Comments Concerning Report of Defective NIST SRM 909a Vials

To the Editor:
We have carefully reviewed the paper by De et al., reporting defective vials of NIST SRM 909a [1]. We thank the authors for initially alerting us to the problems they describe in some detail. While we do not disagree with their findings, we believe your readers should have additional information on SRM 909a. The Standard Reference Materials Program receives letters from SRM users from time to time and we take each one seriously as a source for investigation.

De et al. point out a serious problem with the glucose concentration value in 909a. During the 14-year course of monitoring the stability of SRM 909, Human Serum, and its renewal, SRM 909a, we have found that the certified values for glucose decrease at an annual rate of ~1%, whereas the concentrations of other analytes in these SRMs remain unchanged. As a result, all purchasers of this SRM have been periodically provided updated certificates with revised glucose values and uncertainties. Observations of degradation of measured glucose values in a lyophilized human serum matrix with time have also been documented in the literature [2].

After one of the authors contacted us about the glucose problem described in their paper, we investigated the remaining material in our inventory. We found that the beads of lyophilized serum in ~10–15% of the vials had clumped together on the walls of the vials. Further inspection also revealed that some of the vials had improperly seated rubber septa and metal seals, which allowed moist air to seep in during storage. All vials with such clumping were removed from inventory and selected vials were analyzed. Later analyses confirmed that the glucose in the vials with the clumped material had decreased significantly (recoveries were <25%). Unfortunately, some customers had already received vials containing clumped material, and De et al. apparently were among this group of customers. Subsequent analyses of randomly selected vials from the remaining material without clumping found the glucose concentrations to be within the certified values and its uncertainties. It was further determined that the average moisture content (by mass) in the normal vials of SRM 909a serum was 0.4%, whereas the clumped material contained ~10–12%.

We applied the lessons learned concerning the moisture and storage problems with SRM 909a (no longer available) to the currently available SRM 909b. More-extensive monitoring and sampling protocols to detect substantive changes in the certified values of analytes such as glucose have now been designed and implemented. We thank De et al. for alerting us to the problem of defective vials in SRM 909a and regret any inconvenience that may have been caused by the use of the defective material.

References

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Serum Thiocyanate Concentrations in Patients with Normal or Impaired Renal Function Receiving Nitroprusside

To the Editor:
Sodium nitroprusside was introduced for widespread use in the 1970s in treating hypertensive emergencies and producing controlled hypotension for surgery [1]. Two potential toxicological effects can result from nitroprusside therapy: cyanide poisoning and thiocyanate toxicity [2]. Cyanide released from nitroprusside (sodium nitroprusside contains five cyanide molecules, 44% by wt) is normally metabolized to thiocyanate (SCN) via sulfation by thiosulfate in the liver. Cyanide (half-life in blood, 30–60 min) is converted to thiocyanate, which is eliminated by the kidney and has a half-life of 2–3 days in patients with normal kidney function and up to 9 days in those with severe renal insufficiency [3]. A healthy patient should have enough thiosulfate to metabolize the cyanide accumulated after release from nitroprusside.

When thiosulfate stores are depleted through poor nutrition, chronic disease, or surgery, blood and tissue cyanide concentrations can increase. Cyanide's main toxic effect is to bind and inhibit cytochrome oxidase, preventing oxygen consumption and oxidative phosphorylation, followed by metabolic acidosis (increasing lactate concentrations). This is characterized by dysfunction of the central nervous and cardiovascular systems, resulting in disorientation, agitation, lethargy, convulsions, coma, cerebral death, hypotension, shock, or cardiac arrhythmias (features often indistinguishable from thiocyanate toxicity).

It appears that thiocyanate is not converted to cyanide, and unlike cyanide, thiocyanate toxicity is not characterized by metabolic acidosis. Serum thiocyanate concentrations are of no value in detecting cyanide toxicity; however, they are diagnostic of thiocyanate toxicity [1]. Serious toxicity does not occur until concentrations exceed 100 mg/L and is rarely noted by clinicians [1]. Furthermore, studies have shown that thiocyanate toxicity does not become apparent until 7–14 days of continuous nitroprusside infusion at a rate >2 μg/kg per min in patients with normal renal function [4,5]. Patients with renal impairment can develop toxicity in 3–6 days at similar infusion rates.

A common question often presented to clinical laboratories has been, what is the appropriate clinical utility for measuring serum thiocyanate concentrations in patients receiving sodium nitroprusside? The purpose of this study was to determine whether the clinical laboratory needs to measure serum thiocyanate concentrations after nitroprusside therapy to assist clinicians concerned with the potential toxic effects of increased thiocyanate concentrations in patients receiving variable infusion rates.

Serum thiocyanate concentrations were measured over 2 years (1993–1994) in 17 patients receiving variable infusion rates of nitroprusside for treatment of hypertensive emergencies. Serum thiocyanate concentrations were measured spectrophotometrically at 460 nm after
complexion with ferric nitrate in an acidic solution. Nine patients had normal renal function [group 1, mean creatinine 7 (SD 2) mg/L] and eight patients had impaired renal function [group 2, mean creatinine 28 (SD 16) mg/L].

Clinically, no patient displayed features of thiocyanate toxicity before measurement by clinicians. Table 1 shows the findings in both groups of patients for nitroprusside infusions over time and thiocyanate concentrations drawn during the last day indicated (from days on nitroprusside). Only one thiocyanate concentration was measured in each subject. Group 1 received nitroprusside therapy longer than group 2 (6.7 vs 4.1 days) and had higher peak infusion rates (7.2 vs 5.2 μg/kg per min). However, mean nitroprusside infusion rates 3 days before obtaining thiocyanate concentrations were similar in group 1 (3.20 μg/kg per min) and group 2 (3.3 μg/kg per min). Also similar were mean (range) thiocyanate concentrations in group 1 [28 (11–66) mg/L] and group 2 [21 (13–33) mg/L], well below toxic concentrations (100 mg/L). These findings demonstrate that quantification of serum thiocyanate concentrations rarely demonstrates toxicity, whether or not long periods of high nitroprusside infusion rates or impaired renal function were present. This confirms the fact that the utility of therapeutically monitoring thiocyanate concentrations is of little value, especially in patients exhibiting no toxicity features [6]. Studies have shown that red blood cell concentrations of cyanide begin to rise substantially when nitroprusside infusions exceed 2 μg/kg per min, with doses up to 10 μg/kg per min resulting in cyanide concentrations that patients cannot detoxify [7]. These same doses are not problematic if nitroprusside is infused along with the appropriate dose of sodium thiosulfate (1 g of sodium thiosulfate added for every 100 mg of nitroprusside) [1]. Patients receiving the nitroprusside–thiosulfate mixture rapidly convert cyanide to thiocyanate and therefore have higher thiocyanate concentrations than patients receiving nitroprusside alone [7]. Under the conditions of concurrent thiosulfate administration, quantification of cyanide concentrations is not necessary because toxicity is averted. This is helpful for the laboratory, since there are no simple, rapid, quantitative cyanide procedures that can be used to assist the clinician in a real-time diagnosis of cyanide toxicity.

Although the patients in the present study did not receive concomitant thiosulfate, since completion of this study we have since demonstrated that a patient with impaired renal function (creatinine = 34 mg/L) receiving high nitroprusside infusion rates (6.5 to 9.5 mg/kg per min) over 3 days, and who concurrently was receiving thiosulfate to convert cyanide to thiocyanate, did have a toxic thiocyanate concentration of 128 mg/L. However, this patient did not display any features of thiocyanate toxicity. This additional finding indicates that quantification of serum thiocyanate may be indicated in the assessment of thiocyanate toxicity in patients receiving various infusion rates of nitroprusside (regardless of renal function) when also receiving concurrent infusion of thiosulfate. In either case, the clinical laboratory should consult with clinicians before thiocyanate analysis to assist in appropriate test utilization.

On the basis of our findings, we have instituted a policy requiring pathology staff approval of all thiocyanate test requests, with clear justification needed on clinical grounds or concomitant high-infusion nitroprusside therapy with thiosulfate administration before quantification. This has resulted in approval of only 2 of the past 14 requests during 1995.

References

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