CLINICAL AND LABORATORY STANDARDS INSTITUTE®

September 1997

C38-A

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline

SAMPLE

This document provides guidelines for patient preparation, specimen collection, transport, and processing for the measurement of trace elements in a variety of biological matrices.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

Clinical and Laboratory Standards Institute

Setting the standard for quality in medical laboratory testing around the world.

The Clinical and Laboratory Standards Institute (CLSI) is a not-for-profit membership organization that brings together the varied perspectives and expertise of the worldwide laboratory community for the advancement of a common cause: to foster excellence in laboratory medicine by developing and implementing medical laboratory standards and guidelines that help laboratories fulfill their responsibilities with efficiency, effectiveness, and global applicability.

Consensus Process

Consensus—the substantial agreement by materially affected, competent, and interested parties—is core to the development of all CLSI documents. It does not always connote unanimous agreement, but does mean that the participants in the development of a consensus document have considered and resolved all relevant objections and accept the resulting agreement.

Commenting on Documents

CLSI documents undergo periodic evaluation and modification to keep pace with advancements in technologies, procedures, methods, and protocols affecting the laboratory or health care.

CLSI's consensus process depends on experts who volunteer to serve as contributing authors and/or as participants in the reviewing and commenting process. At the end of each comment period, the committee that developed the document is obligated to review all comments, respond in writing to all substantive comments, and revise the draft document as appropriate.

Comments on published CLSI documents are equally essential, and may be submitted by anyone, at any time, on any document. All comments are managed according to the consensus process by a committee of experts.

Appeals Process

When it is believed that an objection has not been adequately considered and responded to, the process for appeals, documented in the CLSI Standards Development Policies and Processes, is followed.

All comments and responses submitted on draft and published documents are retained on file at CLSI and are available upon request.

Get Involved—Volunteer!

Do you use CLSI documents in your workplace? Do you see room for improvement? Would you like to get involved in the revision process? Or maybe you see a need to develop a new document for an emerging technology? CLSI wants to hear from you. We are always looking for volunteers. By donating your time and talents to improve the standards that affect your own work, you will play an active role in improving public health across the globe.

For additional information on committee participation or to submit comments, contact CLSI.

Clinical and Laboratory Standards Institute
950 West Valley Road, Suite 2500
Wayne, PA 19087 USA
P: +1.610.688.0100
F: +1.610.688.0700
www.clsi.org
standard@clsi.org

SAMPLE

NOTE: This document is no longer being reviewed as part of the CLSI consensus process. However, because of its usefulness to segments of the health care community, it is available for its informational content.

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline

Abstract

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline (CLSI document C38-A) is intended for persons responsible for the collection and processing of samples used for trace element determinations. The guideline addresses patient preparation, as well as considerations for collection, transport, and processing of specimens by element. Contamination control and quality assurance programs are also discussed.

Clinical and Laboratory Standards Institute (CLSI). *Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline.* CLSI document C38-A (ISBN 1-56238-332-9). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 1997.

The Clinical and Laboratory Standards Institute consensus process, which is the mechanism for moving a document through two or more levels of review by the health care community, is an ongoing process. Users should expect revised editions of any given document. Because rapid changes in technology may affect the procedures, methods, and protocols in a standard or guideline, users should replace outdated editions with the current editions of CLSI documents. Current editions are listed in the CLSI catalog and posted on our website at www.clsi.org. If your organization is not a member and would like to become one, and to request a copy of the catalog, contact us at: Telephone: 610.688.0100; Fax: 610.688.0700; E-Mail: customerservice@clsi.org; Website: www.clsi.org.

SAMPLE

C38-A
ISBN 1-56238-332-9
September 1997
ISSN 0273-3099

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline

Volume 17 Number 13

Gillian Lockitch, M.D., F.R.C.P.C.
Jack D. Fassett, Ph.D.
Benjamin Gerson, M.D.
David E. Nixon, Ph.D.
Patrick J. Parsons, Ph.D.
John Savory, Ph.D.

SAMPLE

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Copyright ©1997 Clinical and Laboratory Standards Institute. Except as stated below, any reproduction of content from a CLSI copyrighted standard, guideline, companion product, or other material requires express written consent from CLSI. All rights reserved. Interested parties may send permission requests to permissions@clsi.org.

CLSI hereby grants permission to each individual member or purchaser to make a single reproduction of this publication for use in its laboratory procedure manual at a single site. To request permission to use this publication in any other manner, e-mail permissions@clsi.org.

Suggested Citation

CLSI. *Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline.* CLSI document C38-A. Wayne, PA: Clinical and Laboratory Standards Institute; 1997.

Proposed Guideline
December 1994

Approved Guideline
September 1997

SAMPLE

ISBN 1-56238-332-9
ISSN 0273-3099

Contents

Abstract i

Committee Membership v

Active Membership vii

Foreword xiii

1 Introduction 1

2 Scope 1

2.1 Definitions 1
2.2 Reporting Units 2

3 Universal Precautions 5

4 Contamination Control 5

4.1 Background 5
4.2 Contamination from Collection Materials 5
4.3 Contamination from the Laboratory Environment 6
4.4 Testing Contamination in Phlebotomy Tubes 7

5 Specimen Selection and Collection Protocols 8

5.1 Blood, Plasma, or Serum 8
5.2 Urine 11
5.3 Hair and Nails 12
5.4 Tissues 13
5.5 Human Milk 13
5.6 Stools 13

6 Specific Elements 14

6.1 Aluminum 14
6.2 Arsenic 14
6.3 Cadmium 15
6.4 Chromium 15
6.5 Cobalt 15
6.6 Copper 16
6.7 Iron 17
6.8 Lead 17
6.9 Manganese 18
6.10 Mercury 18
6.11 Molybdenum 19
6.12 Nickel 19
6.13 Selenium 19
6.14 Uranium 20
6.15 Vanadium 20
6.16 Zinc 20

SAMPLE

References 22

Bibliography 25

Summary of Comments and Subcommittee Responses 26

Related NCCLS Publications 30

SAMPLE

Foreword

Preanalytical factors are probably the most important cause of erroneous trace element reference data in biological matrices today. The development of sensitive, specific, and accurate analytical technology at an acceptable cost has moved determination of trace and ultratrace elements from research facilities into a wide range of clinical laboratories. Expanding knowledge of trace element nutrition and toxicity has increased clinical demand for these assays. However, with increased sensitivity and lower limits of detection, the problem of specimen contamination with the element of interest has been magnified. It is vital that the accurately determined trace element concentration reflects the condition of the patient and not contamination introduced during collection and handling. Elements are classified according to the level at which they occur in the body as "trace" (body content 0.01 to 100 μg/g; 10 to 10^4 μg/L) or "ultratrace" (body content less than 0.01 μg/g; less than 10 μg/L).

Earlier attempts to define reference interval data for many of the trace and ultratrace elements provided ranges that were far wider than are now accepted as "normal." This resulted from a lack of awareness that the ubiquity of many trace elements in the environment required special precautions from preanalytical processes through the actual analysis.

In this document, the components of specimen collection and preanalytical processing that can contribute to trace element contamination are addressed and protocols for prevention of contamination are described. The trace elements most commonly tested for clinical purposes are individually listed. For each element, the optimal specimen for assessment, preanalytical factors to consider in patient preparation and reference intervals, or concentrations suggesting toxicity or deficiency, are described.

Key Words

Trace element, ultratrace element, essential elements, specimen collection, contamination control.

SAMPLE

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline

1 Introduction

It is recognized that much of the pioneering research published in trace element literature is based on erroneously derived reference interval data.[1] The source of the problem was in the lack of recognition of exogenous specimen contamination, which could have occurred at the collection, transport, processing, or analytical stages. Thus, reference intervals for ultratrace elements, such as chromium, or acceptable blood concentrations for toxic elements, such as aluminum, have decreased several fold over the past two decades.

The use of increasingly sensitive methods, such as electrothermal atomic absorption spectrometry (ETAAS) or inductively coupled plasma mass spectrometry (ICPMS); increasing interest in ultratrace elements; and the need for precise and accurate analyses for elements such as lead, at extremely low levels, have accentuated the problems of analytical and preanalytical contamination.[2]

The intent of this guideline is to (1) develop an awareness of the factors that affect the determination of trace elements in a variety of specimen types, (2) foster communication between the laboratorian performing the test and those responsible for collecting the specimen, and (3) provide definitive protocols for eliminating preanalytical variability.

If a specimen is to be sent to a reference trace element laboratory for analysis, it is suggested that the laboratory be consulted in advance for special collection and handling instructions.

2 Scope

This guideline provides directions for patient preparation, specimen collection, transport, and processing for analysis of trace elements in biological matrices (i.e., body fluids, such as blood, urine, breast milk, and tissues). Specific reference is made to those elements that are known to be essential or toxic for humans and are, therefore, most likely to be measured for clinical reasons.

2.1 Definitions

For the purposes of this document, the following definitions apply:

Trace element, *n* - An element that occurs at a level of 0.01 to 100 μg/g (10 μg/L to 10^4 μg/L).[1]

Ultratrace element, *n* - Arbitrarily defined as one that occurs at a level of less than 0.01 μg/g (less than 10 μg/L).[1]

From the perspective of preventing preanalytical or analytical contamination, classification of an element as trace or ultratrace depends on (1) the expected concentration in the sample matrix and (2) the sensitivity of the analytical method used for that element in a specific matrix. Thus, for example, while aluminum occurs in the serum of healthy persons as an ultratrace element, in a patient on dialysis who has aluminum toxicity, aluminum may be considered a trace element. Tables 1 and 2 categorize clinically important elements found in blood and urine.

Essential element, *n* - That a specific trace element is consistently detectable in human tissues or fluids does not imply that it is essential. Many trace elements are so ubiquitous in the environment (e.g., Al, Pb) that it is hardly surprising that they are "normally" found in human tissues and fluids. As analytical detection limits are improved further, other rare elements could also be detected at ultratrace levels. The criteria used to establish essentiality in other areas of life science, e.g., plant growth[3,4] can be adapted, with some qualification, to the animal kingdom. An element is considered essential (a) if without it, the species cannot achieve normal, healthy growth or complete its normal life cycle and (b) if it is part of a molecule of an essential constituent or metabolite. In addition, the element must be specific and not be replaceable by another, and it must exert its effect, directly on growth or metabolism

SAMPLE

and not by some indirect effect, such as antagonism of another element present at toxic levels.

Based on these criteria, a number of trace elements have been clearly identified as essential for normal, healthy growth in humans. While there may be some elements that are not universally accepted, due to the paucity of data supporting claims for essentiality, they may be considered borderline candidates. The concept of essentiality, and arguments over accepted criteria, are discussed in detail by Davies.[5]

Tables 1 and 2 list those trace and ultra trace elements, which are the focus of this document, in alphabetical order. Some are considered essential for normal, healthy growth in humans, others are borderline. Several are nonessential toxic elements. Elements in Groups I, II, and VII (i.e. the alkali and alkaline earth metals, and the halogens) are not included, although some of these are essential.

2.2 Reporting Units

A variety of units are currently used throughout the United States for reporting trace element concentrations in human body fluids and tissues (see Table 3). Although NCCLS documents generally use units that are fully acceptable within the Système International d'Unités (SI), these do not always coincide with the units recommended by the International Union of Pure and Applied Chemistry (IUPAC) and by the International Federation of Clinical Chemistry (IFCC) for reporting results of clinical laboratory measurements. Because SI units are used worldwide but there is not yet a consensus in the United States, NCCLS documents include the IUPAC/IFCC recommended units of volume (L) and substance (molecular) concentration (mol/L) in parentheses, where appropriate. In this document, wherever possible, we use conventional mass/volume (e.g., μg/dL) units, or mass/mass (μg/g) units, to describe normal and abnormal concentration ranges, followed by IUPAC/IFCC-recommended equivalents in parentheses.

Results for trace elements in urine can be calculated as an excretion rate if a timed specimen is obtained. Usually, such results are reported as μg (or mg) element per 24 hours, or as μg element per g (urinary) creatinine (see Section 5.2.2). In the analytical laboratory, it is commonplace to use "bench" units, such as parts-per-million (ppm) or parts-per-billion (ppb) for concentration. *These units should not be used to report trace element concentrations in clinical specimens*. They are confusing and ambiguous to nonanalytical personnel, since they do not indicate if the concentration is based on a mass/volume or a mass/mass ratio.

SAMPLE

Related NCCLS Publications[‖]

C3-A3 **Preparation and Testing of Reagent Water in the Clinical Laboratory—Third Edition; Approved Guideline** (1997). C3-A3 addresses the requirements for purified water, methods for monitoring quality and testing for specific contaminants, and system-design considerations.

GP16-A **Routine Urinalysis and Collection, Transportation, and Preservation of Urine Specimens; Approved Guideline** (1995). GP16-A discusses procedures that address materials and equipment, macroscopic examinations, clinical analyses, and microscopic evaluations. Also, the document offers information on collection, specimen criteria, and storage.

H3-A3 **Procedures for the Collection of Diagnostic Blood Specimens by Venipuncture—Third Edition; Approved Standard** (1991). H3-A3 discusses methods of collection, as well as a training program for increasing integrity and for minimizing error.

H4-A3 **Procedures for the Collection of Diagnostic Blood Specimens by Skin Puncture—Third Edition; Approved Standard** (1991). H4-A3 describes proper collection techniques and discusses hazards to patients.

H14-A2 **Devices for Collection of Skin Puncture Blood Specimens—Second Edition; Approved Guideline** (1990). H14-A2 gives specifications of disposable devices for collecting, processing, and transferring diagnostic blood specimens obtained by skin puncture.

H18-A **Procedures for the Handling and Processing of Blood Specimens; Approved Guideline** (1990). H18-A addresses the multiple factors involved in the handling and processing of specimens that can introduce imprecision or systematic bias into results.

H24-T **Additives to Blood Collection Devices: Heparin; Tentative Standard** (1988). H24-T contains a technical description of heparin compounds used in devices. The document also addresses evaluation of the suitability of heparin-containing devices and the quantitation of heparin.

H31-P **Collection Containers for Specimens for Toxicological Analysis; Proposed Guideline** (1986). H31-P discusses the recommended toxicology/drug monitoring requirements.

H35-T **Additives to Blood Collection Devices: Edta; Tentative Standard** (1992). H35-T offers a technical description of ethylenediaminetetra-acetic acid (EDTA) and its use in blood collection products.

SAMPLE

[‖]Proposed- and tentative-level documents are being advanced through the NCCLS consensus process; therefore, readers should refer to the most recent editions.

CLINICAL AND LABORATORY STANDARDS INSTITUTE®

Explore the Latest Offerings From CLSI!

As we continue to set the global standard for quality in laboratory testing, we are adding products and programs to bring even more value to our members and customers.

By becoming a CLSI member, your laboratory will join 1,600+ other influential organizations all working together to further CLSI's efforts to improve health care outcomes. You can play an active role in raising global laboratory testing standards—in your laboratory, and around the world.

Find out which membership option is best for you at **www.clsi.org/membership.**

Find what your laboratory needs to succeed! CLSI U provides convenient, cost-effective continuing education and training resources to help you advance your professional development. We have a variety of easy-to-use, online educational resources that make *e*Learning stress-free and convenient for you and your staff.

See our current educational offerings at **www.clsi.org/education.**

When laboratory testing quality is critical, standards are needed and there is no time to waste. eCLIPSE™ Ultimate Access, our cloud-based online portal of the complete library of CLSI standards, makes it easy to quickly find the CLSI resources you need.

Learn more and purchase eCLIPSE at **clsi.org/eCLIPSE.**

For more information, visit www.clsi.org today.

SAMPLE

SAMPLE

CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

950 West Valley Road, Suite 2500, Wayne, PA 19087 USA

P: 610.688.0100 **Toll Free (US):** 877.447.1888 **F:** 610.688.0700

E: customerservice@clsi.org **www.clsi.org**

ISBN 1-56238-332-9