UNIVERSITY OF CINCINNATI

Date: __3/3/2006_________

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hereby submit this work as part of the requirements for the degree of:

Master of Science

in:

Environmental Health

It is entitled:

A Comparison of the Accuracy of Measurement of Urine Thiocyanate by Spectrophotometry and Ion Chromatography in a Population Without Known Exposure to Cyanide

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James Donovan_________________
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A Comparison of the Accuracy of Measurement of Urine Thiocyanate by Spectrophotometry and Ion Chromatography in a Population Without Known Exposure to Cyanide

A thesis submitted to the

Division of Research and Advanced Studies
of the University of Cincinnati

in partial fulfillment of the requirements for the degree of:

Master of Science in Environmental Health

in the Department of Environmental Health
of the College of Medicine

March 3, 2006

by

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Abstract

**Background:** Urine thiocyanate (UTC) has been used as a marker of cyanide exposure. In 1996, 65 of 75 (87%) workers in a TN plant had elevated UTC. After this, the testing laboratory (NMS) changed their testing method from spectrophotometry (SP) to ion chromatography (IC). Subsequently, only 1 of 13 (8%) workers had elevated UTC. This prompted further investigation. **Methods:** 55 subjects without exposure to cyanide were tested for UTC by SP and IC. Known amounts of thiocyanate were added to a sample, and the resulting specimens were tested. A survey of laboratories was conducted. **Results:** The mean UTC level (μg/ml) by IC was 3.24 (σ = 3.75). The mean UTC level by SP was 16.84 (σ = 9.78). The RMS error was 8.06 for IC. The RMS error was 60.31 for SP. Three laboratories perform approximately 2400 UTC tests yearly in the US. **Conclusions:** The UTC testing by NMS in 1996 using the SP method overestimated levels.
Acknowledgements

I would like to thank my Mother for giving birth to me, my Father for inspiring me, Dr. Lockey for motivating me, Dr. Donovan for accepting me into this program, Dr. Freeman for presenting this research idea to me, and my wife for her patience.
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Background

Cyanide is one of the most well known and rapidly acting lethal poisons. It also has a normal role in the metabolism of plants and animals. Under normal conditions, cyanide is found in small amounts in the blood as a result of vitamin B\textsubscript{12} metabolism. Cyanide is present in many common foods such as apples, apricots, almonds, bamboo, cassava, cherries, lima beans, mustard, peaches, and pears\textsuperscript{1}, and is a metabolite of certain medications including nitroprusside.\textsuperscript{2} Cyanide is also present in many products of combustion, including cigarette smoke.\textsuperscript{3} Most occupational cyanide exposure occurs in conjunction with electroplating, metal processing, photographic processes, chemical synthesis, and plastic and pesticide manufacturing.\textsuperscript{3} Approximately 144,000 workers still have potential exposures to cyanide.\textsuperscript{4}

Chronic exposure to cyanide has been associated with optic atrophy, peripheral neuropathy, and decreased thyroid function.\textsuperscript{5,6} The most commonly reported symptoms occurring with chronic, low-level cyanide exposure are fatigue, headache, memory loss, and dizziness.\textsuperscript{7,8}

Numerous methods have been developed to measure exposure to cyanide. A commonly used measurement of cyanide exposure is urine thiocyanate. Several methods have been developed to measure urine thiocyanate. An older method involves the use of spectrophotometry with ferric nitrate as a reagent\textsuperscript{9}, while a more recent method involves the use of ion chromatography\textsuperscript{10}. Thiocyanate is the principal metabolite of cyanide, and is excreted almost exclusively in urine.\textsuperscript{2} Urine thiocyanate has been suggested for use as a marker of exposure to cyanide. However, there are only a few studies (each with small numbers of subjects) that have examined the normal range of urine thiocyanate values in individuals unexposed to cyanide.\textsuperscript{11,12}
Furthermore, there are no studies linking urinary thiocyanate values to adverse health effects. With the paucity of available data concerning urine thiocyanate, the National Institute for Occupational Safety and Health (NIOSH), the Occupational Safety and Health Administration (OSHA), and the American Conference of Governmental and Industrial Hygienists (ACGIH) do not recommend this testing for workplace exposure monitoring.

In 1996, workers at the K-25 plant in Oak Ridge, Tennessee, became concerned about possible workplace exposure to cyanide. The workers had started to experience a wide variety of symptoms, which included fatigue, memory loss, and headaches. Some local physicians noted that these symptoms resembled the constellation of findings associated with low-level, chronic cyanide exposure. Other physicians felt that the majority of symptoms experienced by the workers were vague in nature, and not specific to cyanide. An extensive search was begun to uncover possible sources of cyanide exposure at the worksite. Air sampling did not find cyanide in the tested areas. Additionally, work processes were reviewed. The Industrial Hygiene Department at K-25, the University of Alabama-Birmingham, and the National Institute for Occupational Safety and Health each performed separate investigations. No source of cyanide exposure was found.

Seventy-five of the K-25 plant workers underwent spot urine collections for thiocyanate, and 65 (87%) of these urine thiocyanate levels were elevated when compared with the normal reference range.\textsuperscript{13} The mean level for nonsmokers was 14.3 $\mu$g/ml and 23.5 $\mu$g/ml for smokers. Almost all of the testing was done at a single laboratory, National Medical Services, Inc. (NMS), where the normal range for urine thiocyanate was based upon a study conducted in 1955. In this study, the normal range for a nonsmoker was 1-4 $\mu$g/ml, and the normal range for a smoker was
7-17 μg/ml. This study included only fourteen subjects (six smokers and eight non-smokers), and utilized twenty-four hour rather than spot urine collections.\textsuperscript{11}

On June 1, 1996, NMS began to transition from using a spectrophotometric method to using an ion chromatography method. After this change in laboratory method, only one out of 13 (8%) K-25 plant workers tested had elevated urine thiocyanate levels. The mean of the urine thiocyanate levels obtained using ion chromatography at NMS was significantly lower than the mean of the levels that had been obtained using the spectrophotometric method at NMS.

The ion chromatography method may be more specific because spectrophotometric methods detect any substance in urine that absorbs light at the measured wavelength. For this reason it is possible that the spectrophotometric method used at NMS had measured substances other than thiocyanate in the urine samples from the K-25 plant workers.

Therefore, a study was conducted to compare the potentially exposed workers of the K-25 plant in Oak Ridge, Tennessee, to a population with no known exposure to cyanide, as well as to assess the accuracy of the two testing methods in question (spectrophotometry and ion chromatography).

**Methods**

The 55 study subjects were selected to be representative of the general working population with regard to age and sex. Any subjects with known exposures to cyanide, (or to substances metabolized to cyanide or thiocyanate) and those outside the age range of 18 to 65, were excluded from the study. Subjects were volunteers recruited from among residents, faculty, and staff of the Division of Occupational and Environmental Medicine at the University of Cincinnati. The study was conducted in the Center for Occupational Health (COH) at the
University of Cincinnati. To increase the generalizability of the results, the results from this study were combined with another study in progress at the JSI Center for Environmental Health Studies in Boston, Massachusetts, which examined urine thiocyanate levels in subjects recruited from an inner-city working population. Informed consent was obtained from Cincinnati subjects under approval of the University of Cincinnati Institutional Review Board (#97-4-4-1EE, approved 4/7/97).

During the University of Cincinnati study each subject was asked to complete a dietary, medication, smoking, and cyanide exposure questionnaire. All questionnaires were administered at the COH. The questionnaire was completed by the subject immediately before the urine sample was collected. All of the urine samples were stored at COH prior to laboratory analysis. All of the urine samples were analyzed at National Medical Services (NMS) in Willow Grove, Pennsylvania. Data from the questionnaire and from the urine thiocyanate analysis was entered into a spreadsheet created in Microsoft® Excel 2002 on a personal computer. Thirty milliliters of urine were collected from each subject in a spot sample. Ten milliliters were sent for immediate analysis, and a random selection of the remainder was analyzed later for purposes of quality control. These ten milliliter samples were split, and the thiocyanate content of the urine samples was analyzed using both the spectrophotometric method and the ion chromatography method.

The spectrophotometric method used was based on the reaction of urinary thiocyanate with added ferric nitrate in the presence of 3-methyl-1-butanol, yielding an iron-thiocyanate complex with a characteristic orange color. Light absorption measured at 470 nm was quantified relative to the absorption properties of a set of prepared standard samples.

The ion chromatography method used was performed with a column specifically designed for retention of thiocyanate, while allowing other commonly encountered ions to pass
quickly through the column. Separation of thiocyanate was accomplished by passing an isocratic eluent through a column composed of divinylbenzene and ethylvinylbenzene polymers, cross-linked with alkanol quaternary ammonium functional groups. The chromatograph reading for each sample was compared to a linear regression curve derived from a set of standards of known concentration which had been prepared and analyzed on the same day.

Additionally, in order to test the accuracy of both methods, known amounts of potassium thiocyanate were added to six fractions of a urine sample from a single subject, and the resulting specimens were submitted to NMS for analysis by both methods, without telling NMS that the samples were adulterated. The additions were such that final thiocyanate concentrations of 0, 33, 50, 66, 83, and 100 μg/ml should have been achieved. These six urine specimens were subsequently split into twelve specimens, and tested by both the ion chromatography and by the spectrophotometric methods.

Finally, a list of laboratories that conduct urine thiocyanate measurements was generated using multiple internet search engines and personal communications (Table 1). These laboratories were each contacted by letter, phone, and/or email in order to gather data on the exact method by which urine thiocyanate measurements are made, how many urinary thiocyanate tests are performed each year, what percentage of values are above the upper limit of normal, and what they use for normal values (Table 2).

**Results**

The mean urinary thiocyanate level for the 55 unexposed subjects as measured by ion chromatography was 4.89 μg/ml (σ = 12.79). The levels ranged from 1.0 μg/ml to 94 μg/ml. Visual inspection of a histogram (Figure 1) showed nonsmokers (subjects 1-38) to have a
distinctly lower level of measured urinary thiocyanate than smokers (subjects 39-55), except for Subject 1, whose level was 94 μg/ml. This single subject had a thiocyanate level approximately seven standard deviations above the mean, and was considered a potential outlier. Removal of this subject reduced the mean thiocyanate level by ion chromatography to 3.24 μg/ml (σ = 3.75), with a range of 1.0 to 16.0 μg/ml for the remaining 54 subjects. Additionally, removal of this potential outlier reduced the coefficient of variation from 261% to 115%, and the standard error of the mean declined from 1.72 to 0.52. These findings support the assertion that Subject 1 was an outlier, and, unless otherwise specified, all subsequent analyses reflect the removal of this subject from the data set. Nonsmokers had a lower mean urine thiocyanate level (1.35 μg/ml) with less variance (σ = 0.6 μg/ml), when compared to the level for smokers (7.36 μg/ml, σ = 4.43).

The mean urine thiocyanate level for all 55 unexposed subjects as measured by spectrophotometry was 17.87 μg/ml (σ = 12.29). The levels ranged from 1 μg/ml to 73 μg/ml. Visual inspection of a histogram (Figure 2) showed that the levels for nonsmokers (subjects 1-38) were more heterogeneous than those seen with ion chromatography. In contrast to the ion chromatography data (Figure 1), the levels obtained for nonsmokers were not readily distinguished from smokers (subjects 39-55). The potential outlier (Subject 1) again had the highest measured value, but also was not as easily distinguished from the rest of the population. Removal of this subject reduced the mean urine thiocyanate determined by spectrophotometry to 16.84 μg/ml (σ = 9.78), with a range of 1 to 47 μg/ml for the remaining 54 subjects. Additionally, removal of this potential outlier reduced the coefficient of variation from 68% to 58%, and the standard error of the mean declined from 1.65 to 1.2. The mean urine thiocyanate
level for nonsmokers was 15.85 μg/ml (σ = 10.36), while the mean value for smokers was 19 μg/ml (σ = 8.23).

The paired-sample t-test was chosen to test the null hypothesis that there was no significant difference in the means of urinary thiocyanate determined by ion chromatography and spectrophotometry. With α=0.05, the critical value for the two-tailed t-test with 54 degrees of freedom is 2.00. The calculated value of the t statistic was –9.47, which is associated with a p value of 0.00458, allowing confidence in the rejection of the null hypothesis. Performing paired t-tests on the smoking and non-smoking subpopulations also allowed confident rejection of the null hypothesis of no significant difference between the two assay methods with p<10⁻⁵.

Regression analysis of ion chromatography and spectrophotometry yielded a best-fit equation of \( SCN_{IC} = 0.70 SCN_{spectrophotometry} - 7.65 \). While this regression model provided a good linear “fit” (\( r=0.67 \)), the regression coefficient and y-intercept are significantly different from their ideal values of unity and zero, confirming that direct comparison of spectrophotometry and ion chromatography values is not appropriate.

There was good qualitative agreement of the ion chromatography test results with the known thiocyanate concentrations of the adulterated specimens (Figure 3). For ion chromatography, the correlation coefficient between the measured levels and the known levels of the adulterated samples was \( r=0.99 \), with a regression equation, \( SCN_{assay} = 1.06 SCN_{known} + 0.78 \). The root mean squared error for ion chromatography analysis of the adulterated samples was 8.06 μg/ml.

The comparison of the spectrophotometric test results with the known thiocyanate concentrations of the six adulterated samples showed a lower degree of qualitative agreement (Figure 4). Regression analysis of spectrophotometric data achieved a good correlation
coefficient, \( r = 0.96 \). The regression equation for the data, \( \text{SCN}_{\text{spectrophotometry\ assay}} = 1.92 \text{SCN}_{\text{known}} - 8.57 \), had a significant deviation from the desired unity coefficient and zero y-intercept. The root mean squared error for spectrophotometric analysis of the adulterated samples was 60.31 \( \mu g/ml \).

Eight commercial laboratories were found that offer urine thiocyanate testing (Table 1). Of the eight laboratories that offer urine thiocyanate testing, only three (ARUP, MEDTOX, and NMS) will actually perform urine thiocyanate testing at their laboratory (Table 2). The remaining five laboratories currently send out the tests to one of the other three. Of the three laboratories that actually perform urine thiocyanate testing onsite at their laboratory, only ARUP and NMS are actively performing testing at this time. Based upon the data received from these sources, it appears that approximately 2400 urine thiocyanate tests are conducted each year at commercial laboratories within the United States.

**Discussion**

Subject 1 had a urinary thiocyanate level seven standard deviations above the population mean for the ion chromatography assay. This subject also reported having consumed cassava, one of nature’s most cyanogenic foods, shortly before sample acquisition. Exclusion of this subject from the normal population had a significant effect on the standard deviation relative to the mean, halving the coefficient of variation. For a single subject to have such a strong influence on the statistical analyses suggests that inclusion will produce spurious findings. Given that cassava consumption is not “normal” for an American diet, and has clearly been demonstrated to be cyanogenic, exclusion of this subject’s data seems justified in order to limit
the analyses to members of the population with environmental exposures typical of the American working population.

There was a considerable difference in the overall mean thiocyanate values for ion chromatography (3.24 μg/ml, σ = 3.75) and spectrophotometry (16.84 μg/ml, σ = 9.78). Comparison of the means by paired t-test confirmed a significant difference (p<0.005). Clearly, both methods of testing cannot be correct, and either one or both of them must be inaccurate. A determination of accuracy was made using samples with known thiocyanate concentrations.

The twelve urine specimens of various known thiocyanate concentrations prepared from a single urine sample allowed unbiased evaluation of each test’s accuracy by blinding the laboratory to the knowledge of specimen adulteration. The thiocyanate levels of the two urine specimens which had no potassium thiocyanate added, were correctly reported to be 1 μg/ml by both ion chromatography and spectrophotometry, which is the lower limit of detection for both. However, inspection of the distribution of the known samples shows poor agreement for spectrophotometry, especially at higher thiocyanate concentrations (Figure 4). This is confirmed by a calculated regression equation with coefficient and intercept far from the ideal. Ion chromatography, on the other hand, performed well over the range of thiocyanate concentrations, and had a regression equation approximating the ideal of a zero intercept and unity regression coefficient. The root mean squared error for ion chromatography was 8.06 μg/ml, and could be nearly completely attributed to measurements in two of the five samples (83 and 66 μg/ml), both of which had 17% error in the assayed value. This was far less than the root mean squared error observed for spectrophotometry (60.31 μg/ml), where some sample assays had errors over 100%. Since the same urine sample was used for all adulterated specimens, the presence of non-specific chromogens is an unlikely explanation for the poor performance of spectrophotometry.
Before June 1, 1996, about 87% of the workers at the K-25 plant in Oak Ridge, Tennessee, tested for occupational cyanide exposure had an abnormal result. These findings understandably generated a great amount of interest and concern in the potential health effects caused by cyanide exposure at their workplace. However, extensive investigation failed to reveal a source of cyanide exposure. The mean level as measured by spectrophotometry for K-25 nonsmokers was 14.3 μg/ml, and 23.5 μg/ml for K-25 smokers. The mean level as measured by spectrophotometry in this study of an unexposed population for nonsmokers was 15.9 μg/ml and 19.0 μg/ml for smokers. In nonsmokers, there was no significant difference in urine thiocyanate levels between unexposed subjects and K-25 workers. In fact, the unexposed subjects had a higher mean level of urine thiocyanate (15.9 versus 14.3 μg/ml). In smokers, the urine thiocyanate levels were higher in K-25 workers than the unexposed subjects (23.5 versus 19.0 μg/ml), but not significantly.

After NMS began to use ion chromatography, only a single worker was found to have an elevated level of urine thiocyanate. Because of this result and because of this study’s ability to recreate similarly elevated results in an unexposed study population using the same spectrophotometric testing method at NMS, it can be concluded that the urine thiocyanate tests conducted by NMS on K-25 plant workers prior to June 1, 1996, had no clinical relevance.

The question remains, however, whether ion chromatography, in general, is truly more accurate in measuring urine thiocyanate than spectrophotometry. In this study it appears to be much more accurate; however, this author suspects that laboratory error may have been the main factor in the conflicting results. It is possible that the ferric nitrate spectrophotometric method used at NMS is incapable of providing accurate results. Our results can easily be explained, though, by human error or by equipment malfunction. Therefore, it would not be appropriate to
conclude from our results that ion chromatography is superior to spectrophotometry in the measurement of urine thiocyanate. It is essential, however, for each laboratory providing such testing to perform frequent quality control checks to ensure that measured levels correlate well with actual levels, especially after significant numbers of abnormal results.

After a study such as this one, this researcher thinks that the subject of normal values should be re-examined. The previously mentioned study in 1955 by Malisziewski and Bass consisted of 14 subjects, and resulted in normal values of 1-4 \( \mu g/ml \) for nonsmokers, and 7-17 \( \mu g/ml \) for smokers. Our current study included 54 subjects in the analysis. Because the lower limit of normal of 1 \( \mu g/ml \) for nonsmokers corresponds with the lower limit of detection for both spectrophotometry and ion chromatography, one could argue that normal actually extends to zero, but is simply limited by these methods. Based on this study’s ion chromatography data, the upper limit of normal for nonsmokers of 4 \( \mu g/ml \) corresponds with a level 4.4 standard deviations above the mean for nonsmokers. This result varies considerably from the conventional use of two standard deviations from the mean to include 95% of the population, and yet preserve sensitivity. However, in a time when smoking status can be used to make employment decisions and urine thiocyanate levels might be used to make these determinations, the higher specificity offered by keeping this level high seems justified. With regards to the normal range for smokers, one could also argue that a normal level could also extend to zero; however, one would have to question whether the subjects have actually been smoking if their levels are less than 4 \( \mu g/ml \). The upper limit of normal of 17 \( \mu g/ml \) corresponds with a level 2.2 standard deviations above the mean for smokers from this study’s ion chromatography data. This level seems appropriate, as it is close to the conventional two standard deviations from the
mean, and preserves sensitivity. To summarize, this author proposes normal levels of urine thiocyanate to be 0-4 μg/ml for nonsmokers, and 0-17 μg/ml for smokers.

Conclusions

These results provide strong evidence that the measurements of urine thiocyanate performed by NMS in 1996 using the ferric nitrate spectrophotometric method significantly overestimated actual levels. Consequently, the occupational cyanide exposure testing performed at the K-25 plant in Oak Ridge, Tennessee, yielded many false positive test results. Therefore, the urine thiocyanate testing performed by NMS in 1996 and earlier, using the ferric nitrate spectrophotometric method, should not be used as evidence of cyanide exposure. Commercial laboratories must be encouraged to perform frequent quality control checks to ensure the accuracy of their measurements.
Bibliography

13. Personal Communication between Andrew Freeman, MD and National Medical Services, Inc.
Figure 1. Urine thiocyanate levels as measured by ion chromatography for the 55 unexposed subjects in the study. Non-smokers (subjects 1-38) appear to have noticeably lower values than smokers (subjects 39-55), with the exception of the potential outlier (Subject 1).
Figure 2. Urine thiocyanate levels as measured by spectrophotometry for the 55 unexposed subjects in the study. Nonsmokers (subjects 1-38) are not obviously different from smokers (subjects 39-55). While still having the single largest value in the population, Subject 1 is not as distinct here as in the ion chromatography measurements.
Figure 3. Urine thiocyanate levels as measured by ion chromatography (blue diamonds) from samples with known urine thiocyanate concentrations (purple squares).
Figure 4. Urine thiocyanate levels as measured by spectrophotometry (blue diamonds) from samples with known urine thiocyanate concentrations (purple squares).
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Methodology</th>
<th>Phone</th>
<th>Website</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARUP Laboratories</td>
<td>Spectrophotometry(SP)</td>
<td>800-522-2787</td>
<td><a href="http://www.arulab.com">www.arulab.com</a></td>
</tr>
<tr>
<td>Cleveland Clinic</td>
<td>Sends out to ARUP</td>
<td>800-628-6816</td>
<td><a href="http://www.clevelandclinic.org">www.clevelandclinic.org</a></td>
</tr>
<tr>
<td>LabCorp</td>
<td>Sends out to NMS</td>
<td>800-282-7300</td>
<td><a href="http://www.labcorp.com">www.labcorp.com</a></td>
</tr>
<tr>
<td>LabOne</td>
<td>Sends out to ARUP</td>
<td>800-332-0053</td>
<td><a href="http://www.labone.com">www.labone.com</a></td>
</tr>
<tr>
<td>MEDTOX</td>
<td>SP</td>
<td>800-832-3244</td>
<td><a href="http://www.medtox.com">www.medtox.com</a></td>
</tr>
<tr>
<td>National Medical Services(NMS)</td>
<td>Ion Chromatography(IC)</td>
<td>800-522-6671</td>
<td><a href="http://www.nmslab.com">www.nmslab.com</a></td>
</tr>
<tr>
<td>Specialty Laboratories</td>
<td>Sends out to NMS</td>
<td>800-421-7110</td>
<td><a href="http://www.specialtylabs.com">www.specialtylabs.com</a></td>
</tr>
<tr>
<td>Quest Diagnostics</td>
<td>Sends out to NMS</td>
<td>800-222-0446</td>
<td><a href="http://www.questdiagnostics.com">www.questdiagnostics.com</a></td>
</tr>
</tbody>
</table>

Table 1. Laboratories that offer urine thiocyanate testing.
<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Procedure</th>
<th># per year</th>
<th>% above Normal</th>
<th>Normal Values (μg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARUP Laboratories</td>
<td>SP: TCA precipitates a supernatant, chloramine is added and absorption is measured at 540 nm.</td>
<td>Approximately 2000</td>
<td>Not monitored</td>
<td>&lt;20</td>
</tr>
<tr>
<td>MEDTOX</td>
<td>SP: 5% TCA precipitates a supernatant, ferric nitrate is added and absorption is measured at 480 nm.</td>
<td>No data</td>
<td>No data</td>
<td>Reference range has not been established</td>
</tr>
<tr>
<td>National Medical Services(NMS)</td>
<td>IC: Specialized columns retain thiocyanate, measurements are compared to a curve generated by controls.</td>
<td>Approximately 400</td>
<td>Less than 1%</td>
<td>1-4 Nonsmoker 7-17 Smoker</td>
</tr>
</tbody>
</table>

**Table 2. Information provided by laboratories that perform onsite urine thiocyanate testing**