Z Rechtsmed (1984) 93:219–225

Zeitschrift für
Rechtsmedizin

Interlaboratory Survey on Thallium in Urine*

M. Geldmacher-von Mallinckrodt[1], D. Stamm[2], and P. Enders[1]

[1] Institut für Rechtsmedizin, Universitätsstr. 22, D-8520 Erlangen, Federal Republic of Germany
[2] Max-Planck-Institut für Psychiatrie, Kraepelinstr. 10, D-8000 München, Federal Republic of Germany

Summary. Quality assurance of analytic results was legalized in the Federal Republic of Germany by the law regulating the calibration of measuring devices of July 11, 1969, and the ordinance concerning the exception from compulsory calibration dated June 29, 1970. Accordingly, in the field of health care the Guidelines of the Medical Society of West Germany for the realization of quality assurance activities have to be followed. Since January 1, 1974, the law regulating the calibration of measuring devices has been fully effective.

In the field of legal medicine the clinico-toxicologic analysis is considered to be a part of health care. As far as quantitative determinations are considered, these analyses have to follow the regulations mentioned above. To fulfil the basic program, adequate control samples are necessary. For toxicologic analysis there have been no control samples so far. Therefore, a control sample for thallium has been developed which can be used for long- and short-term interlaboratory surveys. The results are reported.

Key words: Quality assurance, thallium – Interlaboratory survey, thallium – Thallium, quality assurance

Zusammenfassung. Die Qualitätssicherung von Analysenergebnissen erhielt in der Bundesrepublik Deutschland durch das Eichgesetz vom 11.7.1969 und die Eichpflicht-Ausnahmeverordnung vom 29.6.1970 eine gesetzliche Basis. Danach sind im Bereich der Heilkunde bei Verwendung nicht geeichter Volumenmeßgeräte die Richtlinien der Bundesärztekammer zur Durchführung von Maßnahmen der Qualitätssicherung zu befolgen. Seit dem 1.1.1974 hat das Eichgesetz seine völlige Gültigkeit erlangt.

Von den in rechtsmedizinischen Instituten durchgeführten Untersuchungen stellen mindestens die klinisch-toxikologischen eine Tätigkeit im

* Dedicated to Prof. Dr. Oskar Grüner on the occasion of his 65th anniversary

Offprint requests to: Prof. Dr. Dr. Marika Geldmacher-von Mallinckrodt (address see above)

Bereich der Heilkunde dar. Soweit es sich um quantitative Bestimmungen handelt, unterliegen sie damit sicher den Bestimmungen des Eichgesetzes bzw. den Richtlinien der Bundesärztekammer.

Zur Durchführung des Basisprogrammes der Bundesärztekammer sind geeignete Kontrollproben und die Durchführung von Ringversuchen erforderlich. Für toxikologische Fragestellungen gibt es hierfür praktisch noch keine Basis. Deshalb wurde ein Kontrollurin für Metalle konzipiert, mit dem lang- und kurzfristige Ringversuche zur Thalliumbestimmung durchgeführt wurden. Über die Ergebnisse wird berichtet.

Schlüsselwörter: Thallium, Qualitätskontrollen – Ringversuch, Thallium – Qualitätskontrollen, Thallium

Internal and external quality control are essential for quality assurance in the analysis of biologic material. This is true for samples with environmental, occupational, and clinico-toxicologic relevance.

Quality assurance for the results of analyses in the Federal Republic of Germany has a legal basis by the law regulating the calibration of measuring devices of July 11, 1969 (Eichgesetz). This law has to be applied to all laboratory equipment which is used for quantitative measurements and, in principle, consists of a calibration of laboratory equipment under official control. This is not feasible in practice; therefore, some exceptions have been made by governmental regulations (Eichpflicht-Ausnahmeverordnung).

Practically all quantitative analyses in the FRG related to health care have to be performed strictly according to the Guidelines of the Medical Society of West Germany (Bundesärztekammer 1974). These Guidelines include the following basic program (Stamm 1974, 1980).

1. Internal quality control: The first part of the internal quality control is the control of the precision at the most frequent decision limits by analyzing samples of the same control specimen in every run of analysis. The second part is the control of accuracy over the whole clinically relevant range of measurements by analyzing an accuracy control specimen in every 4th run of analysis, the control specimen being selected from a number of different control specimens kept on hand.

2. External quality control: The external quality control takes place in the form of short-term interlaboratory surveys with two control specimens having different concentrations.

In this basic program control specimens are used both for internal precision and accuracy control and for interlaboratory surveys. The *same* control specimens are used in short-term (Stamm 1969, 1971) and long-term interlaboratory surveys.

There are three approaches for the evaluation of interlaboratory surveys: The concentration of the analyte in each control sample is determined by

- consensus value approach,
- assigned value approach,
- reference method value approach.

In the consensus value approach all participants in an interlaboratory survey submit one analytic result each for the analyte concentration in one control sample. Results are grouped by the methods used. Mean ($\bar{x}_p$) and standard deviation (s_p) are computed. All results outside of $\bar{x} \pm 3s_p$ are eliminated. After this elimination new values for the mean ($\bar{x}_{pc}$) and for the standard deviation (s_{pc}) are computed (onion skin procedure). $\bar{x}_{pc}$ is the consensus value.

Using the assigned value approach, a limited number of highly qualified, especially selected reference laboratories submit in a long-term interlaboratory survey two analytic results for at least 10 working days. Results are obtained in all laboratories under the same carefully defined conditions (method, standard, equipment) in routine runs. The assigned interval and the assigned values are determined from the results according to a set of non parametric procedures (Stamm 1979; Hansert and Stamm 1980).

In the reference method value approach the decision limits for the interlaboratory surveys are fixed on the basis of the reference method values for the analyte concentration and the clinical requirements (Stamm 1982a).

For the operation of all these programs adequate control samples with a matrix most similar to the actual patient sample are required. Control samples suitable for toxicologic analyses have not been available so far. Therefore, as a starting point a relatively simple matrix was appropriate.

For these reasons the working group "Quality Control" of the Senate Commission on Clinico-Toxicologic Analytics of the German Research Society made up in collaboration with the Behringwerke Marburg (FRG) a synthetic matrix using the well-known physiologic compounds of human urine. To keep the costs for the samples low the synthetic urine was spiked with a large number of analytes. The constituents of this control urine for metals are shown in Table 1.

The analytes were added as stable salts. After preparation of the synthetic urine it was lyophilized.

For the determination of assigned values and decision limits long-term interlaboratory surveys were carried out.

Table 1. Constituents of control urine for metals

Lanonorm	
Arsenic	Nickel
Lead	Mercury
Cadmium	Thallium
Chromium	Fluoride
Copper	Trichloroacetic acid 5-Aminolevulinic acid
$c < 1\,\mu mol/l$	
Na^+, K^+, Cl^-	Electrolytes in physiologic concentrations
Albumin	
Yellow dye	
Other organic constituents	

The concentration of thallium was analyzed by reference laboratories separately using three routine methods: (1) Atomic Absorption Spectrometry (AAS), (2) Differential Pulse Anodic Stripping Voltametry (DPASV), and (3) Photometry according to the following protocol (Stamm 1982b):

1. at least three reference laboratories for each method
2. at least ten duplicate determinations per reference laboratory and method on different working days under routine conditions
3. computer evaluation for each reference laboratory and method (1st and 2nd results separately)
   3.1 frequency distribution of the analytic results
   3.2 statistical parameters: – mean
   – standard deviation from day to day
   – standard deviation of the series.

The quantitative determination of thallium in the control samples yielded the results shown in Table 2. For reference, the thallium concentrations determined by Isotope Dilution Mass Spectroscopy (IDMS) are shown, too. As can be seen in Table 2 a remarkably good agreement between DPASV and IDMS values has ben obtained. Assigned values measured by AAS or photometric methods are slightly but significantly higher.

After the establishment of the assigned values a short-term interlaboratory survey was conducted. The organization of the survey was carried out according to the Guidelines of the Medical Society of West Germany. The survey included the four important steps as follows (Stamm 1982b):

1. The participant receives two specimens: specimen A and specimen B.
2. The participant analyzes the specimens, codes his method according to the attached key and sends both the analytical results and the code of his method used to the survey organizer.
3. The survey organizer evaluates the results using the decision limits fixed previously during the assigned value determination. A Youden plot is constructed for each method.

Table 2. Assigned and IDMS values of Tl-concentrations in control urine (in µg/l)

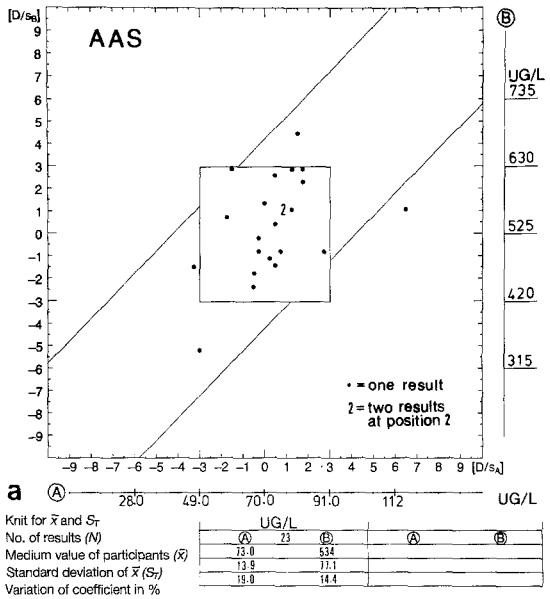
Analytic principle	Lot no.				k
	38880		38900		
	$\bar{x}$	$\bar{x} \pm 3s$	$\bar{x}$	$\bar{x} \pm 3s$	
Photometry	95	65–125	510	420–600	2
AAS[1]	70	45– 95	525	460–590	5
DPASV	69	61– 77	475	440–510	3
IDMS	66.3		483		1[2]

[1] AAS-GF and AAS-flame

[2] Mean of five determinations

k, number of laboratories

IDMS, isotope dilution mass spectrometry



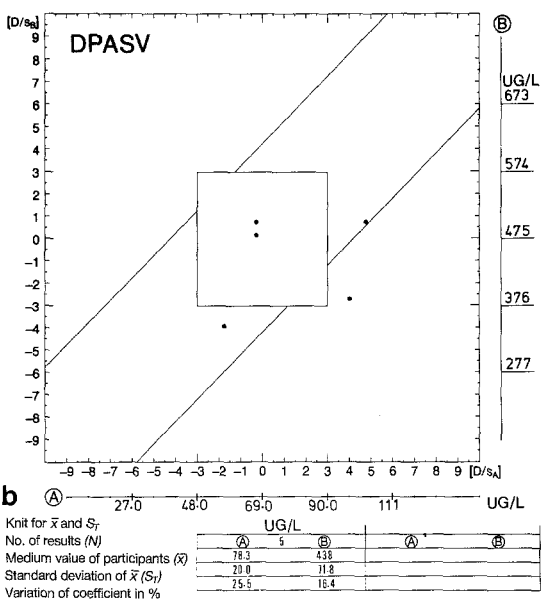


Fig. 1a–c. Results of the short-term interlaboratory survey on thallium in urine (Youden plots) according to methods used. **a** AAS, **b** DPASV, and **c** photometry after extraction

4. Each participant receives different computer printouts: The evaluation of his results in the interlaboratory short-term survey, a certificate for those constituents where his results had been acceptable, and a results booklet with the assigned values and decision limits, the means and the standard deviation of all participants, and a Youden plot.

A participant has successfully completed the survey if his results for both specimens (specimen A and B) are within the decision limits set by the reference laboratories. The success rate is different for different constituents.

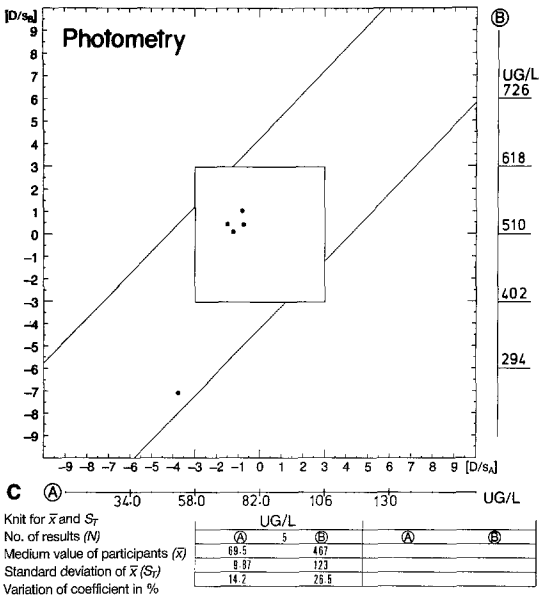


Fig. 1c

Thirty-five laboratories participated in the short-term interlaboratory survey on thallium in urine prepared by the Senate Commission on Clinico-Toxicologic Analysis of the German Research Society (DFG), organized by the German Society of Forensic Medicine and evaluated by the German Society of Clinical Chemistry. Of the 35 participating laboratories, 25 used AAS, five DPASV, and another five photometry with preceding extraction. The results are shown in the following graphs (Fig. 1).

Of the 25 participating AAS laboratories, 19 (76%) found results within the $\bar{x} \pm 3s$ range ($\bar{x}$ = assigned value); six laboratories did not meet this goal; two results were identified as totally erroneous (not shown in Fig. 1a). The coefficients of variation were between 19 and 14.4%.

Five laboratories participated using Differential Pulse Anodic Stripping Voltametry (DPASV), two of which met the goal. Three laboratories were outside of the accepted range ($\bar{x} \pm 3s$). The coefficients of variation were 25 and 16.4%, respectively.

Another five laboratories used photometric methods to measure the thallium concentration. Four of these laboratories met the goal, one laboratory had a result with great deviation from the assigned values. The coefficients of variation were 14.2 and 26.5%.

With the three methods of analysis it could be shown that the precision in the short-term interlaboratory surveys were significantly worse than those obtained by the selected reference laboratories during the long-term interlaboratory survey.

We consider these interlaboratory surveys as a first step for quality assurance in the clinico-toxicologic and forensic-toxicologic analysis of thallium. Further investigations will have to show whether a synthetic urine matrix should be used for the constitution of control samples which would still not be identical

with physiologic urine. Therefore, the use of pooled human urine may better control the influence of the matrix.

For further investigations of this kind heavy metals bound to organic molecules should also be used since this may represent the "real world" of metal analysis in physiologic specimens. At any rate the matrix should be such that critical steps in the analysis may be controlled better.

It will also have to be discussed whether in further surveys we should use the method-dependent assigned value approach, the method-independent reference method value approach (Stamm 1982a), or another approach in evaluating interlaboratory surveys.

References

Bundesärztekammer (1974) Richtlinien zur Durchführung der statistischen Qualitätskontrolle und von Ringversuchen. Dtsch Ärztebl 71:959–965

Eichgesetz (1969) Gesetz über das Meß- und Eichwesen vom 11. Juli 1969. Bundesgesetzbl Teil I:759ff

Eichpflicht-Ausnahmeverordnung (1970) Verordnungen über Ausnahmen von der Eichpflicht vom 26. Juli 1970. Bundesgesetzbl Teil I:960ff

Hansert E, Stamm D (1980) Determination of assigned values in control specimens for internal accuracy control and for interlaboratory surveys. J Clin Chem Clin Biochem 18:461–490

Stamm D (1971) Ringversuche in der Klinischen Chemie. Schweiz Med Wochenschr 101: 429–437

Stamm D (1974) Einführung der Qualitätskontrolle für die quantitativen klinisch-chemischen Untersuchungen in der Bundesrepublik. Mittlg Dtsch Ges Klin Chem 5:65–78

Stamm D (1979) Reference materials and reference methods in clinical chemistry. J Clin Chem Clin Biochem 17:283–297

Stamm D (1980) Die Meßsicherheit bei quantitativen klinisch-chemischen Untersuchungen. PTB-Mittlg 90:134–146

Stamm D (1982a) A new concept for quality control of clinical laboratory investigations in the light of clinical requirements and based on reference method values. J Clin Chem Clin Biochem 20:817–824

Stamm D (1982b) Long-term and short-term interlaboratory surveys within the framework of quality control in clinical laboratory investigations. In: Egan H, West TS (eds) IUPAC collaborative interlaboratory studies in chemical analysis. Pergamon Press, Oxford NewYork, pp 37–44

Stamm D, Büttner H (1969) Ringversuch zur Qualitätskontrolle 1968. Z Klin Chem Klin Biochem 7:393–403

Received March 2, 1984