The use of internal quality control materials for the preparation and maintenance of reliable methods for the measurement of lead in blood

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Verwendung internen Qualitätssicherungsmaterialien für die Erarbeitung und Anwendung zuverlässiger Methoden zur Messung von Blei in Blut

Summary. The performance of a group of reference laboratories measuring lead in blood, has been monitored by an extensive external quality assessment programme, since 1974. Performance was similar to that observed in other, larger quality control surveys but rapidly improved following detailed investigations of critical factors in the analytical methodology. The introduction of a rigorous internal quality control protocol, with all laboratories using the same well-characterised materials, has produced external quality control results that are both accurate and very tightly distributed. Between-laboratory coefficients of variation of less than 5%, less than 6% and less than 20% are now observed at concentrations of over 1.0 μmol/l (20.7 μg/dl), 0.5–1.0 μmol/l (10–20 μg/dl) and less than 0.5 μmol/l (10 μg/dl), respectively. These results represent the best that can be achieved by current methodology and instrumentation in regular, daily use.

Introduction

Reference materials may be used to measure or control accuracy and precision. While both are important there are many situations, e.g. for series of measurements within a single laboratory where long-term precision (reproducibility) is more important than accuracy. However, when data from different laboratories have to be examined it is essential that accuracy is known and ideally will be the same so that results can be directly compared.

Internal quality control procedures are used primarily for the control of analytical precision. Internal quality control (IQC) specimens are used with a working range around a target (Fig. 1) and the level of reproducibility achieved by a laboratory depends on the span of the range. If the working range is wide, the results obtained on the IQC samples will be acceptable even if a very poor method is used. The consequences will be very imprecise sets of results for the IQC specimens and for unknown samples and these will be of limited value for investigation of clinical or other problems (Fig. 1 a). If a tighter range is employed the poor precision will be apparent and the laboratory should be constrained to improve or change the methodology (Fig. 1 b). A good method would only appear out of control if the working range is set too close around the target (Fig. 1 c) or if a real problem (e.g. instrument fault) develops.

The working range should be set, therefore, at a level which is consistent with (i) the performance of laboratories that use reliable methods on equipment that is in good condition and performed by experienced, well-trained staff, and (ii) the precision required for effective clinical use of the results (Fig. 1 d).

Target values assigned to the IQC specimens can be determined by several procedures, e.g. weighing-in of analyte, consensus or method means derived from results reported by many laboratories or from reference centres, analysis by a definitive method, analysis together with certified reference materials used as the standard for calculation of the concentration, repeated analysis by the working method within the user’s laboratory. Depending on the procedure used the target value may or may not be close to the “true” concentration. Of the methods noted above the last is probably most often used and is least likely to provide an accurate result.

Thus, IQC specimens with a combination of tight working limits and a target which is close to or equal to the true value, allow the consistent reporting of accurate results. These principles have been widely employed within general clinical chemistry and other laboratories for many years but the absence of suitable material has prevented similar developments for more specialist applications.

Furthermore, working procedures are often quite dissimilar in different laboratories and these practical variations are reflected in the between-laboratory variation reported from external quality assessment programmes [2, 3, 5, 6]. In an initiative to reduce between-laboratory variation and improve accuracy for monitoring lead in blood, the United Kingdom Trace Elements Laboratories of the Supraregional Assay Service (SAS) agreed on a common internal quality control protocol [1]. The impact of this protocol, in terms of long-term precision and accuracy has been monitored by the performance of these laboratories within a restricted SAS external quality assessment programme.

* Presented on behalf of the Trace Elements Sub-group of the Supraregional Assay Service (SAS) of the UK National Health Service
Experimental

Internal quality control materials

Preparation and characterisation of the internal quality control specimens used by the SAS laboratories has been described [1]. These specimens are analysed within a batch according to an agreed protocol. The procedure is to measure:

- the standards,
- the three IQC samples,
- test samples (maximum of 10),
- the three IQC samples,
- test samples (maximum of 10)... etc.

Results determined on test samples are reported only if the values for the IQC specimens before and after, are within the accepted working ranges (the same target values and working ranges are used by all seven laboratories).

External quality assessment programme

The restricted SAS laboratories EQA programme is organised from Guildford and is similar in design to the open Trace Elements EQA scheme [8] but is much more intensive. Ten pools are prepared from a single sample of human blood. Nine are supplemented with known amounts of lead, the tenth is untreated to give the endogenous concentration and allow calculations of recovery of the added lead.

Each pool is sent to participants on two separate occasions and 5 samples are distributed every week. The programme lasts, therefore, for four weeks and is repeated each month. A weekly report (Fig. 2) gives results obtained on the previous set of 5 specimens and the monthly report summarises the 20 results for each laboratory. These results are expressed as

- proximity to the mean $\bar{X} - \bar{X}$,
- difference between duplicated samples $X_1 - X_2$,
- recovery of added lead,

and plotted on charts that show target zones appropriate for any concentration (Fig. 3). The percentages of results falling within the inner and outer target zones for each parameter are added together to produce the performance score. The maximum possible score is 600 and it has been agreed among the participants that 420 is the minimum satisfactory score. Results are known by all participants and there is no anonymity. Performance is reviewed at the regular meetings of laboratory directors and deputies.

Laboratories and methods

The seven SAS laboratories are located in London (2), Birmingham, Southampton, Guildford, Leeds and Glasgow. One laboratory has two separate methods in regular use and returns two sets of results. All centres analyse several hundred specimens per year for clinical, occupational monitoring and other purposes and have been established for at least 15 years. Initially, all used the microsampling cup with flame atomic absorption spectrometry (AAS) except for one laboratory with electrothermal atomisation-AAS (ETA-AAS). As instruments have been replaced in recent years the methodologies have changed and those in use now are - microsampling cup (1), ETA-AAS with L'vov platform and Zeeman effect background correction (1), ETA-AAS with deuterium background correction (6). All laboratories prepare their own calibration solutions with addition of lead to human or bovine blood.

Results

Between-laboratory coefficients of variation (CV's) averaged for two concentration ranges, over a succession of 6-monthly periods, are shown in Fig. 4. At the start of the
Fig. 4. Mean inter-laboratory coefficients of variation at blood lead concentrations of 0–2.0 (△) and more than 2.0 μmol/l (○) during a series of six-monthly periods.

Table 1. Mean between-laboratory coefficients of variation at different lead concentrations, October—December 1987

<table>
<thead>
<tr>
<th>Lead (μmol/l)</th>
<th>0–0.5</th>
<th>0.51–1.0</th>
<th>1.01–2.0</th>
<th>2.01–3.0</th>
<th>3.01–4.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oct</td>
<td>20.2 (2)</td>
<td>5.9 (4)</td>
<td>4.1 (8)</td>
<td>3.7 (4)</td>
<td>3.0 (2)</td>
</tr>
<tr>
<td>Nov</td>
<td>9.8 (2)</td>
<td>5.3 (2)</td>
<td>4.1 (8)</td>
<td>4.8 (4)</td>
<td>4.3 (4)</td>
</tr>
<tr>
<td>Dec</td>
<td>13.7 (4)</td>
<td>2.7 (2)</td>
<td>4.5 (6)</td>
<td>3.9 (6)</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>(i) NEQUAS</td>
<td>—</td>
<td>—</td>
<td>9.4 (2)</td>
<td>6.6 (4)</td>
<td>6.3 (1)</td>
</tr>
</tbody>
</table>

(i) SAS EQA programme, (ii) National EQA scheme, Birmingham. Numbers in brackets = number of results at that concentration range.

SAS external quality assessment programme the agreement between these laboratories was no better than that reported by other EQA schemes [2, 3, 5]. A series of detailed investigations to determine critical factors associated with the microcup technique led to considerable reduction of this variation [7] which was well in advance of improvements subsequently noted elsewhere [3]. At the inception of the environmental lead survey of the Commission of the European Community a further stimulus was deemed necessary and the IQC strategy was introduced in 1979–1980 with further reductions of the between-laboratory CV’s to around 7–10%. The most recent phase, 1982–1987, has been characterised by replacement of all the original atomic absorption instruments and a move in all except one laboratory, to furnace technology.

The levels of performance which are now consistently attained are shown by the data in Table 1. For samples with lead concentrations greater than 1.0 μmol/l (20.7 μg/dl) it is unusual to find a between-laboratory CV greater than 5%. At lower concentrations, nearer to the limit of detection, there is the expected increase in variation but this is very much less than has previously been reported [2, 3, 5, 6].

Performance scores for the participants are regularly in excess of the target value of 420 and there is no evidence to indicate that a particular methodology, instrument etc. produces superior or inferior results compared to others represented among the group. The same laboratories partici-

ate in other national and international EQA programmes and continually return satisfactory results.

Discussion

It would be expected that specialist laboratories should be able to demonstrate good precision. It is at such centres that the most recent equipment should be available and that staff will have greater experience with relevant techniques. If good precision was not possible at these laboratories it would be concluded that fundamental problems were present. It is at the specialist centres, therefore, that improvements in the standards for measurement of lead in blood would be anticipated to occur first. The results of the EQA scheme provide objective evidence to support this proposition (Fig. 4). This scheme with an intensive distribution of specimens and the short interval before the preparation of reports, has allowed very sensitive monitoring of individual and group laboratory performance.

The common protocol for the use of the IQC materials, with the same system for use, target values and working ranges, has assisted the improved precision but, equally importantly, has ensured accurate analytical results. The target values were very carefully assigned by independent procedures and the materials were shown to be homogeneous and stable [1]. Thus, as the SAS laboratories introduced these IQC materials into their analytical protocols, so the results obtained with the EQA specimens showed much narrower variation and were appropriate to the amounts of lead added during preparation.

Adoption of the rigorous system for IQC allowed all participants to progress through transition periods such as the setting up of new instruments, changing methods, relocation of laboratories, without fluctuation in the quality of results (Fig. 4). The accuracy and precision demonstrated by the EQA data represents the best that can be achieved by current methodology and instrumentation in regular daily use. Results obtained by the SAS laboratories in other EQA schemes indicate that this level of performance can be matched by only a few other laboratories.

The standard of performance revealed by the data in Table 1 provides confidence in results reported for investigations and projects such as diagnosis of lead toxicity in children, occupational monitoring, evaluation of lead exposure among specific population groups. However, the variation found at concentrations below 0.5 μmol/l (10 μg/dl) and which also reflects between-batch precisions for individual laboratories, is such that recent data relating neurobehavioural measurements in children to low levels of exposure to lead [4], have to be interpreted with great caution.

The laboratories of the SAS Trace Elements subgroup have used an EQA programme to demonstrate that a common IQC protocol can produce very accurate and precise results for the measurement of lead in blood. The same approach has recently been successfully applied to the measurement of cadmium in blood and aluminium in serum [9] and could be extended to any other quantitative analytical task.

Acknowledgements. I would like to acknowledge the contribution of Mr. W. B. Yeoman, who first developed the common IQC concept, and the Directors and staff of the SAS Trace Elements Laboratories.
References


Received June 9, 1988