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September 1997

C38-A

Control of Preanalytical Variation in Trace Element Determinations; Approved Guideline

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.

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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.

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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.

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

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.

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.

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

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