a serious problem despite the imposition of maximum allowable concentrations by the European Commission.

At home: Paints, toys, medicines etc. are regularly involved with incidents of actual toxicity.

Measurement of exposure to and absorption of, toxic agents is achieved by determining the agent involved (or a metabolite) in an appropriate specimen (urine, blood etc.). Such determinations are also necessary to the follow-up of incidents of overt toxicity. Occupational and environmental exposure assessment by biological monitoring is, therefore, an essential activity and such monitoring is undertaken in a large number of laboratories, of varying sophistication and competence, throughout the EU.

The implications of undue exposure to harmful agents have been recognised by the implementation of programmes for risk evaluation and reduction. Such actions may be undertaken at many different levels involving e.g. national and international agencies, single industrial organisations or the relevant trade association, health care professionals, laboratories or even individuals. The analysis of biological specimens, feature in risk assessments as obligatory regular programmes of occupational biological monitoring, in specific epidemiological investigations, and in studies of miscellaneous clinical problems. Measurements may be made because of legal requirements, as in EU Directives or Resolutions, or as part of a considered, planned approach to investigate a problem.

Employers within the EU are required to implement measures to limit exposure of workers to hazardous substances. The rationale for such action and the protocols to be followed are given in national guidelines and in EU Directives (see for example refs 1-9). In some situations action that has to be taken is dependent on laboratory data (e.g. blood lead concentrations) and the accuracy of results has important legal consequences. Protective equipment, ventilation and other engineering controls can be extremely costly to install, operate and maintain. Effectiveness of these safety measures is ultimately determined by results of environmental and biological monitoring exercises. Where monitoring indicates unacceptable exposures continue to take place the employer has to decide whether to install further controls, to introduce alternative working practices or to abandon the activity.

Inaccurate laboratory data can have two outcomes for an organisation.

- negatively biased results will underestimate exposure so that workers might remain in an unsafe environment and become unwell e.g. develop lead poisoning. Quite apart from the distress to these individuals the employer is

then faced with the financial consequences of increased sickness and absenteeism, early retirements, loss of productivity and possible later claims for compensation. At the same time the employer will have less expense on safety matters, giving a financial advantage compared with competitors.

- positively biased results overestimate risk so that the employer is forced to take unnecessary and expensive action to reduce exposures, which are not harmful.

It is accepted that truly independent assessments of laboratory performance are provided by properly constructed and managed surveillance programmes or external quality assessment schemes (EQAS) and laboratories involved with occupational and environmental laboratory medicine should participate in at least one scheme. Schemes, and the standards of performance which they set, are the only mechanisms to ensure that laboratory errors do not give inappropriate advantage or disadvantage to industry within and between member states of the EU. As there is evidence to suggest that performance standards may vary from scheme to scheme it cannot be assumed that, in the context of exposure to hazardous substances, industry (management and workforce) receives identical treatment throughout Europe.

Community interest in the health of the general population has been widely expressed. In the context of environmental air, drinking and recreational waters, foodstuffs, medicines etc., which are fundamental to the lives of every member of the population, standards have been presented to prevent undue exposures to toxic agents and carcinogens [10-14]. Compliance within member states to the policies and standards of the EU does not directly involve measurements in clinical specimens but situations do develop where it is suspected or it is known that there have been failures to meet the European standards e.g. nitrates from fertilisers in drinking water, lead in meat and milk from contaminated cattle feed. In these situations there are likely to be assessments of the impact on affected communities with studies to relate exposure (biological measurements) to health outcomes. One recent study, for example, showed a definite association between aluminium in drinking water and the incidence of Alzheimer's disease [15]. Community attention has also been given to very specific situations such as the risk of aluminium toxicity in patients with chronic renal failure who require treatment by dialysis [13]. The EU action to meet such special concerns makes reference to the need for analysis of biological specimens and to the importance of EQAS. Where there are environmental exposures the involvement with industry is less direct than for occupational biological monitoring, but laboratory results still impact on the measures taken e.g. by water companies, the agricultural industry etc. and both for the health of individuals and for effective management decision taking, data must be demonstrably accurate. The same arguments apply to incidents within the home where exposure to a hazardous substance is suspected and/or confirmed. Cases of toxicity from lead in paints and certain ethnic remedies and cosmetics are frequently reported. These and many other examples involve the accurate analysis of biological specimens. The preceding discussion shows the crucial importance of accurate measurements in laboratory medicine to the pursuance of EU policies for the protection of individuals at work and in the community, and to the establishment of equivalent controls and requirements on industry throughout the EU. Protection and conformity are the consequences of EQAS organised to provide the same agreed standards, to be applied to

all involved with occupational and/or environmental laboratory medicine throughout the Community.
The procedures used to analyse biological specimens are often complex. Nevertheless, the determination of accurate results is crucial. As discussed above, decisions with far reaching implications are made and action taken, entirely dependent on the laboratory data. For this reason there is increasing awareness of the importance of using properly validated methods with each laboratory going through a process of determining its own accuracy and uncertainty (ISO 1993) using certified reference materials such as those available from the Commission of the EU. Indeed, most laboratories normally have their own systems for analytical quality assurance and some will be formally accredited to a particular standard (e.g. ISO series). However, the rate at which laboratory accreditation is proceeding is not equal throughout the EU. EQA schemes not only measure performance of the participants but also provide a stimulus for improvements in accuracy and precision. Schemes relating to occupational and/or environmental laboratory medicine are organised from at least nine countries of the EU. Most operate on a national basis but some have a wider scope, which allows for formal or semi-formal links and representation from smaller countries. All laboratories involved in biological monitoring within the EU have access and input, therefore, to appropriate EQAS.
Most schemes use similar protocols to monitor performance but each has its own technique to define a satisfactory standard of performance. Often these techniques are complementary to those used by other 'clinical EQAS' within the same country so as to provide for harmonisation within that nation. However, it has been demonstrated that different schemes have the potential to give conflicting conclusions, even from the same raw data. Following from the evidence of possible inconsistencies, discussions among the EQAS organisers identified important topics for closer collaboration within this Thematic Network. These topics are described in detail in the following sections but have the aim of creating a common quality base to improve analytical accuracy and provide for comparability of analytical performance among laboratories working in the field of occupational and environmental medicine throughout the EU, thereby to support Industry and Community policy. The consequences of this aim will be to improve the quality of health and well-being of the population in relation to occupational and environmental exposures to toxic and carcinogenic agents, and to assist industry to operate with fair and equivalent demands with respect to safety and health. This aim was to be realised by:

1. Harmonizing the goals of individual schemes with respect to setting common standards for laboratory performance, and provision of mutual support.

2. Undertake programmes of education and training for laboratories involved in occupational and/or environmental laboratory medicine.

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Participants

The *Contractor* and the *Associated Contractors* (hereinafter referred to jointly as "the Participants") contributing to the Network were:

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Except for Eurometaux, the Participants are all organisers of European external quality assessment schemes related to occupational and environmental medicine. Eurometaux was included as a full partner in order that industrial interests could be represented and that requirements for occupational health and safety could occupy a high priority.

2. OBJECTIVES

In order to work towards the two fundamental objectives a series of projects, or "work packages" were set up

Objective 1. To harmonize the goals of individual schemes with respect to setting common standards for laboratory performance, and provision of mutual support.

WP1. Develop standards of performance for the measurement of lead and aluminium to meet national and EU requirements
WP2. Co-ordination of national activities
WP3. Initiation of collaborative work and avoid duplication of effort among different schemes

Objective 2. To undertake programmes of education and training for laboratories involved in occupational and/or environmental laboratory medicine.

WP4. Education and training

3. WORK PROGRAMME

WP1. Develop standards of performance for the measurement of lead and aluminium to meet national and EU requirements.

The Network focussed on problems encountered with the measurement of lead in blood and aluminium in serum, water and dialysis fluids, as exposure to these two elements is widespread and subject to EU and national legislation. Conclusions from these projects may be applied to other analytes including important organic compounds such as hydroxypyrene in urine. The steps were to:

i. compare procedures used to evaluate laboratory performance in external quality assessment schemes.

This project developed when it was recognised that the EQA schemes evaluate performance of participants in quite different ways and that it is not possible at the moment to have quality specifications, which are applicable to all schemes. Thus, evaluation of laboratory performance across member states is not necessarily equivalent. To address this matter the statistical calculations employed by each scheme were defined and applied to common data sets. Different protocols for introducing a harmonised approach to data processing were tested, based on analytical criteria and on clinical requirements. A unified procedure to allow comparison of performance for these assays, by laboratories throughout the EU, was prepared and tested.

ii. prepare a comparison of European national legislation relating to blood lead concentrations in occupational settings. Legislative requirements in each of the countries represented by the Participants have been tabulated with respect to blood lead monitoring for occupational lead exposure.

This project developed from discussions to decide which are the critical concentrations of lead in blood for assessment by EQA schemes. It became apparent that implementation of EU Directives was not the same in all member states and that the concentration of lead in blood that initiates further action, for example, is quite varied throughout the Community. The members agreed that it would be valuable to compile a summary of the national legislations relating to biological monitoring for occupational exposure to lead.

iii. prepare a comparison of European national guidance values relating to measurements of aluminium for monitoring patients with renal failure who are treated by dialysis.

This project followed from that described for lead in blood, above.

WP2. Co-ordination of national activities

The Participants were aware that each undertook various organisational and management studies and that the value of these would be greater if the information were shared. Two projects were developed to initiate such co-operation.

i information relating to participant laboratory statistics and interests

It is known that factors such as the size and activity of a laboratory, the equipment used etc. are associated with analytical quality. Only two of the Participants collect this information from their own schemes participants although such detail is regularly recorded by EQA schemes not related to occupational and environmental medicine. In addition, the Network Participants planned to gather some further information from participants of schemes to assist with planning other projects (see below).

A questionnaire was prepared with the following purposes

- to identify laboratory management features which may be associated with good/poor analytical performance
- to identify analytical activities not covered by EQA schemes
- to determine how widespread the concept of uncertainty is understood or is in place

each scheme organiser translated (if required) and sent copies to their own scheme participants. Annonymised responses were collected together for data analysis.

ii. organisation of EQA Schemes

Participants recognised that there were opportunities for collaboration (see WPs 3 and 4) but that this would raise questions of mutual recognition, particularly where schemes were formally accredited or were applying for accreditation. As a preliminary step it was decided to collate details of the organisation and working procedures of the EQA Schemes organised by the Participants, to identify where tasks, documentation etc. may be harmonised and/or shared so as to improve efficiency and comparability.

A questionnaire was prepared, for completion by each scheme organiser, to identify common activities and readiness for accreditation.

WP3. Initiation of collaborative work and avoid duplication of effort among different schemes

The Participants were confident that there were analytical procedures relevant to occupational and environmental medicine, that were not subject to any external quality assessment. Primarily, this would be because the number of laboratories undertaking the assay in any one country was very small and, therefore, a national scheme would not be effective. The Participants recognised that a European-wide scheme would offer a solution to this problem but were unsure whether such an initiative would conflict with legislation and objectives at a national level. To assess the feasibility of collaborative work the Participants resolved to:

i. evaluate a software programme, which had been developed to perform the data handling, and report generation activities in accordance with recommendations given in ISO 43.

Copies of the software were distributed to all of the Participants for evaluation and comment.

ii. investigate a methodology for introducing results from participants in different countries into a single database via a web-site interface.

Following from the experience of one partner involved with other schemes, a concept was elaborated whereby common specimens could be sent to participants by each national organiser and all results entered into a shared database. All the results, not just those reported by the national scheme members would then be available for the data processing functions of each scheme. A feasibility study was undertaken by the lead partner in preparation for submission to the EU as an Expression of Interest.

Results from the questionnaire sent to participating laboratories were used to inform decisions concerning the rare assays suited to a single European-wide EQAS and which might be candidates for initiating this project.

WP4. Education and training

During discussions, particularly those concerning procedures to evaluate laboratory performance, collecting participant statistics and interests, and the concept of common EQA scheme, the issue of estimating uncertainty was repeatedly raised. Participants agreed that this was important, from the perspective of participants' results and the concentrations that they report to the scheme organiser, the computations to assess performance and the target values assigned to test materials. Participants also agreed that further education into the measurement of uncertainty and the application of these measurements, to their own work, was necessary. Therefore, meetings of the Network included sessions on these topics. The group also contributed to a paper presented at the CITAC/Eurachem Workshop on Measurement Traceability and Uncertainty in Analytical Chemistry, 16th- 18th June 2002, in Luzern.

4 RESULTS AND ACHIEVEMENTS

WP1. Develop standards of performance for the measurement of lead and aluminium to meet national and EU requirements.

i. compare procedures used to evaluate laboratory performance in external quality assessment schemes.

A project report was sent to the Commission in March 2002 and subsequently submitted to Clinical Chemistry for publication. The paper was considered by peer reviewers and has been accepted for publication. The important conclusions of the project were to propose:

> "that the CLIA88 (Clinical Laboratory Improvement Amendments of 1988) recommendations for blood lead (±40 μg/L or ±10% of the target concentration, whichever is the greater) could be used as a quality specification although a revision to ±30 μg/L or ±10% is recommended. For serum aluminium a suitable quality specification of ±5 μg/L or ±20% of the target concentration, whichever is the greater, is suggested. These specifications may be used to compare laboratory performance across schemes."

The scheme organisers are continuing to work together on a project that seeks to put these recommendations into practice so that multi-scheme performance assessment across Europe may be undertaken.

ii. prepare a comparison of European national legislation relating to blood lead concentrations in occupational settings. Legislative requirements in each of the countries represented by the Participants have been tabulated with respect to blood lead monitoring for occupational lead exposure.

Copies of current legislation from each of the countries represented in the Network have been obtained and a standardised format for summarising the relevant information was agreed. A simple tabulation of the data and some commentary is presented in Appendix 1. The main conclusions are:

- There is considerable variation in the blood lead concentration (25-60 μg/dL) that triggers further action.
- There is less, but still some, variation in the blood lead concentration that triggers suspension from work with lead. Some countries make allowance for the results of other measurement parameters.
- A small number of countries include differences in legislation between male and female workers.
- Demand for surveillance of analytical quality is inconsistent. No scrutiny is required in some countries while others demand extremely high standards of measurement.

The Participants are now drafting an extended version with additional descriptive text that will be submitted for publication when complete.

iii. prepare a comparison of European national guidance values relating to measurements of aluminium for monitoring patients with renal failure who are treated by dialysis.

Monitoring requirements applied to measurements of aluminium in serum. (EEC Council Resolution 86/C184/04 of 16/6/86). Recommendations for good practice from countries represented in the Network were obtained.

Finland

The upper reference limit for serum aluminium in non-exposed subjects is 0.1 µmol/L (2.7 µg/L). For patients on dialysis the limit is at 3.7 µmol/L (100 µg/L). There is no legislation associated with these concentrations.

Italy National Health Council recommends patients undergoing dialysis should be monitored for serum/plasma aluminium at least once a year, or more often in subjects at higher risk. Laboratories wishing to perform aluminium determinations within the NHS are required to be accredited and to participate in EQAS; standards of performance exist but are not enforced by law.

UK There are no established requirements in addition to the Council Resolution. The Renal Association has presented "recommended standards and audit measures" for the Treatment of Adult Patients with Renal Failure (November 1997) which state that a water treatment plant should be tested at three-monthly intervals with full chemical analysis, including measurement of aluminium, in the plant supply and plant product. The limit value for aluminium is set at 10 µg/L.

WP2. Co-ordination of national activities

i information relating to participant laboratory statistics and interests

A review of the responses to the questionnaire is included as Appendix 2. In summary, 75% of the laboratories that replied (n = 190) operate in the public sector. The laboratories are usually small, with less than 5 members of staff although around 70% are part of larger analytical organisations. Many (40%) are using equipment purchased before 1990. Examples of the total number of assays undertaken by all the respondents, per year, are; lead >150,000, aluminium, copper, zinc > 30,000 each, chromium, mercury, lead, cadmium > 20,000 each, methyl hippuric acid, hippuric acid > 50,000 each, muconic acid > 30,000 each. Between them the participants undertake a very wide range of analytical procedures and there are a considerable number dealing with "rare" analyses for which there are no reference materials and in some cases, even no EQAS. Eighty five percent of respondents indicated a willingness to participate in European EQAS (which may be the only way to achieve traceability for these analyses). Few laboratories report the uncertainty of a result and only a very small number have determined the measurement uncertainty according to the ISO Guide. (Collaboration at a European level among EQAS will strengthen the European metrological infrastructure.) A formal summary of the responses is being prepared so that this work may be submitted for publication.

ii. organisation of EQA Schemes

Responses to the questionnaire concerning scheme management, documentation and

accreditation are summarised in Appendix 3. Only one EQAS has received accreditation although most of the schemes appear to be organised in such a way that they would be likely to be accredited, or could easily become so, if they were required so to do.

WP3. Initiation of collaborative work and avoid duplication of effort among different schemes

i. evaluate a software programme which had been developed to perform the data handling and report generation activities in accordance with recommendations given in ISO 43.

There was a demonstration of the WINAMIQAS programme at one meeting, of how the software took data and presented displays of performance in different formats. It was also explained that the software provided for other functions including scheme administrative work and internal quality control. Copies were provided to each of the Participants who attempted to evaluate the appropriateness of the software for their own schemes. However, a number of Participants were unable to operate their demonstration versions and in their comments organisers indicated that each needed something different to address their own scheme design and other constraints. At least two were moving in the direction of direct participant input of results. As a consequence the idea of collaboration based on the WINAMIQAS software was concluded.

ii. investigate a methodology for introducing results from participants in different countries into a single database via a web-site interface.

Following considerable development work which demonstrated the viability of databases with information input via web-site interfaces, a proposal to "Develop a concept for harmonization of external quality assessment schemes (EQAS) in occupational and environmental laboratory medicine which allows the setting of common standards for laboratory performance in a context which warrants the national identities and interests of the involved EQAS organisers" was submitted to the Commission as an Expression of Interest in response to Work program 6.2.1. "Methodologies to support standardisation and community policies". However, the proposal was not accepted.

The Participants continue to believe that there is merit to this concept, particularly for the harmonisation of scheme activities to promote comparability among schemes and for the introduction of new EQAS identified by the responses to the laboratory questionnaire (WP2 i). Thus, the Participants prepared a proposal "Quality, Traceability and Comparability of European Proficiency Testing Schemes (in Occupational and Environmental Laboratory Medicine)" which is built on the work described in WP1 i, WP2 i, WP2 ii, WP3 ii and WP4. It is planned to seek funding for this proposal from approriate organisations so that the collaboration now established among the Participants can be maintained.

WP4. Education and training

Individual Participants have prepared teaching material relating to the uncertainty of measurement, the use of reference materials for calculating uncertainty, and the use of

EQA schemes for estimating uncertainty of measurement.

The abstract of the paper to describe the application of data from scheme organisers to estimating uncertainty of measurement presented at Luzern (16th- 18th June 2002) is reproduced here.

> **Estimating uncertainty of measurement in occupational and environmental laboratory medicine**
>
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> on behalf of the Thematic Network "European Organisers Of External Quality Assessment/ Proficiency Testing Schemes Related To Occupational And Environmental Laboratory Medicine"

Proficiency Testing Schemes (PTSs) are important means to improve comparability of analytical data and participation of analytical laboratories in PTSs is required for accreditation to certain standards. In 1999 formal collaboration as an EU Thematic Network was initiated among 9 organisers of PTSs in occupational and environmental laboratory medicine (OELM). The aim was to evaluate areas for possible harmonisation in order to achieve equivalent judgement of laboratory performance. Strengthening the traceability to SI of analytical measurements in PTSs in OELM was identified as a key issue, both in terms of determining the uncertainty of the target values of test materials and providing guidance to participants. As a first step in this process, the uncertainties estimated by each PTS organiser for determinations of Pb in blood and Al in serum were compared. Uncertainty was estimated using equivalent data from validation studies according to the model in the EURACHEM/CITAC Guidelines.

5. EXPLOITATION

Publications

The following paper has been accepted for publication in Clinical Chemistry.
Comparison of procedures used to evaluate laboratory performance in external quality assessment schemes for lead in blood and aluminium in serum demonstrates the need for common quality specifications. Andrew Taylor, Jurgen Angerer, Francoise Claeys, Jesper Kristiansen, Olav Mazarrasa, Antonio Menditto, Marina Patriarca, Alain Pineau and Ilse Schoeters

The following papers are being prepared for publication

Differences in implementation of European legislation concerning occupational exposure to lead

Environmental and occupational medicine in Europe: a survey of workload and needs for quality assurance.

The following paper was presented at the CITAC/Eurachem Workshop on Measurement Traceability and Uncertainty in Analytical Chemistry, 16th- 18th June 2002, in Luzern
Estimating uncertainty of measurement in occupational and environmental laboratory medicine. M. Patriarca and A. Menditto (on behalf of the Network participants)

Website
A website giving contact information of the participants and the work being undertaken is being established.

Ongoing projects
European-wide scoring system based on z-score and En numbers. A cross-scheme, European-wide comparison of laboratory performance using a scoring system based on the data derived from the work of the Network will be implemented in 2002-03.

Planned projects
The following projects have been planned and are ready for implementation as funding is secured.
Development of methodologies to warrant traceability of target values of test samples in EQAS
Development of a Web-based system for sharing data derived from the same test materials, between different EQAS
Implementation of harmonised quality management systems in EQAS in occupational and environmental medicine.
A programme for further education on specific topics in the field of metrology to provide support to participants in EQAS in occupational and environmental medicine.

The planned projects are dependent upon financial support for (i) annual meetings of the group to work on the planning and implementation of the proposed studies, (ii) construction of the Web-based system for sharing data among schemes, (iii) purchase of reference materials to permit traceability studies.

6. CONCLUSIONS

Projects undertaken by the Participants have enabled a firm foundation for harmonising EQA schemes to be established. Despite national priorities and obligations it is possible to utilise results for assessments of performance that are either alongside, or may even replace, current protocols. The steps that permit this development include; quality specifications for analytical techniques, a common results database with web-site data input, and identification of assays not included in EQA schemes.

The Network Participants have learnt from each other about the need to involve key metrological principles such as traceability and measurement uncertainty. These principles are not yet widely employed in EQA schemes for laboratory medicine. With

a relative abundance of reference materials, occupational and environmental medicine provides an arena in which a start may be made.

The Participants have established effective cooperation and, if funding can be obtained, they plan to continue working together on projects that further the aims and objectives of the Network.

Appendix 1.

European national legislation relating to blood lead concentrations in occupational settings.

The compilation of blood lead concentrations, which feature in national legislation passed for the protection of persons with occupational exposure to lead, is given in Table 1. This also includes the EU limits as set out in Council Directive 98/24/EC. The Table is not intended to provide a summary of all aspects of the legislation. Other features such as measurements to define significant exposure, protection of young adults and new employees, how to define women of child-bearing capacity, of exemptions for workers with many years experience in lead-industries, interpretation of results in the context of other parameters of exposure - are relevant to the use of these concentrations for the purposes of occupational monitoring.

The purpose of preparing the table was to identify whether there are critical blood lead concentrations, which are common to all/most countries and should, therefore, be the focus for quality assessment. It can be seen that most of the countries use several different concentrations, which act as "triggers" for further levels of occupational surveillance. There are no concentrations which are common to all, for either (i) introduction of further action or (ii) suspension from occupational lead exposure but 40 μg/dL and 70 μg/dL, respectively, are the most usual. These are also the limits given in the Council Directive.

In the course of this project to compare blood lead concentrations set out in national legislation it was agreed to identify the “weight of concern” applied to the quality of measurements carried out to satisfy the legislation. Data towards this objective were obtained by asking if laboratories undertaking such measurements were required to meet a quality threshold (accreditation) and to have their analytical performance open to independent scrutiny (external quality assessment/ proficiency testing). The evidence collected is shown in Table 2.

Table 1. European National Legislation on Blood Lead Measurements for the Biological Monitoring of Persons with Occupational Exposure to Lead (units are µg/dL)

Country	Action	Suspension	Other Details
EU*	40	70	Action is related to Pb concentration: • if > 40; information is supplied to workers • if > 40 and < 50; biological monitoring is set up • if > 50; measure Pb in air and start medical surveillance • if > 60; clinical examination
BE	40	80	• if > 40; information is supplied to workers • if > 40 and < 50; biological monitoring is set up • if > 50; specific zones are established (canteen) Limit is at 70 but 80 is allowed if ALAU < 20 mg/g creatinine or ZPP < 20 µg/g Hb or ALAD > 6 european units
DE	40 (M) 30 (F)	40 (M) 30 (F)	
DK	25	40	Medical surveillance is related to Pb concentration: • if < 25; no control • if > 25 and < 40; once a year • if >40; every six months
ES	40 (M) 30 (F)	70	Pregnant and breast feeding women cannot be exposed. 80 is allowed if other parameters (ALA, ZPP etc) are OK Monitoring is related to Pb: • if < 50; once a year • if > 50 and < 60; every six months • if >60; every three months
FI	40	50	
FR	40	80	
IT	60 (M) 40 (F)	70 (M) 40 (F)	Women of child bearing age withdrawn from work if Pb > 40. Medical surveillance is related to Pb concentration: • if < 40; once a year • if >40 and < 50; every six months

			• if > 50; every three months
NL	30	70	
UK	50 (M) 25 (F)	60 (M) 30 (F)	Monitoring is related to Pb: • if < 30; once a year • if > 30 and < 40; every six months • if > 40 and < 60; every three months • if > 60; at doctors discretion but within three months

*Council Directive 98/24/EC

The detail is not intended to be complete (see text) but this compilation allows a comparison of key blood lead concentrations in the different countries.

Table 2. Laboratory requirements to be involved in blood lead occupational monitoring programmes

	Obligatory EQAS participation ?	Performance criteria to be achieved ?
EU	No	No
BE	No	No
DE	Yes	Yes
DK	Yes + accreditation	Yes, related to uncertainty
ES	To be introduced soon	Yes
FI	No	Uncertainty
FR	Yes	Yes, but not published
IT	Yes + accreditation	Yes, but not published
NL	Yes + accreditation	No
UK	Yes	Yes

Notes:
Italy and UK, accreditation is required only for laboratories wishing to work for the respective National Health Services.

Appendix 2.

The European Questionnaire

European external quality assessment on analysis of human biological fluids for occupational/environmental health monitoring

Number of responding laboratories by EQAS (No. = 190)

EQAS	Labs	Responding
Belgium	32	16 (8.4%)
Finland	45	18 (9.5%)
Italy	79	64 (33.7%)
Spain	114	47 (24.7%)
The Netherlands	24	8 (4.2%)
UK	149	37 (19.5%)
Total	443	190 (100%)

Question n. 2

- **Type of Laboratory (Public or Private)**

Number of laboratories by EQAS

EQAS	Public	Private	Total
Belgium	9	7	16
Finland	12	6	18
Italy	53	11	64
Spain	30	17	47
The Netherlands	7	1	8
UK	31	5	36
Total	142 (75%)	47 (25%)	189 (100%)

Number of laboratories by geographical regions

	Countries	Laboratories
European Union	9	150
Other European countries	4	6
Extra European countries	12	32
Missing		2
Total	25	190

Question n. 3

- To which of the following field(s) do the measurements carried out by your laboratory related?

Working Field(s)

Field	Number of laboratories
Occupational	118 (62.1%)
Environmental	56 (29.5%)
Clinical	97 (51.1%)
Others	39 (20.5%)
Total	190 (100%)

Question n. 4

- How large is the laboratory expressed in terms of permanent personnel members?

Permanent personnel members

No. personnel	No. (%) of labs
<5	44 (23.2%)
6-10	34 (17.9%)
11-20	39 (20.5%)
21-50	37 (19.5%)
>50	32 (16.8%)
Missing	4 (2.1%)
Total	190 (100%)

Question n. 5

How many non-permanent personnel members are there?

Non-Permanent personnel members

No. personnel	No. of labs
<5	136 (71.6%)
6-10	19 (10.0%)
11-15	5 (2.6%)
16-20	1 (0.5%)
21-30	0 (0.0%)
31-50	1 (0.5%)
>50	1 (0.5%)
missing	27 (13.7%)
total	190 (100%)

Question n. 6

- How many of the personnel members are working on analyses of human biological fluids for occupational / environmental health monitoring?

Permanent personnel members*

* Labs participating in Spanish EQAS non included

No. of permanent personnel members	No. (%) of labs
1-5	90 (63.4%)
6-10	24 (16.9%)
11-20	8 (5.6%)
>20	5 (3.5%)
Missing	11 (7.7%)
Total	142 (100%)

Non-Permanent personnel members*

* Labs participating in Spanish EQAS non included

No. of non-permanent personnel members	No. of labs
1-5	81 (57.0%)
6-10	2 (1.4%)
11-20	0
>20	0
Missing	59 (41.5%)
Total	142 (100%)

Question n. 7

- Specify the proportion of time spent by your personnel on analysis of human biological fluids for occupational / environmental health monitoring?

Time spent by personnel

Time (%)	No. of labs
<10%	59 (31.1%)
11-20%	27 (14.2%)
21-40%	21 (11.1%)
41-40%	20 (10.5%)
61-80%	17 (8.9%)
>80%	35 (18.4%)
missing	11 (5.8%)
Total	190 (100%)

Question n. 8

- Please specify the year when your laboratory's analytical equipment for analyses in human biological fluids for occupational/environmental health monitoring was installed

Year of installation of instrument (Number of laboratories = 164)

Year	No. of instruments
<=1970	12 (2.4%)
1971-80	36 (7.1%)
1981-1990	158 (31.0%)
1991-2001	292 (57.4%)
Missing	11 (2.2%)
Total	509 (100%)

Question n. 9

- Specify the number and type of all analyses carried out yearly on human biological fluids for trace elements or for the monitoring of exposure to organic substances and the analytical techniques used.

Trace Metals in Whole Blood (or Blood/Urine, Blood/Serum, Blood/Air)

Element	Laboratories	Analyses
Pb	146	158,835
Cd	69	12,753
Hg	34	5,458
Mn	20	2,271
Cr	8	1,831
Cu	8	1,688
Zn	8	1,272
Co	8	1,113
Ni	7	1,100
As	6	897
Al	4	665
Se	4	201
U	3	360

Trace Metals in Serum/Plasma (or Plasma/Urine, Serum/Urine)

Element	Laboratories	Analyses
Al	71	34,889
Zn	64	37,884
Cu	62	36,540
Se	26	9,324
Mn	9	492
Mg	6	12,650

Trace Metals in Urine (or Plasma/Urine, Serum/Urine) - 1

Element	Laboratories	Analyses
Cr	79	24,109
Hg	78	38,034
Pb	73	25,824
Cd	57	20,282
Cu	54	7,221
Ni	52	16,014

Trace Metals in Urine (or Plasma/Urine, Serum/Urine) - 2

Element	Laboratories	Analyses
As	37	17,615
Co	33	6,618
Mn	32	4,056
Zn	32	17,166
Al	16	2,767
Tl	12	584
V	11	1,458

Organic Compounds in Urine - 1

Compound	Lab.	Analyses
Methylhippuric acid	71	56,916
Hippuric acid	67	64,351
Mandelic acid	64	18,205
Phenylglyoxylic acid	49	12,708
Trichloroacetic acid	49	9,406
2,5-Hexanedione	43	15,943
Phenol	39	16,712

Organic Compounds in Urine - 2

Compound	Lab.	Analyses
t,t-Muconic acid	38	33,435
δ-Aminolevulinic ac.	31	22,270
Acetone	16	4,218
1-hydroxypyrene	15	7,489
Methylethylketone	14	12,314
N-Methylformamide	14	2,986
Tiocyanate	13	3,244

Gaseous Anaesthetics in Urine

Compound	Labs	Analyses
Nitrous oxide	17	12,548
Isoflurane	7	4,448
Sevofluorane	5	2,675
Anaesthetics (generic)	8	2,389

Organic compounds in Whole Blood

Compound	Labs	Analyses
ZPP	22	26,674
Benzene	9	1,834
Toluene	6	404
Xylenes	6	365

Question n. 10

• Do you routinely report measurement results with an associated uncertainty for any of the analyses in the table?

Measurement results with an associated uncertainty

	No. of labs
No	87 (45.8%)
Yes *	22 (11.6%)
Not applicable	1 (0.5%)
Missing	80 (42.1%)
Total	190 (100%)

* for at least one analyte

Question n. 11

• If you normally report any results with uncertainty, has the uncertainty been estimated according to the "Guide to the Expression of Uncertainty in Measurements, ISO 1995"?

Estimate of uncertainty according to ISO Guide (GUM)

	No. of labs
YES	7 (3.7%)
NO/Missing	183 (96.3%)
Total	190 (100%)

Question n. 12

- Does your laboratory participate in national PT/EQA schemes?
- Trace elements
- Organic compounds

Participation in national EQA schemes for trace elements

	No. of labs
Yes	155 (81.6%)
No	25 (13.2%)
Missing	10 (5.3%)
Total	190 (100%)

Participation in national EQA schemes for organic compounds

	No. of labs
Yes	39 (20.5%)
No	86 (45.3%)
Missing	65 (34.2%)
Total	190 (100%)

Question n. 13

- Does your laboratory participate in other PT/EQA schemes?
- Trace elements
- Organic compounds

Participation in other EQA schemes for trace elements

	No. of labs
Yes	91 (47.9%)
No	71 (37.4%)
Missing	28 (14.7%)
Total	190 (100%)

Participation in other EQA schemes for organic compounds

	No. of labs
Yes	52 (27.4%)
No	75 (39.5%)
Missing	63 (33.1%)
Total	190 (100%)

Question n. 14

- Are there any assays for which PT/EQA schemes are not available?

PT/EQA schemes not available for Organic Compounds - 1

Compound	Matrix	Labs
Hippuric acid	Urine	14
Mandelic Acid	Urine	10
Methylhippuric acid	Urine	10
Phenylglyoxylic Acid	Urine	8
ALA	Urine	6
1,1,1-Trichloroethane	Urine	5
2,5-Hexanedione	Urine	5
Phenols	Urine	4
o-Cresol	Urine	3

PT/EQA schemes not available for Organic Compounds - 2

Compound	Matrix	Labs
Cyclohexanol	Urine	2
Dimethylbenzoic Acid	Urine	2
Furoic Acid	Urine	2
1-hydroxypyrene	Urine	2
Mercapturic Acid	Urine	2
2-Phenyl-2-Propanol	Urine	2
t,t-Muconic Acid	Urine	2
Toluene	Urine	2
Nitrous Oxide	Urine	2
2-Hexanol	Urine	2

PT/EQA schemes not available for Organic Compounds - 3

Compound	Matrix	Labs
Solvents/Solvent metabolites	Urine	6
Organic metabolites	Urine	4
Anaesthetics	Urine	4

PT/EQA schemes not available for Organic Compounds - 4

Compound	Matrix	Labs
PCBs, Pesticides, Phitoestrogens	Serum	2
PCBs, Pesticides, Phitoestrogens	Amniotic fluid	1
PCBs, Pesticides, Phitoestrogens s	Breast milk	1
Pesticides	Urine	1
ZPP	Blood	5

PT/EQA schemes not available for Trace elements

Compound	Matrix
Hg, Mn, Ni	Blood
Cu, Fe, Ni, Ni, Se, Zn	Serum
Ag, As, Au, B, Ba, Br, Cd, Co, Cr, Cu, F, Fe, Hg, I, Li, Mn, Ni, Pb, Pd, Pt, Sr, V, Zn	Urine
As, Hg	Hair

Question n. 15

- Would the laboratory be willing to participate in a European-wide QC scheme ?

Willingness to participate in a European-wide QC scheme

	No. of labs
Yes	160 (84.2%)
No/Missing	30 (15.8%)
Total	190 (100%)

Appendix 3.

European Organisers of External Quality Assessment/Proficiency Testing Schemes Related to Occupational and Environmental Medicine

Scheme Organisation and Management

	Yes	No
Do you have a quality manual:	4	2
Do you have a participant's manual:	4	2.
Do you have a formal complaints procedure:	2	4
Do you audit the quality of specimen containers:	5	1
Do you audit the raw materials (blood, urine etc.) to determine that basal concentrations are appropriate:	6	0
Do you audit the accuracy of spiking:	6	0
Do you audit specimen stability:	5	1
Do you audit specimen homogeneity:	6	0
Do the tests have performance standards/scores:	5	1
Do the tests have definitions of unacceptable performance:	5	1
Do you audit the time taken to prepare your reports after the deadline for receipt of results:	6	0.
Are you separate from any commercial interests in reagent, calibrant or equipment manufacturer/distributor:	6	0
Are you accountable to an independent advisory group:	2	4
Is the scheme accredited:	1	5

Responses were received from six of the nine schemes

June 2002