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Differentiating between Sensitivity and Limit of Detection

To the Editor:

Authors of scientific articles and of manufacturers' information sheets share a confusion: their assumption that "sensitivity" and "lower limit of detection" are synonymous.

The lower limit of detection is the lowest concentration of analyte detectable by the method. It is usually determined by extrapolating a plot of concentration (x) vs measurement unit (y) to the x-axis. The intercept is the lower limit of detection.

Sensitivity is the smallest concentration change that the method is capable of detecting. It is determined from the slope of the previously described plot.

Authors often confuse these two measurements and report sensitivity as detection limit, resulting in a misconception of the method’s capabilities.

I recommend that the American Association for Clinical Chemistry adopt standardized definitions for sensitivity and lower limit of detection, thereby preventing further confusion.

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Ed. note: Reader Rudy is correct. His definitions essentially correspond to those in "Nomenclature and Definitions for Use in the National Reference System for the Clinical Laboratory," vol. 5, no. 21 (Villanova, PA 19085: NCCLS, 1985; ISSN 0273-3099, order code NRSCL8-P), prepared by Ralph Thiers (q.v.). Those are the definitions that most clinical chemists are or should be aware of, and the ones implicitly endorsed by AACC.

A document that might be considered even more authoritative is "International Vocabulary of Basic and General Terms in Metrology" (published in 1984 by the International Organization for Standardization, the authors being a joint working group consisting of experts appointed by four international organizations, including ISO and International Bureau of Weights and Measures, ISBN 92 67 010328). It does not define detection limit, but it defines sensitivity as "the change in the response of a measuring instrument divided by the corresponding change in the stimulus" (italics in the original). The IFCC, on the other hand, earlier rather vaguely defined detectability ("often referred to as sensitivity") as "the ability of an analytical method to detect small quantities of the component," and detection limit as the "smallest single result which, with a stated probability, can be distinguished from a suitable blank" (Approved Recommendation (1978) on Quality Control in Clinical Chemistry. Part 1. General Principles and Terminology; Clin Chem 1976;19:532).

As usual, there are other, older, and conflicting definitions by self-appointed authorities that we need not bother with here (cf. Clin Chem 1988;34:1001).

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Quality Control of Glucose Monitors Outside the Clinical Laboratory: Use of Commercial Nonhuman Erythrocyte Preparations Supplemented with Additional Glucose

To the Editor:

The use of monitors of blood glucose at the bedside or in the clinic often means that quality-assurance procedures are neglected (1). Increasingly, however, laboratory groups suggest that a quality-assurance program be an integral part of the operating procedure for such devices (2). For example, the assessment of a monitor's performance should regularly include the testing of an unknown specimen. However, such materials are scarce, particularly as heparinized human blood is unsuitable for several reasons, aqueous solutions are unrealistic, and quality-control sera are often inadequate (3). Streck Laboratories, Inc. (Omaha, NE 68137) supply, at three glucose concentrations, preparations of stabilized nonhuman erythrocytes (Sugar-Chex) for use with a wide variety of glucose monitors. However, the laboratory loses the benefit of such preparations because operators very quickly learn their expected values.

We have also used mixtures of these preparations, but the available concentrations in the original preparations limit the range of possible glucose concentrations of these mixtures. The Streck preparations have no metabolic activity, and the addition of glucose to them produces genuinely "unknown" quality-control materials. We use these supplemented preparations within a few hours of the addition of glucose, although they are stable for at least two weeks. They give satisfactory performance for out-of-laboratory quality control (Table 1). For the "Accu-Chek II" glucose monitor (Boehringer Mannheim Canada Ltd., Dorval, Quebec), which this hospital uses, results obtained for the Sugar-Chex controls coincide with results from the ASTRA-8 glucose assay (Beckman Instruments, Inc., Brea, CA 92621) when we use the serum from the Streck preparations (4). Such agreement therefore provides a link with glucose results issued by the hospital's laboratory and adds to the reliability of the entire quality-control procedure.

Table 1. Glucose Measured in the Three Sugar-Chex Glucose Controls Supplemented with Additional Glucose

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<th>3</th>
<th>4</th>
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<td>Approximate supplementation to</td>
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*Each value is the mean of triplicate determinations.
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Differences between Alkaline Phosphatase Activities in Serum and Lyophilized Controls in AMP Buffer Explained

To the Editor:

Lim et al. (1), in an investigation of alkaline phosphatase (EC 3.1.3.1) activities of some quality-control materials, found some discrepancies between the method of Bowers and McComb (2, reagent 1) and that of the AACC (3) and IFCC (4, reagent II). No differences were observed with patients' samples. Activation of lyophilized samples on reconstitution was not the cause, and Lim et al. (1) offered no specific explanation for their results.

Subsequently, Tietz (5) suggested in a Letter that the differences were attributable to the varying zinc content of the quality-control materials and the incorporation of this cation in both the AACC and the IFCC procedures. However, reagent I contains 2-amino-2-methyl-1-propanol (AMP) at a concentration of 900 mmol/L, whereas reagent II contains only 350 mmol/L. Earlier, Van Belle (6) had reported increasing activities of the placental, intestinal, liver, and bone isoenzymes of human alkaline phosphatase in transphosphorylating buffers and that these increases were concentration-dependent. Quality-control materials contain added alkaline phosphatase from a number of different tissues and animals, and we wondered if this could explain the discrepant results of Lim et al. (1).

Figure 1 shows the relative effects, at pH 10.4 and with p-nitrophenyl phosphate (16 mmol/L) as substrate, of varying the AMP concentrations from 300 to 900 mmol/L in several quality-control materials and in a pooled specimen of human plasma. Zinc ions were not added. The plasma pool was slightly activated as the AMP concentration increased from 300 to 900 mmol/L, but, in contrast, the activities of alkaline phosphatase derived from bovine kidney, porcine kidney (used in the Wellcome Clinical Chemistry Quality Assessment Program; personal communication), and chicken intestine (used by Armtrol, Northern Ireland, and Gibco Diagnostic, New Zealand; personal communications) were significantly inhibited. The extent of inhibition was similar to that found by Lim et al. (1) when they compared reagent I and reagent II.

The results demonstrate the difficulties caused when the isoenzyme configurations of quality-control materials are overlooked and it is assumed that any alkaline phosphatase activity will behave in a manner similar to the mix of liver, bone, and intestinal isoenzymes in human plasma samples.

The use of nonhuman-based quality-control materials continues to increase, so such problems can be expected to proliferate.

References


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Direct Determination of Free Thyroxin in Undiluted Serum by Equilibrium Dialysis/Radioimmunoassay

To the Editor:

I do not wish to detract from Nelson and Tomei's (1) recent detailed description of the direct determination of free thyroxin (FT4) in "undiluted" serum by equilibrium dialysis/radioimmunoassay, but two points merit comment:

1. The direct determination of FT4 and FT3 by dialysis/sensitive RIA was first described by my colleagues and me some 15 years ago (2–4), and was subsequently used as a routine diagnostic test in this laboratory for a number of years. We continue to rely on it to calibrate serum standards used in our routine "two-step" immunoassay procedures. In slightly modified form, the methodology has also been adopted by a number of other groups, including, for example, Helenius and Liewendahl (5), Weeke and Ørskov (6), Jiang and Tse (7), and Giles (9). Prolonged validation studies closely comparable with those undertaken by Nelson and Tomei (1) underpinned our