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]. Severe 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