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Evaluation of Isotope Dilution Mass Spectrometry for Bioassay Measurement of Uranium, Plutonium, and Thorium in Urine

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Prepared for the
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EVALUATION OF ISOTOPE DILUTION MASS SPECTROMETRY FOR BIOASSAY MEASUREMENT OF URANIUM, PLUTONIUM, AND THORIUM IN URINE

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ABSTRACT

A study was made to evaluate the sensitivity, precision and accuracy, and practicality of isotope dilution mass spectrometry (IDMS) for bioassay of uranium, plutonium, and thorium in human urine. The study showed that uranium at a concentration of 0.06 μg/L (0.04 pCi/L natural uranium), plutonium at 3 pg/L (0.2 pCi/L Pu-239), and thorium at 0.1 μg/L (0.01 pCi/L Th-232) could be measured with an uncertainty (RSD) of ten percent using 10 ml samples. The lower limits of detection for uranium and thorium were set by background contamination, whereas the detection limit for plutonium was determined by chemical yield and intrinsic instrumental sensitivity factors. Precision and accuracy is excellent (~1-3%, RSD) at concentration levels where background contamination is insignificant and instrumental sensitivity is adequate.

Comparison of IDMS with other methods shows the technique is more sensitive than conventional fluorometric methods but is similar in sensitivity to alpha-radioactivity measurement methods that utilize large sample volumes (1 L). Costs for urine analysis by IDMS ($60-$100 per sample) are estimated to be considerably higher than cost for fluorometric analysis and approximately the same as the cost for alpha-radioactivity methods. Other methods that have been used or are currently under development are discussed.

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EXECUTIVE SUMMARY

The method of isotope dilution mass spectrometry (IDMS) was investigated for the determination of uranium, thorium, and plutonium in human urine. The technique of loading these elements on anion exchange resin beads with subsequent mass spectrometric analysis of the adsorbed elements was employed. Major emphasis was placed on an evaluation of the sensitivity, precision, and accuracy of the experimental method. In addition, an assessment was made, based on a literature survey, of other methods that are currently used or have potential for use for determining the very low levels of these elements that may be present in human urine. All of the methods, including IDMS, were compared regarding their practicality, cost, applicability to elemental and/or isotopic analysis, and reported measurement sensitivity.

This study has shown that IDMS combined with the resin bead technique can detect uranium in urine at a concentration of 0.02 µg/L (0.01 pCi/L natural uranium), plutonium at 1 picogram/L (0.06 pCi/L Pu-239) and thorium at 0.04 µg/L (0.004 pCi/L Th-232). At slightly higher concentrations, 0.06 µg/L (0.04 pCi/L) for uranium, 3 picograms/L (0.2 pCi/L) for plutonium, and 0.1 µg/L (0.01 pCi/L) for thorium, measurements can be made with a relative standard deviation (RSD) of ten percent. At higher concentrations, uncertainties of analyses are of the order of 1-3 percent RSD. Most of the study was concerned with the analysis of urine or synthetic urine samples containing known amounts of either uranium or plutonium and therefore directly addressed the question of accuracy. Observed differences between the measured and known concentrations were essentially equal to differences observed between replicate measurements. Thus, no evidence was found for significant systematic errors.

The lower limit of detection for uranium and thorium is set by the variability of the procedural blank and not by instrumental sensitivity factors. The procedural blank for uranium found in this study was 0.030 ± 0.005 µg/L. The blank value is highly dependent on the laboratory conditions in which the chemical procedures are performed. Pickup of uranium contamination from laboratory air, labware, and chemical reagents is a problem at these exceedingly low concentration levels. The detection limit for uranium is, therefore, limited by the care and attention given to contamination control. In these studies, a moderate level of contamination control was maintained; conventional chemical laboratories with laminar-flow hoods, limited personal access, and careful sample screening were routinely used. More stringent measures for contamination control may be too impractical and costly for routine use in bioassay monitoring programs. With moderate efforts to control contamination, it has been demonstrated that IDMS can determine uranium that is in the range of the lowest indigenous levels reported in the urine of nonoccupationally exposed human population groups.

Comparison of IDMS methods with the currently used methods for bioassay measurements of uranium indicates that it is about two orders of magnitude more sensitive than classical fluorometric methods in

which 0.1 ml of urine is analyzed directly. Costs per analysis by IDMS ($60-$100) are considerably higher than for fluorometric analysis (<$20), but IDMS can be used to determine all three elements and provides isotopic composition whereas fluorometry determines only elemental uranium. The sensitivity of the IDMS method is comparable with the intrinsic sensitivity of alpha-radioactivity measurement techniques for uranium, plutonium, and thorium. Likewise, costs for analysis are very similar ($50-$100). Even though the sensitivity for the alpha counting method is comparable with IDMS, a large volume of urine (1 liter) is necessary for the alpha counting method whereas only 10 mL of urine is required for IDMS. Also, the detection limit for alpha counting methods cannot be greatly improved by reduction of contamination, whereas improvements in contamination control can greatly improve the sensitivity of the IDMS method. Objective comparison of IDMS with resonance ionization mass spectrometry and laser fluorometric methods is not yet possible because the latter techniques have not been experimentally demonstrated for the lowest indigenous levels of uranium in urine. It is likely that the ultimate sensitivity attainable for analysis of uranium and thorium in urine by resonance ionization mass spectrometry and laser fluorometry will be determined by the degree of contamination control that can be achieved and not by intrinsic instrumental sensitivity factors.

The main disadvantages of IDMS for urine bioassay measurements are the high cost required for the purchase of mass spectrometers and the limited throughput of samples caused by the time consuming procedures necessary for thermal ionization of the elements. At this time, we believe that the IDMS - resin bead technique, except for costs considerations, has many desirable features for high sensitivity analysis of uranium, plutonium, and thorium in urine. Future developments in the mass spectrometry instrumentation and automation of chemical operations could make the technique cost competitive with other methods. Because of the high costs, the need for high-quality maintenance services, and the requirements for very strict control of background contamination it does not seem likely that small analytical laboratories, particularly ones located near uranium mining and milling facilities, could successfully apply IDMS to very low-level bioassay measurements. There are, however, a number of high quality commercial analysis laboratories in this country that would be capable of establishing the IDMS capability for bioassay measurements. For these laboratories, the main requirement would be that the number of samples analyzed (sample load) would be sufficient to justify the capital expenditures needed to purchase instrumentation and provide special laboratories for chemical processing in a low uranium background area.

1. INTRODUCTION

1.1 Purpose and Experimental Approach of This Study

The principal objective of this study was to critically evaluate the method of isotope dilution mass spectrometry (IDMS) for the determination of uranium, thorium, and plutonium in human urine by analyzing anionic resin beads on which these elements had been loaded. This method was investigated because it is relatively well advanced and understood and its potential sensitivity for these measurements is perhaps greater than other methods. The great sensitivity of the method was first demonstrated by Carter et al., who reported that uranium and plutonium had been detected at concentrations of 2×10^{-3} and 2×10^{-5} µg/L, respectively, using samples with 1-mL volumes (Ca80). The method is isotope specific and thus has the potential for measuring the isotopes of all three elements in a single sample; often, information about the different isotopes is of significant value. In addition, mass spectrometry instrumentation, albeit relatively expensive, is readily available.

The approach to the study has been to carefully evaluate and understand: (1) the control and diminution of the reagent or procedural blank, (2) the optimum conditions for chemical separations, (3) the optimum conditions for loading the resin bead, and (4) the accuracy and precision of the overall method by measurements on real and synthetic urine samples containing known amounts of these elements, and (5) the factors that contribute to an efficient and economical use of the method. Because uranium is relatively more important to bioassay programs than thorium or plutonium, we have concentrated most of our effort on uranium. Although the effort would be interesting and useful, we have not had the resources in this study to measure these elements in a large number of urine samples. We have summarized in Chapters 2 and 3 of this report the principles of the method and the details of the procedures that were used in this study. The experimental results are presented in Chapter 4 along with discussions and conclusions about possible improvements in the method.

A secondary objective of this study was to review the recent literature and evaluate the various methods that are used or have the potential for being used to determine these elements in human urine. We have summarized in the appendix of this report the factual information found in this review about methods other than IDMS. In Chapter 5 of this report, we have evaluated the benefits of IDMS for wide applications, drawing upon the literature survey and other sources of information to compare the various methods currently in use or proposed for use in bioassay measurements.

1.2 Purpose of Urine Bioassay

Within the health physics literature, the terms bioassay and radiobioassay refer to the determination of the quantity of radionuclides in the human body. Such determinations are inferred from the results of measurements made on human excreta (in vitro) or by direct (in vivo) measurements of radiations (x-rays or gamma rays) emitted from the body. These analytical and radioanalytical measurements are usually termed bioassay measurements. Urine bioassay measurements are widely used to permit inference of body burdens of radionuclides particularly for uranium. Another purpose served by bioassay measurements is to provide evidence about the proper functioning of protective measures, e.g., air filtering systems, used to prevent assimilation of radioactivity by humans.

The legal basis for bioassay in occupational situations exists in the code of Federal Regulations, Title 10, Part 20 (10CFR20) "Standards for Protection Against Radiation". Nuclear Regulatory Guide 8.11, "Applications of Bioassay for Uranium," provides criteria for the development and implementation of a bioassay program for mixtures of U-234, U-235, and U-238 for licensees of the Nuclear Regulatory Commission. The technical basis for the bioassay criteria of NRC Guide 8.11 are provided in WASH-1251 (A174), "Application of Bioassay for Uranium". NRC Regulatory Guide 8.22 "Bioassay at Uranium Mills" details specifically the requirements for bioassay at uranium mills. Because of the more limited extent to which individuals are exposed to thorium and plutonium, no similar extensive guides and treatments of their bioassay have appeared.

1.3 Nonoccupational Levels of Uranium and Thorium in Human Urine

Uranium and thorium occur naturally in human urine, and the normal baseline concentrations of these elements are important in establishing limits for monitoring of urine to detect occupational exposure. Although important, not much is known about normal baseline levels of uranium and thorium in human urine. Information available up to about 1975 concerning levels of all the elements in diet and drinking water and measured levels in human excreta were published in ICRP Publication 23(IC75). Nonoccupational levels of uranium in urine were reported to lie in the range 0.01 to 26 µg/L. Where low-level drinking water is consumed, the rate at which uranium is excreted in urine was estimated to be 0.04 to 0.4 µg per day. Welford, et al., (We60) measured uranium in urine in the New York City area and found 0.03 to 3 µg/L. From food measurements, Welford and Baird (We67) estimated typical dietary intakes of uranium in New York City (1.3 µg/d), Chicago (1.4 µg/d), and San Francisco (1.3 µg/d). They also measured uranium in urine in Chicago (0.04-0.18 µg/L) and in tap water in New York City (0.02-0.04 µg/L). Although the concentration of uranium in urine does not appear to be linearly dependent on daily intake (We67), one would expect a rather wide variation in urinary uranium among different geographical areas within the United States in view of the wide variation of uranium in drinking water supplies (0.01-29 µg/L) that has recently been estimated to exist (Co83, Dr81). Municipal drinking waters actually

measured by the Environmental Protection Agency were found to contain uranium in the range of 0.01 to 4.8 µg/L (Co83).

Much less is known about the thorium baseline in human urine. The daily urinary excretion rate was estimated to be 0.1-2 µg (IC75). Clifton, (Cl71) using a neutron activation analysis method with a sensitivity of 0.001 ng, reported values of 0.001 µg/L in five subjects who had not been exposed to thorium. Wren, et al., (Wr81) published an excellent study of thorium in human tissue and summarized the knowledge of this subject that was available up to about 1981.

1.4 The Sensitivity Needs of Bioassay Measurements

The requirements for measurement sensitivity for the determination of uranium, thorium and plutonium in human excreta are complex and depend on the purpose of the measurement. Measurement sensitivities required in official bioassay programs to determine uranium for the purpose of estimating internal dose or chemical toxicity are presented in NRC Guide 8.11 and described thoroughly in WASH-1251. As discussed in these publications, the requirements for measurement sensitivity depend on many factors including the nature (class) of the uranium containing material to which a worker is exposed, the isotopic composition of the uranium, the frequency of exposure, and the frequency of the bioassay measurements.

It should be emphasized that within the context of official bioassay programs, the term measurement sensitivity refers to a true measurement of concentration with an uncertainty that is small and estimable. The terms are used in the sense that Currie (Cu68, Ko78) defines a quantitative determination limit or that Watson (Wa80) defines a minimum detectable concentration and not in the sense that much of the analytical chemistry literature speaks vaguely of detection sensitivity. It should be noted, as Watson has explained (Wa80), that the minimum measurable concentration of any analytical method depends on the conditions of the measurement and can be lowered by increasing sample size and counting time and decreasing blanks, etc., usually with added expense.

The lowest measurement level indicated to be required by NRC Regulatory Guide 8.11 for measurements of uranium in urine is 0.2 µg/L (0.14 pCi/L for natural uranium). For bioassay measurements of uranium in the urine of uranium mill workers, NRC Regulatory Guide 8.22 states that a measurement sensitivity of 5 µg/L or less should be provided. In view of this requirement, and the fact that normal urinary levels of uranium can be in the range of 0.01 to 26 µg/L, a measurement sensitivity of about 0.1 µg/L with a relative standard deviation of about $\pm$10% would seem to be adequate for most applications.

2. PRINCIPLES OF ISOTOPE DILUTION MASS SPECTROMETRY AND RESIN BEAD METHODOLOGY

Mass spectrometry is based on the ionization of a material in a vacuum, and the measurement of the number of ions formed after they are separated either by magnetic fields according to their mass-to-charge ratio or by travel time in time-of-flight instruments. Design details of two mass spectrometry systems typical of the one used in this study are described by Lagergren and Stoffels (La70) and Smith et al. (Sm 72). These systems are based on magnetic and electrostatic separations of ions with digital ion counting and storage of mass spectra in pulse height analyzers. Mass spectrometry is a vast, evolving field and the reader interested in aspects not pertinent to the current subject is directed to the literature (Hi62, Dr67).

Thermal ionization mass spectrometry is one of the methods used to analyze solids that melt and vaporize at high temperatures. A sample is placed on a filament of tungsten or rhenium and heated to a temperature sufficient to vaporize and ionize the elements of interest. Isotope dilution mass spectrometry (IDMS) is a technique used in many types of mass spectrometry to quantitatively determine the isotopes of an element. Thermal ionization mass spectrometry combined with the techniques of IDMS is commonly used to determine the isotopes of uranium and plutonium. The determination of the isotopes of natural uranium is exemplary of this method. A known amount of an isotope of uranium, e.g. U-233, that is not originally present in the sample is placed in a solution containing an unknown amount of natural uranium. The U-233 is called a mass tracer, and the amount added is often called a spike. Usually at this point, it is necessary to chemically isolate the uranium. After the separation is completed, a portion of the resulting solution is dried (or otherwise placed) on a filament and analyzed by thermal ionization mass spectrometry. The quantity of U-238, Q8, originally present in the sample can then be calculated from the measured signals (usually counts) of U-238, S8, and U-233, S3, and the quantity of U-233 added, Q3, by

$$Q8 = Q3\ (S8/S3).$$

The amounts of other isotopes of uranium are similarly estimated. Reagents and procedural blanks can be similarly analyzed to discount the amounts of U-238, etc., in the reagents and on labware. Small amounts of other uranium isotopes that are present in the U-233 mass tracer can be similarly discounted. Mass tracers that can be used for Pu-239 and Th-232 are Pu-242 and Th-230, respectively. Calculations of concentrations can become much more complex than the simple model above suggests, e.g., when isobars such as Pu-238 and U-238 are present (Wa 79).

The technique of loading samples on resin beads for isotopic mass

spectrometric analysis was first suggested by Freeman et al. (Fr70) and first applied to uranium measurements by Lagergren and Stoffels (La70). The technique has since been developed into a comprehensive methodology and applied extensively to measurements of uranium and plutonium (and to a lesser extent thorium) in a variety of nuclear fuel materials and environmental samples (Wa74, Ca80, Wa79, Fa80, Sm82). Although the technique has been used to determine uranium in animal tissue as mentioned below, it has apparently not been used to analyze human excreta.

Anionic Dowex 1 resin beads with diameters of about 150-250 μm and a cross linkage of 2% are normally used. As applied to solutions of nuclear fuel materials, the beads in the nitrate form are loaded with uranium and plutonium from solutions that are 7-8 molar in nitric acid. The solutions are spiked with Pu-242 and U-233 or U-236 (Wa74). In nitric acid, plutonium is adsorbed much more strongly than uranium making it possible to emphasize a much more sensitive and accurate measurement of small traces of plutonium in the presence of much larger amounts of uranium. After the beads are loaded, recovered, and dried, one bead is loaded onto a rhenium V-shaped filament for mass analysis. Details of the procedure are described by Walker et al. (Wa76). In reactor fuel analysis each bead is loaded with 1-3 ng of both uranium and plutonium. The bead is carbonized, and plutonium is measured by thermal ionization mass spectrometry at temperatures of 1400 to 1500°C. Plutonium is then removed by vaporization at 1700°C, and uranium is measured at about 1750°C. In many cases it is necessary to heat to 1900°C to measure thorium. Although static contact for up to 40 hours between beads and solution was originally used in loading, solution agitation for 10 minutes was found to produce adequate loading for some analyses (Ca80). The resin bead method has resulted in vast improvements in IDMS measurements of uranium and plutonium. Foremost in the improvements is a sensitivity increase over conventional IDMS of a factor of 10, due to the point source nature of the ion emitter and the chemically reducing environment of the carbonized bead. The method is highly convenient to use because of the simplicity of separations and because of the ease of introduction of the sample into the mass spectrometer. The small samples lessen problems of spectrometer contamination, and the integrity of the beads provides for ease of sample storage. The accuracy and precision obtained with the resin bead technique is as good as can be obtained by conventional thermal ionization mass spectrometry with uncertainties of the order of a fraction of one percent when beads containing about 1-3 ng uranium and plutonium (Ca80, Fa80) are measured. Isotope dilution mass spectrometry was used by Dupzyk and Dupzyk (Du79) to determine uranium in urine and to compare the results with those found by fluorometry. Samples of 10 mL were measured by both methods, and although much higher precision was indicated for the IDMS method, few details about the measurements were given.

At the time this work was nearing completion, an excellent study

by Kelly and Fasset (Ke83) was described in which isotope dilution mass spectrometry coupled with resin bead methodology was used to determine uranium in National Bureau of Standards bovine liver SRM 1577a. The procedures used, which were similar to those employed in this study, were described in detail. The work was outstanding in its measurement sensitivity and in the very low procedural blanks that were obtained. It was reported that 0.1 ng could be measured with an uncertainty of 0.5 percent, and procedural blanks of a few picograms were obtained.

3. EXPERIMENTAL PROCEDURES

3.1. Introduction

Special experimental procedures were developed to evaluate IDMS for determination of uranium, plutonium, and thorium in urine. Because of the need to obtain the highest possible sensitivity, special precautions were taken to prevent inadvertent contamination of urine samples. These precautions included careful attention to the procurement of high purity reagents and the purification and storage of chemicals. In addition, great effort was exercised in the cleaning of laboratory glassware and equipment and in the careful handling of samples and reagents in a laboratory environment that was essentially free of contaminants. The procedures used in this work are described in detail in this chapter. The rationale for selection of the procedures and experimental results obtained in the study are presented in Chapter 4.

3.2 Isotopic Spikes, Special Reagents, and Equipment

Uranium-233 and Pu-242 were used as mass tracers for the IDMS analysis of uranium and plutonium, respectively. Both tracers were obtained from the Isotope Sales Department of Oak Ridge National Laboratory and were assayed by IDMS against certified reference materials obtained from the National Bureau of Standards. The uranium tracer, assayed against natural uranium SRM-950B, contained 65.6 ng U-233 per mL and had the following isotopic composition expressed as atom percent: U-233 (99.960), U-234(<0.001), U-235(<0.001), U-236(<0.001), U-238 (0.040). The plutonium tracer, assayed against SRM-949E, contained 9.64 ng Pu-242 per mL and had the following isotopic composition: Pu-238(<0.0001), Pu-239(0.0010), Pu-240(0.0003), Pu-241(0.0007), Pu-242(99.998). Thorium-230 was used as a mass tracer for thorium. This solution contained 1.024 µg Th-230 per mL and had an isotopic composition of Th-230(99.86), Th-228(0.14). In addition to the mass spectrometry tracers, a U-238 tracer and a Pu-239 tracer (NBS SRM-4331-17) were used as standard addition spikes. The U-238 tracer was prepared by dissolving a weighed amount of uranium metal in nitric acid. All tracers were prepared with 2 M HNO_3 and stored in glass bottles.

Several special reagents were employed during the experiments. Electronic grade HNO_3 was used to prepare the 4 M HNO_3 for cleaning purposes. For ion exchange separations and resin bead loading, Ultrex grade HCl, HNO_3, and $HClO_4$ (supplied by J. T. Baker Chemical Company) and triply-distilled H_2O were used. Battelle Pacific Northwest Laboratory supplied two synthetic urine samples: 1) an artifical urine matrix with no added uranium (No. U-0452-5337-029) which was used as a control and 2) the same artificial matrix spiked with 7.024 µg/kg natural U (No. U-0561-5337-029). The synthetic urine composition closely

resembles that of natural urine, and the major components (g/kg) were as follows: urea (16.0), NaCl (2.32), KCl (3.43), creatinine (1.10), Na_2SO_4 (4.31), hippuric acid (0.63), NH_4Cl (1.06), citric acid (0.54), $MgSO_4$-anhyd. (0.46), $NaH_2PO_4 \cdot H_2O$ (2.73), $CaCl_2 \cdot 2H_2O$ (0.6), oxalic acid (0.02), lactic acid (0.094), glucose (0.48), $Na_2SiO_3 \cdot 9H_2O$ (0.071), pepsin (0.029), HNO_3-70% (50.00), and yellow food coloring (0.06).

Extra precautions were taken to maintain a low uranium background for all operations. All glassware was limited to Pyrex. Plasticware, glassware, glass wool, glass beads, resin columns, and other equipment were cleaned by soaking in 4 M HNO_3 for 24 hours, rinsing in distilled water for 24 hours, and drying with reagent grade acetone or 100% ethanol. Ion exchange resin was cleaned in 4 M HNO_3 and stored in distilled water. All chemical operations were performed in a laboratory specifically designed for low-level work. Personnel access to the laboratory was regulated, and the samples being analyzed were carefully screened. Triply-distilled water prepared with a quartz still was used for all phases of the work except as mentioned above.

A variety of special materials and equipment were needed to perform the work. The anion exchange resin was Dowex 1x8 (quaternary ammonium) in the chloride form (50-100 mesh) supplied by Bio-Rad Laboratories Ltd. Plastic ion exchange columns, 6.9 mm in diameter and 89 mm length, were constructed from 1-mL disposable transfer pipets and 15-mL plastic bottles, which were attached to the top to serve as a reservoir. Plastic vials with a 1.5-mL capacity were used for the bead loading step of the procedure. Polyethylene filter funnels with polethylene discs and caps were used to filter the final loading solutions and to store the loaded beads prior to mass spectrometry analysis. All bead-loading work was performed in a laminar-flow hood.

3.3 Chemical Procedures for Separation and Concentration of Uranium, Plutonium, and Thorium

3.3.1 Uranium Method

Ten milliliters of urine were placed in a 50-mL Pyrex beaker, and 6.56 ng U-233 and 0.964 ng Pu-242 were added as mass tracers for the isotope dilution mass spectrometry measurements. The sample was adjusted to 8 M HCl by adding approximately 20 mL of concentrated Ultrex HCl. A few drops of concentrated Ultrex nitric acid were added to maintain plutonium in the +4 oxidation state, and the sample was allowed to digest overnight at room temperature. The ion exchange column was prepared by adding a small amount of glass wool to the plastic column followed by a resin slurry made from 1 gram of Dowex 1x8 resin in distilled water. A small amount of glass beads was added to the top of the column. The resin was pre-equilibrated with 5 mL of 8 M HCl, the digested sample was slowly loaded onto the column, and the effluent

was allowed to drain into a waste container. The column was washed with 6 mL of 8 M HCl to elute various organic and inorganic compounds of the urine. Uranium was eluted from the column with 5-6 mL of 0.1 M HCl into a 10-mL beaker. This eluate was then dried slowly on a hot plate equipped with a heat lamp. The residue was dissolved with 0.3 to 0.4 mL of 8 M Ultrex HCl and 10 microliters of Ultrex HNO_3. The samples were then ready for loading onto 2 or 3 resin beads for mass spectrometry measurements.

3.3.2 Plutonium Method

The procedure described above was followed except plutonium was eluted with 5-6 mL of 0.4N HCl-0.01 M HF. The eluate was collected in a Teflon beaker and evaporated twice after additions of 1 mL of concentrated Ultrex HCl. The residue was then dissolved in 8 M HCl for final bead loading.

3.3.3 Thorium Method

Ten milliliters of urine were placed in a 50-mL Pyrex beaker and 102.4 ng of Th-230 was added to serve as a mass tracer for Th-232. The sample was adjusted to 8 M HNO_3 by adding approximately 10 mL of concentrated Ultrex HNO_3 and allowed to digest overnight at ambient temperature. The ion exchange column was prepared by the method described in Section 3.3.1. After being placed in the column, the resin in the chloride form was washed with 8 M HNO_3 until tests with a silver nitrate solution indicated that no chloride was in the effluent. The digested sample was slowly added to the column, and the effluent was discarded. Thorium was eluted from the column with 15 mL of 8 M HCl into a 50-mL beaker. This eluate was then dried slowly with a hot plate and heat lamp. Two subsequent dryings with Ultrex HNO_3 removed all traces of chloride ions, and the final residue was dissolved in 0.3 to 0.4 mL of 8 M Ultrex HNO_3. The sample was then ready for loading onto 2 or 3 chloride-free resin beads for mass spectrometry measurements.

3.4 Loading of Exchange Beads after Chemical Separation

Solutions containing uranium and plutonium were prepared in 8 M HCl with a final volume of about 0.5 mL. Two or three anion exchange resin beads with diameters in the 150-400 micron range were selected and placed in the loading vials, and 100-200 microliters of 8 M HCl were added to pre-equilibrate the beads. The samples were transferred to the loading vials which were capped, enclosed in plastic bags, and placed on a wrist-action shaker to equilibrate for about 2 hours. During this time, uranium and plutonium were loaded onto the resin beads. The loading solution was filtered through a small polyethylene filter funnel to remove the majority of the liquid. The beads that remained in the

funnels were analyzed by mass spectrometry. Thorium was loaded on resin beads from 8 M HNO_3 solutions in the same manner.

3.5 Direct Loading of Ion Exchange Beads

In addition to the procedures described above, a series of samples were analyzed by loading the plutonium and uranium isotopes directly from the urine onto 2 or 3 resin beads. Aliquots of both 0.5 and 1.0 mL were analyzed. The sample was pipetted directly into a loading vial, and 6.56 ng of U-233 and/or 0.964 ng of Pu-242 isotopes were added as mass tracers. The sample was adjusted to 8 M HCl by adding concentrated Ultrex HCl. Two or three resin beads in the chloride form were added, and the mixture was then shaken for about two hours. The solutions were filtered as described earlier, and the loaded beads were analyzed by IDMS.

3.6 Mass Spectrometric Analysis

The mass spectrometer used in this work was a two-stage, 30-cm radius instrument equipped with an electron multiplier for ion detection and pulse counting to obtain the maximum sensitivity. The thermal ionization single-filament technique was used for all measurements. Sample filaments are made from zone-refined rhenium and are prebaked for 30 min. at 2000°C in an auxiliary vacuum system prior to loading of the resin bead samples.

The techniques of loading beads on filaments and details of analysis have been published in several reports (Sm82, Wa74, Wa76, Ca80). The following is a brief outline of the mass spectrometric analysis technique for plutonium, uranium, and thorium.

A single bead is loaded onto a canoe-shaped rhenium filament (Wa76), and the filament is crimped to hold the bead in place and installed in the spectrometer. The filament is slowly heated under high vacuum (10^{-5} Pa) until a pressure burst signals bead decomposition. Plutonium is then analyzed at about 1450°C. After plutonium is analyzed, the excess is evaporated at about 1700°C, and uranium is analyzed at 1750°C. The concentrations of the elements were obtained with the equation below:

$$X = \frac{Y\ I_s\ A_s}{V\ I_t\ A_t}$$

where X and Y are the weights of the element in the sample (ng/mL) and the tracer (ng) respectively, I_s and I_t are corrected counts of the sample and tracer isotopes, A_s and A_t are the atomic weights of the element in the sample and tracer, and V is the volume of the sample (mL).

4. RESULTS AND DISCUSSION

4.1 Discussion of Experimental Procedure

As indicated in Section 1.1 of this report, the method of isotope dilution mass spectrometry was investigated because it is well understood, has high sensitivity, and is capable of measuring individual isotopes of elements. The analysis is carried out by adding isotopic mass tracers to solutions of the elements to be measured, effecting or allowing isotope exchange between the tracers and indigenous elements, recovering the elements on a few resin beads, and measuring the ratio of indigenous-to-tracer atoms on a single resin bead in a mass spectrometer by thermally ionizing and counting the atoms. Validity of the method is assured if isotope exchange occurs and interferences are small. Low limits of detection are favored by high recovery of the elements on the beads and low backgrounds of the elements measured. Previous studies indicated that this method will detect about 0.2 pg of uranium and 0.002 pg of plutonium in one milliliter of water (Ca80). Thus the sensitivity for these elements seemed more than adequate for bioassay measurements. Although the sensitivity for thorium was not so well established, it too was believed to be adequate.

One of the goals of this study was to evaluate the method for analysis of uranium in urine at or below the level of 0.1 µg/L. Because it was known (Wa74) that resin beads containing a sizable fraction of one nanogram of uranium could be analyzed with high accuracy and precision, it was decided that 10 mL of urine would likely be a suitable sample size. This volume with a uranium concentration of 0.1 µg/L would contain one nanogram, and if a sizable fraction of the uranium could be recovered and loaded on a few beads, the analysis could be made with good accuracy and precision. Thus, it was necessary to select and test a procedure that would effectively separate the uranium from urine. After consideration of both solvent extraction and ion exchange procedures described in the literature (Co65, Gr63), a method based on anionic ion exchange that had been used by Dupzyk and Dupzyk (Du79) was selected. Modifications to the method that permit its use with thorium and plutonium will be discussed later in this section.

It should be noted that because of the effects of dilution, interferences, and other factors caused by the macro inorganic constituents of urine such as NaCl and KCl, it is not possible to directly measure uranium and other elements at similar trace levels by thermal ionization mass spectrometry. Such measurements can only be effected if the uranium is isolated and concentrated into a small sample such as a resin bead. The carbon matrix formed from the resin bead prior to actual uranium ion measurements does not present an interference in the measurement.

As applied to uranium, a 10-mL sample of urine is made 8 M in hydrochloric acid and after a mass tracer is added, is allowed to stand

overnight. Following this period, the uranium is adsorbed on an anionic resin column pretreated with 8 M HCl. The column is washed with 8 M HCl, and the uranium is removed from the column with 0.1 M HCl. The resulting solution is evaporated and the uranium is dissolved in a small volume of 8 M HCl (∿1/2 mL) which is equilibrated with 2-3 anionic resin beads. These beads are then mass analyzed for uranium isotopes. This method is referred to in this report as the normal method of analysis and is outlined schematically in Figure 4.1. The method appears to have several advantages over other methods that might be similarly applied. The method makes use of only two reagents, HCl and anion resin, and employs a minimum of simple glassware and throwaway plastic labware. The method is therefore simple and economical to use. Because of its simplicity and the minimum exposure of the solutions to labware surfaces and the atmosphere, the method is expected to have as low a uranium background as might be attained with any other separation scheme. The importance of the uranium background in determining the detection limit of uranium (or thorium) is discussed in Section 4.2.

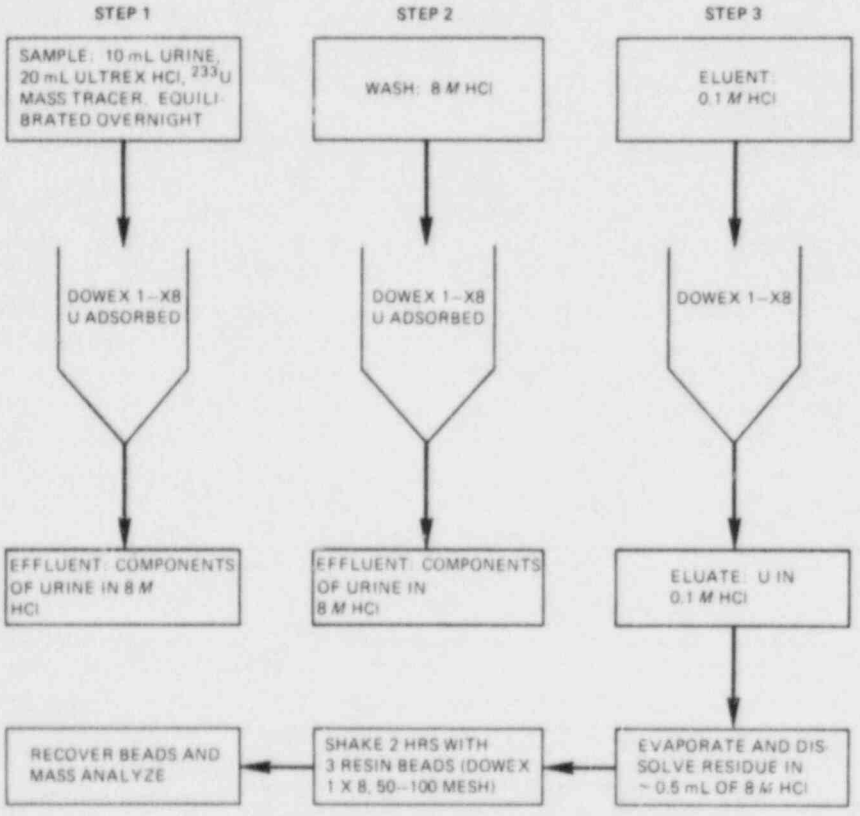

Figure 4.1 Schematic Representation of IDMS Method for Determination of Uranium.

The period that the solution stands prior to the separation step serves to allow isotope exchange to be completed between the added mass tracer and the indigenous uranium. It should be noted that the separation of uranium from urine is accomplished by many published methods after the organic components of the urine are destroyed by oxidizing acids. The present method breaks with that tradition. The possibility exists that the organic components will tie up the uranium in one or more non-labile complexes and/or compounds and thus prevent isotope exchange as well as reduce the chemical yield of the method. Such detrimental effects of the organic components were investigated experimentally.

Partway into this study, it was decided to try to eliminate the chemical separation step of the procedure in the normal method and make the final loading of the resin beads directly from urine acidified to 8 M in hydrochloric acid. This procedure is referred to as the direct bead-loading method and is based on the same chemical principles as the normal method. The direct bead-loading method is discussed in Section 4.7 where results of analyses of urine and synthetic urine samples with uranium concentrations somewhat above one microgram per liter are presented. The direct bead-loading method appears to represent the ultimate in simplicity, efficiency, and economy in the preparation of resin beads for IDMS. Its application to the determination of uranium down to levels below one microgram per liter was not demonstrated.

Modifications of the normal method were made to analyze urine samples for thorium and plutonium. Thorium exists in aqueous media only as the comparatively small highly charged ion Th^{+4}. The ion does not form strong anion complexes with the chloride ion and thus is not adsorbed from HCl solutions on anion resin columns (Hy60). However, anions are formed with nitrate ions, and strong adsorption is obtained on anion columns from solutions that are 7-8 M in nitric acid. The normal method described above for uranium was modified by substituting nitric acid for hydrochloric acid. Results obtained for analysis of urine samples for thorium are presented in Section 4.8.

Plutonium can exist in aqueous solutions in the +3, +4, +5, and +6 oxidation states. All but the +3 oxidation state are strongly adsorbed on anion exchange resins from strong hydrochloric acid solutions. In this work, Pu-239 in the +4 oxidation state was added to urine and measured by IDMS after the mass tracer Pu-242, also in the +4 state, was added. The +4 oxidation state was maintained by the addition of a small amount of HNO_3 as indicated in the procedure described in Section 3.3.1 of this report. In many of the experiments in which uranium was determined, Pu-242 was added to the urine or synthetic urine samples and its ion current (ion counts) in the mass spectrometer was observed to get a measure of the adequacy of the chemical yield for plutonium. These experiments often indicated that the normal method of analysis for uranium, as described above and outlined in Section 3.3.1, did not produce adequate ion currents due to the low chemical yield obtained in

eluting the Pu+4 from the resin column. To obtain adequate recovery of the plutonium, it was necessary to add a small amount of HF to the dilute HCl used to elute the uranium. The results of analyses of urine samples to which plutonium was added are presented in Section 4.8.

It must be emphasized that urine samples containing indigenous plutonium were not measured in this work. Because of the possibility that plutonium might exist in urine in multiple oxidation states, steps would have to be introduced into the procedure to ensure that all plutonium ions are adjusted to the same oxidation state to ensure isotope exchange and proper behavior of the plutonium in the other steps of the procedure.

4.2 Background Measurements and Effect on Detection Limit

The measurement of background is a necessary part of an analytical procedure and serves several important functions in the successful application of the procedure. If the results of background measurements are high with respect to the desired detection limit of the procedure, then the procedure must be changed to decrease the background and meet the needs of the measurements. If the background is unduly erratic, then a lack of contamination or interference control is indicated that must be brought under control. If the background is in control and satisfactorily low, then the results of background measurements can be used to correct for measurement bias that is caused by the background. Even when contamination is well controlled, the background will limit the level at which a measurement can be reliably made.

In this study the term background refers to the uranium or thorium concentration that was observed when a blank sample was analyzed using only the reagents HCl, water, and ion exchange resin without the addition of urine or synthetic urine.* The results of such measurements are often referred to as reagent blanks, but more properly should be called procedural blanks since they include contamination from the walls of containers, ion exchange columns, and the atmosphere as well as instrument background. Background can thus be influenced by many factors including types of reagents used, the degree to which reagents and water are purified, the extent to which labware is cleaned and the degree of protection from ambient contamination that is afforded by the laboratory. Investigations of background control and diminution are an important part of analytical chemistry, and published papers dealing with the purification of acids (Ku72) and the design of low-level laboratories, "clean rooms", (Fs66, Mo82) are exemplary of such studies. Mitchell (Mi82) recently summarized the state of the art in

*Although plutonium is present in the environment as a result of weapons testing (Si83), it is not present in detectable amounts in reagents or cleaned laboratory equipment.

contamination control. In some cases it is possible to measure the various sources of the background as was done recently by Kelly and Fassett (Ke83).

Procedural blanks for uranium were measured in this study by substituting "purified water" for the sample which otherwise would be urine or synthetic urine. It was necessary to use water as a sample substitute to carry out the chemical separation on ion exchange resin in 8 M HCl. The water was processed using all the other reagents as described in Section 4.1. Initially, separations were made in a conventional low-level radiochemical laboratory, rather than the special low-level laboratory referred to in Section 3.1, and the purified water consisted of singly-distilled water further purified with ion exchange resins. Water purified in this manner is normally designated as deionized water. Standard practices of cleanliness were used to ensure low levels of uranium contamination. Levels of uranium observed, when four samples consisting of 10 mL of deionized water and 20 mL of Ultrex HCl were analyzed, showed an average concentration of 0.80 µg/L and a standard deviation of 0.26 µg/L. Based on these results, it was clear that much more stringent control of the uranium contamination would have to be made if accurate analysis below the 0.1 µg/L level were to be realized.

Subsequently, all operations were shifted to the low-level laboratory described in Chapter 3, and the use of triply distilled water prepared with a quartz still, and other precautions described in Section 3.1 and 3.2 to lessen uranium contamination were instituted. Uranium blanks measured under these new conditions using 10 mL of the triply distilled water and 20 mL of Ultrex HCl are listed for 10 samples in Table 4.1. The average of these results, expressed as concentration, was 0.030 µg/L. The standard deviation was found to be 0.0047 µg/L. Comparison of the these results with those found previously indicated that the more stringent control of uranium contamination sources lowered the average blank by a factor of about 30 and the standard deviation by a factor of about 50. The range of blank values measured on the various dates, which are given in Table 4.1, tend to overlap thus indicating no systematic variation of blank levels with time.

The mean of the blank values given in Table 4.1 was used to correct for background in analyses of urine samples. In addition, the results were employed to estimate a detection limit for uranium as measured by this procedure. Because the background is variable, it is necessary to make use of simple statistical concepts in arriving at a detection limit. The statistical principles and the concept of the detection limit have been described by Currie (Cu68, Ko78), Long and Winefordner (Lo83), Watson (Wa80), and others (AC80, CS78). Currie's treatment of the concept of detection limit and associated statistical ideas are followed in this report in establishing a detection limit for uranium.

Table 4.1 Procedural Blanks Observed for Uranium

Sample	Date of analyses	Concentration (µg/L)
1	2-9-83	0.036
2	2-9-83	0.028
3	2-14-83	0.039
4	2-14-83	0.023
5	2-22-83	0.028
6	2-23-83	0.027
7	2-23-83	0.029
8	2-23-83	0.026
9	2-23-83	0.029
10	3-17-83	0.031
Mean		0.030
Standard Deviation		0.0047

As Currie has shown, the detection limit LD for the net concentration (gross-background) can be written as

$$LD = k\sigma_B$$

where σ_B is the standard deviation of the blank based on a large number of measurements, and k is a constant whose value is determined by the "statistical reliability" chosen for the detection. It is worthwhile to point out that the detection limit discussed by Currie is an a priori level that balances the detection capability of the procedure against the probability of nondetection. If the level is set too high detection would always be assured, but the detection capability of the procedure would not be realistically expressed. If the level is set too low then the power of the procedure will appear to be great, but the frequency of nondetection will be excessive. Normally, the value of LD is chosen (by choosing the value of k) so that the probability of nondetection is about 0.05 when the concentration is actually LD. It can be shown using this criteria and principles developed by Currie, that the detection limit derived from the data of Table 4.1 can be expressed as

$$\begin{aligned} LD &= 4.65(0.0047) \\ &= 0.02\ \mu g/L. \end{aligned}$$

Thus, an approximate detection limit of 0.02 µg/L for uranium is established from the blank measurements. The meaning of this limit is that given a solution of 10 mL H_2O plus 20 mL Ultrex HCl with a true net concentration of 0.02 µg/L, the present analysis procedure would detect the presence of uranium about 95 percent of the time. Five percent of the measurements would fail to detect this level.

The detection limit estimated above in no way indicates the ultimate capability of IDMS to measure uranium but merely reflects the contamination levels of uranium that were experienced when the blank measurements were made. It should be remembered, however, that these levels of contamination were obtained after a considerable effort was made to reduce contamination and in this context may reflect what many laboratories would obtain with a similar effort of contamination control. The detection limit could, of course, be greatly lowered if the analysis were carried out with a much greater effort to decrease and control contamination. The recent IDMS measurements by Kelly and Fassett (Ke83) demonstrate that procedural blanks can be lowered to a few picograms of uranium if analysis are made in class 100 clean rooms and reagents of extreme purity are employed. Such attainment is purchased at added expense and with an increase in time required to do the analysis.

Currie also defines a net determination limit, LQ, which is the lowest concentration that can be measured with a relative standard deviation of 10 percent. Again, the determination limit is estimated from the standard deviation of the procedural blank and is given by

$$LQ = 14.1\ \sigma_B$$
$$= 14.1(0.0047)$$
$$= 0.07\ \mu g/L.$$

We therefore estimate from the procedural blank data of Table 4.1 that the uranium in 10-mL samples having a net concentration of about 0.07 µg/L could be determined with a relative standard deviation of 10 percent.

Although the normal method of analysis used in this study employed 10 mL of urine or synthetic urine, it was necessary in some instances to analyze smaller samples. In such cases usually one or two mL were analyzed. Consequently, blanks were also measured using the following reagents: 1) one mL of triply-distilled water combined with two mL of Ultrex HCl and 2) three mL of Ultrex HCl. The Ultrex HCl was used directly without dilution with water. These analyses were made using a resin column preseparation as described for the normal analysis method of Section 3.2.1. In addition, a 1.0-mL sample of Ultrex HCl was analyzed by the direct bead-loading procedure described in Section 3.4 and discussed in Section 4.7. The results of these analyses are given in Table 4.2. The quantity of uranium observed was essentially the same for all small-sample blanks regardless of the quantity of HCl or water used and was slightly less than half of the total uranium observed in the large-sample blanks described above. The small-sample blanks indicate that by the use of either the normal or direct bead loading methods there is a residual level of uranium contamination that could not be eliminated and must be due to some constant features of the two methods. Features that were constant in all experiments (including the large-sample measurements) were the final 2-3 resin beads used in the final bead loading, the U-233 mass tracer (6.56 ng was used in all measurements) and the mass spectrometer instrument background. As indicated in Section 3.2, the mass tracer contained far too little U-238 to account for the small-sample residual blank. Tests also showed that the instrument background would not account for the blank. The resin beads were analyzed for U-235 by delayed neutron counting. After the observed U-235 was converted to an equivalent amount of natural uranium, it was found that the estimated U-238 was far too low to account for the measured blank when 1 mL of Ultrex HCL was analyzed by direct bead loading. Thus, no one source for the blank could be found, and the conclusion was drawn that this blank arose from a combination of these components and/or pickup from containers or dust from laboratory air.

4.3 Chemical Yield

Chemical yield refers to the fraction of uranium, thorium, or plutonium that is recovered in either the separation on the ion exchange column or the adsorption on the resin beads in the final bead-loading step. The overall chemical yield is the fraction of these elements in ehe urine that is recovered on the final beads that are analyzed. In

Table 4.2 Quantities of Uranium Observed in Small-Sample Blanks

Solution	Method	Sample		Uranium Observed (ng)
1 mL H_2O + 2 mL HCl	Normal[a]	1		0.09
		2		0.12
		3		0.21
			Mean	0.14
			SD[b]	0.062
3 mL HCl	Normal	1		0.12
		2		0.16
		3		0.18
			Mean	0.15
			SD[b]	0.030
1 mL HCl	Direct Bead Loading[c]	1		0.15
			Overall Mean	0.15
			Overall SD[b]	0.041

[a]Normal method denotes method in which a preseparation of uranium was made on resin column

[b]SD denotes sample standard deviation

[c]Direct bead-loading method described in Section 3.5

most chemical analysis procedures, it is necessary to determine the yield, because it is used in the calculation of the quantity of the substance that is measured. However, in isotope dilution methods, including IDMS, it is unnecessary to know the yield. The quantity of analyte, e.g. uranium, is calculated from the amount of U-233 mass tracer added to the sample and the ratio of the ion counts of U-238 to U-233. Thus the chemical yield does not enter into the calculation. This simplifying feature is, of course, one of the strong points of isotope dilution methods. All that is required in IDMS is to separate and recover sufficient amounts of the original element to have acceptable counting statistics for the measured ions. It should be noted, however, that acceptable counting statistics are obtained in the shortest possible time, and the analysis is made most efficiently, if the yield is maintained as high as possible. If the yield is too low, it may not be possible to obtain acceptable counting statistics, and as a result it may be necessary to alter the procedure to improve the yield. Thus it is important to know the yield even though it is not used directly to calculate the quantity of the element measured.

In this study, the yields of uranium and thorium in both the column separation and the bead loading step were measured. The yields were measured by alpha counting the mass tracer U-233 (for uranium) and Th-230 (for thorium) to determine the quantity of tracer in the solutions before and after each of the separation steps. In the bead loading step, the quantity of tracer on the beads was determined by burning the beads on an alpha counting plate and then counting the plate. Bead loading was carried out by shaking three beads in the small volume of solution for two hours.

Measured chemical yields are listed in Table 4.3. As can be seen, the measured yields for uranium and thorium in the column separation as well as in the bead loading step were similar, running near 70 percent for the column separation and near one percent for the bead loading step. Since the overall yield is the product of the separate yields, the overall yield lies in the range of 1/2 to 1 percent.

It is instructive to calculate the yield of the bead loading step by making use of published values of the distribution ratio. When the quantity of uranium or thorium ions in solution is in chemical equilibrium with that on the resin bead(s), one can write the distribution ratio K_d as

$$\frac{M_r/V_r}{M_s/V_s} = \frac{M_r/V_r}{(M_s^1-M_r)/V_s} = K_d$$

Table 4.3 Chemical Yields for Separation of Uranium and Thorium

Element	Solution	Solution Volume (mL)	Procedure	Yield Observed (%)	Yield Calculated[a] (%)
Uranium	Urine + HCl	10.	Column Sepn.	68	
Uranium	8 M HCl	0.2	Bead Loading	1.2	2-14
Uranium	8 M HCl	0.2	Bead Loading	2.5	2-14
Thorium	Urine + HNO_3	10.	Column Sepn.	65	
Thorium	8 M HNO_3	1.0	Bead Loading	0.68	0.08-0.7
Thorium	8 M HNO_3	1.0	Bead Loading	0.70	0.08-0.7
Thorium	8 M HNO_3	0.3	Bead Loading	2.1	0.3-2.2
Thorium	Urine + HNO_3	0.3	Bead Loading	1.5	0.3-2.2

[a]The range of calculated yields are for beads that have a range of diameters of 200-400 μm.

where M denotes the quantity of metal ion, V denotes volume and the subscripts r and s refer to the resin and solution respectively. The quantity M_s' denotes the amount of the ion in the solution before the resin beads are introduced. Solving for the chemical yield in the equation above, we have

$$\frac{M_r}{M_s'} = \frac{V_r Kd/V_s}{1 + V_r Kd/V_s}$$

This equation was used to calculate the yield per bead for the volumes of bead-loading solution given in Table 4.3. For the system U-HCl-Dowex 1, the published value of K_d is approximately 1000 (Gr62), and for the system Th-HNO_3-Dowex 1, K_d is approximately 200 (Hy60). At the time that yields were measured, we did not determine the sizes of the individual beads and thus cannot compute yields directly. However, we later measured a large number of beads and found their diameters to lie in the range 200-400 μm. The yield was therefore calculated for beads of these diameters and is given in Table 4.3, as a yield range corresponding to this diameter range. As can be seen in Table 4.3, the measured yields, essentially agree with the calculated yield range. Thus, it seems likely that chemical yields can be adequately estimated from the known chemical equilibrium between solution and resin.

The overall chemical yield for U and Th in most of the analyses made in this study was approximately one percent. Since the quantity of U-233 mass tracer used in all analyses was 6.56 ng, the amount on each bead was about 0.06 ng. From the equation above, it is clear that high yields are favored by small volumes of solution. Reducing the volume of bead-loading solution appears to offer a promising approach to improving the sensitivity of the method, provided that the contamination background can be reduced. Very high yields can apparently be obtained by evaporating the solution in the presence of the beads as was done by Kelly and Fassett (Ke83). It is likely that since the distribution ratio of plutonium in the system Pu(IV)-HCl-Dowex 1 is about 7000 (Co65), the yield for plutonium should be much larger than for uranium and thorium.

4.4 Verification of Isotope Exchange

By isotope exchange is meant the chemical exchange of the isotopes of the added mass tracer with the isotopes that are either indigenous to the sample or those that have otherwise been added. Thus, after isotope exchange occurs, the isotopic composition of the analyte element (uranium, thorium, or plutonium) in all chemical forms in the sample will be equal. Isotope exchange is necessary because unless it occurs, the added mass tracer may behave differently from the rest of the element in the chemical separations, and invalid analyses will be obtained. Isotope exchange may either fail to occur or may be slowed

if the indigenous portion of the element exists either in a valance state that is different from the tracer or in a nonlabile form, i.e., a form that does not disassociate in a dynamic chemical equilibrium. Plutonium, for example, may exist in acidic aqueous solutions as Pu(III), Pu(IV), and Pu(VI). Depending on the types and amounts of complexing agents that may be present, the chemical exchange of atoms with one of these oxidations states with atoms of another may be slow and difficult to attain. Thus, nearly always in the chemical determination of plutonium (even without an isotopic tracer), chemical treatments are carried out to ensure that all plutonium atoms are in the same oxidation state. A review of the chemistry of plutonium in which methods for the adjustment of oxidation states are given has been published by Coleman (Co65). In this work, urine samples were not analyzed for indigenous plutonium but were analyzed for Pu-239 that was added in the same chemical form as the Pu-242 mass tracer. As indicated in Section 3.3.1, a trace of nitric acid was added to the urine samples acidified with HCl to keep the plutonium in the form of Pu(IV) to maximize the adsorption of plutonium on the anion column.

Unlike plutonium, thorium exists in aqueous media in only the +4 oxidation state. Thus, only if the thorium indigenous to urine were tied up in a nonlabile compound would there be a possible hinderance to the attainment of isotope exchange with the added mass tracer. The occurrence of such compounds seems unlikely.

Although uranium can exist in aqueous media in the +3, +4, +5, and +6 oxidations states, the +4 and +6 state, are the only ones stable enough to be of practical importance in analytical separations (Be81, Gr62). Since the +4 oxidation state readily oxidizes to the +6 state in the presence of oxygen, the latter oxidation state is usually the only form encountered in uranium solutions. In aqueous solutions the +6 oxidation state of uranium is present as the uranyl ion UO_2^{+2}. It is likely that uranium is present in urine as the uranyl ion most of which would be combined as complexes or compounds with the many anions that are present.

In this work, both indigenous uranium and added uranium were determined in urine that was allowed to stand overnight following the additions of the mass tracer and enough hydrochloric acid to make the solutions 8 M in HCl. Although it does not seem likely that a nonlabile form of uranium would exist and inhibit isotope exchange under these conditions, it was considered prudent to experimentally demonstrate the occurrence of isotope exchange. Demonstration of isotope exchange was done by analyzing a sample of urine that had been shown by an independent analytical method to have an elevated level of indigenous uranium. Aliquots of the urine were analyzed by the normal method as described in Section 3.3.1 and by a similar procedure after the organic constituents of the urine were chemically destroyed. Destruction of the organic components was accomplished by repeatedly heating and evaporating samples to which nitric and perchloric acids

were added. Samples of this urine were also analyzed by the direct bead-loading method described in Section 3.4. Results of these analyses are given in Table 4.4.

As can be seen in Table 4.4, the uranium concentration observed in the urine after chemical destruction of the organic compounds agrees closely with the concentrations measured without destructive treatment. The mean concentration found with chemical destruction was about two percent higher than the mean observed without chemical destruction. The mean of observed values obtained by the direct bead-loading procedure was about three percent lower than the mean obtained by the normal separation method. When the results were statistically compared by taking into account the standard deviations obtained for the three procedures, no significant differences were found among the three results. Thus, no evidence was obtained in these measurements to indicate that the components of urine influenced isotope exchange.

4.5 Synthetic Urine Analysis

A conventional and useful means of assessing the accuracy of a chemical measurement procedure is to analyze samples that both simulate real samples and have known quantities of the element or compound to be determined. Most useful are standard reference materials (SRMs) that contain certified quantities of the element. In the case of urine no SRM exists, and it was considered neither worthwhile nor desirable to modify the present procedure to measure uranium in other types of SRMs that have certified concentrations of uranium. Nevertheless, it was considered necessary to analyze urine or synthetic urine with known uranium concentrations. It was decided that analyses would be made of samples of human urine prepared by adding known amounts of natural uranium. The results of analysis of such samples and their implications regarding the accuracy and precision of IDMS measurements of uranium in urine are discussed in Section 4.6 of this report.

In this section, results of analyses of a synthetic urine matrix and a sample of the matrix that was spiked with natural uranium at the level of 7.024 µg/kg are presented. Both samples were supplied by D. R. Fisher and A. V. Robinson of the Battelle Pacific Northwest Laboratory. The samples were prepared by PNL for use in a laboratory testing program that serves as a guide to the development of a standard, ANSI 13.30, "Performance Criteria for Radiobioassay". The ANSI standard which is being written by Committee WG 2.5 of the Health Physics Society and which has appeared in a draft form will eventually serve as a basis for certifying bioassay laboratories. The chemical composition of the synthetic urine samples are listed in Section 3.2 of this report. The natural uranium used to spike the synthetic matrix was standarized and supplied to PNL by the National Bureau of Standards.

Table 4.4 Uranium Levels in Human Urine Analyzed for Isotope Exchange Verification

Sample	Method	Sample vol. (mL)		Net Uranium Concentration[a] (ug/L)
Urine	Normal separation	1		2.86
Urine	Normal separation	1		2.81
Urine	Normal separation	1		2.78
			Mean	2.82
Urine	Destructive	1		2.81
Urine	Destructive	1		2.94
Urine	Destructive	1		2.88
			Mean	2.88
Urine	Direct loading	0.5		2.81
Urine	Direct loading	0.5		2.68
			Mean	2.74

[a]Values tabulated were corrected for procedural blank of 0.15 µg/L.

Both the blank synthetic and the spiked synthetic were analyzed to assist in the evaluation of the accuracy and precision of analyses. Five 10-mL aliquots of the blank synthetic were analyzed according to the normal procedure described in Section 3.3.1. The results showed a mean concentration of 0.022 µg/L and a standard deviation of 0.0017 µg/L. Since all of the observations were below the procedural blank mean listed in Section 4.2, it is concluded that no evidence for the presence of uranium was found.

Five 1.00-mL aliquots of the spiked synthetic were analyzed by adding 2 mL of Ultrex HCl and by following the procedure of Section 3.3.1. The observed uranium concentrations, listed in Table 4.5, agreed very well with the specified concentrations of 7.024 µg/kg of solution. Since the specified concentration was given on a weight basis, we measured the density of the synthetic urine and found a value of 1.0299 kg/L which was then used to change the standard value to a volume basis. As can be seen in Table 4.5, the mean uranium concentration was 6.98 µg/kg. The standard deviation was 0.061 µg/kg which was 0.87% of the mean. The mean was 0.6% below the specified concentration as indicated. Thus, it was experimentally demonstrated that the present IDMS method can be used to accurately determine uranium in the synthetic urine matrix at the level of 7 µg/L. No difficulty in the procedure, e.g., in attaining isotope exchange of the U-233 mass tracer with the natural uranium of the sample, was experienced.

4.6 Human Urine Analysis

In evaluating the precision and accuracy of our method we attempted to answer the following questions. What minimum concentration of uranium in human urine can be detected by IDMS? What minimum concentration can be measured with a stated uncertainty - the determination limit? What degree of uncertainty is associated with analyses at concentration levels above the determination limit?

In the study of the procedural blank in Section 4.2 it was estimated from results based on the analysis of 10-mL samples of triply distilled water that net concentrations as low as 0.02 µg/L could be detected 95% of the time and that concentrations of 0.07 µg/L could be measured with a relative standard deviation of 10 percent. In work with human urine, we attempted to ascertain how well these predictions hold.

To answer these questions, we prepared a calibration curve by analyzing samples of urine to which known quantities of natural uranium were added. Samples were prepared at three concentration levels: 0.0873, 0.436, and 3.49 µg/L. Four samples at each level along with four samples of the blank urine were analyzed. Each sample was prepared by pipetting 10 mL of the blank urine into a 50-mL beaker to which was then pipetted the required amounts of solutions containing the natural uranium as well as the mass tracer U-233. The samples were then analyzed according to the procedure described in Section 3.3.1. It

Table 4.5 Uranium Observed in Synthetic Urine Spiked with Natural Uranium[a]

Sample	Total (ng)	Net concentration (µg/L)	Net concentration (µg/kg)[b]
1	7.40	7.25	7.04
2	7.39	7.24	7.03
3	7.35	7.20	6.99
4	7.32	7.17	6.96
5	7.25	7.10	6.89
Mean	7.34	7.19	6.98
Standard Deviation			0.061
Relative Standard Deviation			0.87%
Bias			-0.6%

[a]Spiked sample was obtained from Battelle Pacific Northwest Laboratory; one-mL aliquots were analyzed. Blank value of 0.15 µg subtracted from total.

[b]Calculated using measured density of 1.0299 kg/L.

should be noted that the urine specimen used in the preparation of these samples had been shown in previous measurements to have a uranium concentration barely above the detection limit derived from the procedural blank measurements as given in Section 4.2. The uranium concentrations observed in the blank urine and in the other samples at the three levels of added uranium are listed in Table 4.6. We will refer to the samples containing added uranium as the altered samples and the concentrations produced by the added uranium as the added concentration.

The question of whether or not uranium was detected in the blank urine was addressed initially. As can be noted in Table 4.6, the mean of the observed uranium concentrations are tabulated for all samples along with net concentrations obtained by subtracting backgrounds from the mean of the measured values. Background for the blank urine was taken as the procedural blank mean, 0.030 µg/L, given in Table 4.1. The mean of the observed concentrations, is 0.062 µg/L, and the net concentration is 0.032 µg/L for the blank urine. As explained by Currie (Cu68), the results of a measurement indicates probable detection if the net concentration exceeds one-half of the detection limit discussed in Section 4.2. From Section 4.2 we note that one-half of the detection limit is estimated to be 0.01 µg/L. Since the net concentration is larger than one-half of the detection limit, we conclude that uranium was detected in the blank urine. An alternate, but somewhat related, method of deciding if uranium was detected is to make the decision based on a 95 percent confidence interval on the net concentration of uranium in the blank urine. Here we use the interval based on Student's "t" statistics. This interval is given in Table 4.6 as 0.007 to 0.043 µg/L. Since this interval lies above zero we conclude that uranium was detected. It therefore seems assured that the uranium level observed in the blank urine is significantly above the procedural blank. In other words, uranium was detected. The uncertainty of the net result is indicated by a relative standard deviation of 22 percent given in Table 4.6.

Considering now the analyses of the altered urine samples, we note that the observed uranium concentration should equal the sum of the added concentration and the concentration of uranium that was observed for the blank urine. Thus, if we subtract the concentration observed for the blank urine from the concentrations observed for the altered samples, the value should closely approximate the added concentration. As can be seen, net concentrations which are given in Table 4.6 agree well with the added concentrations. The difference between net concentrations and added concentration represents a bias that is indicative of the accuracy of the analysis. Bias values are tabulated in Table 4.6 as percent of the added concentrations. As can be seen the largest percentage bias, -6.1%, was found for those samples having the lowest uranium level of 0.082 µg/L. The bias at level 2 was 1.1%; the bias at level 3, 3.4%, was somewhat larger than expected.

Table 4.6 Observed Uranium Concentrations in Human Urine Spiked with Natural Uranium.

	Observed Uranium Concentration, µg/L			
Sample	Blank Urine	Level 1 (0.0873 µg/L)	Level 2 (0.436 µg/L)	Level 3 (3.49 µg/L)
1	0.058	[a]	0.490	3.64
2	0.064	0.144	0.527	3.63
3	0.058	0.148	0.494	3.73
4	0.069	0.141	0.502	3.67
Mean	0.062	0.144	0.503	3.65
Net Concentration	0.032[b]	0.082[c]	0.441[c]	3.61[c]
Standard Deviation	0.0071	0.0063	0.018	0.045
RSD(%)[d]	22	7.7	4.0	1.2
Bias (%)	-----	-6.1	1.1	3.4
95% Confidence Interval[e]	0.007-0.043	0.074-0.090	0.419-0.463	3.53-3.64

[a]Experimental problems invalidated this measurement.
[b]Net concentration equals observed mean-0.030 (procedural blank).
[c]Background taken as mean of blank urine values.
[d]Standard deviation relative to net concentration.
[e]Interval applies to net concentration.

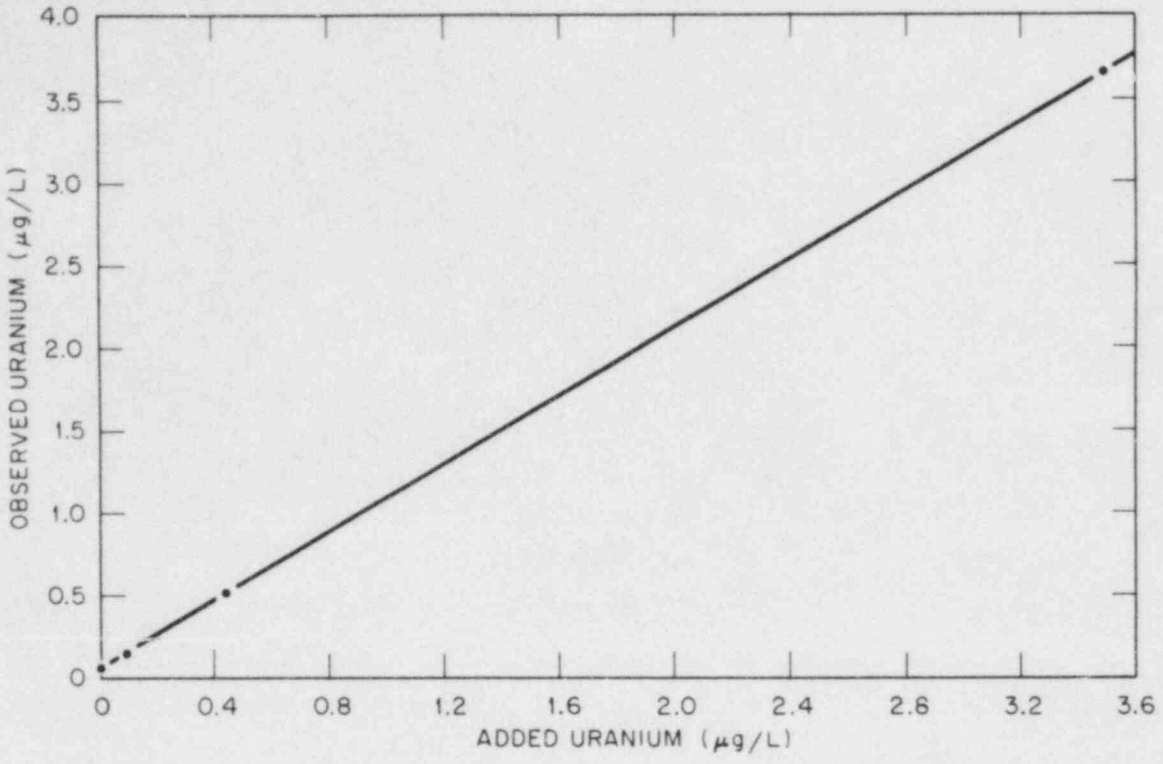

Figure 4.2 Calibration Curve of Observed Versus Added Uranium in Human Urine.

The overall precision of the analysis is indicated by the relative standard deviations (RSD) given as percentages in Table 4.6 and illustrated by the calibration curve shown in Fig. 4.2. The RSD's were calculated by dividing the standard deviation of the net concentration by the net concentration. Values of the RSD range from about 20 percent for the blank urine to slightly over one percent for the level 3 samples whose net uranium concentration was 3.61 μg/L. Samples of level 1 had a net uranium concentration of 0.082 μg/L and an RSD of 7.7 percent; the corresponding quantities for level 2 were 0.441 μg/L and 4.0 percent. We note therefore that a net concentration somewhat below 0.08 μg/L (~0.06 μg/L) would have a relative standard deviation of 10 percent and represent a determination limit LQ as defined by Currie. Thus, from the measurements on the altered urine samples, a determination limit of ~0.06 μg/L is estimated, which is in good agreement with the value 0.07 μg/L that was derived from the procedural blank measurements discussed in Section 4.2.

The calibration curve of Figure 4.2 is a plot of observed versus

added uranium concentration. The high precision of the analyses is illustrated in the plot by the fact the diameters of the data points at each of the levels of added uranium was made approximately equal to the 95% confidence interval for that level.

The conclusions drawn from the measurements of uranium in the procedural blank and in urine are summarized as follows: (1) a net measured concentration in excess of 0.01 μg/L should be regarded as a positive detection, (2) the normal analysis method would nearly always detect uranium in the range of 0.02-0.03 μg/L and (3) concentrations as low as 0.06-0.07 μg/L can be measured with good accuracy and precision; the relative standard deviation would be about 10 percent.

4.7 Analysis by Direct Bead Loading

In Section 4.1 it was pointed out that because of the large quantities of other inorganic constituents in urine, e.g., NaCl, KCl, etc., uranium at the parts per billion level cannot be measured directly by thermal ionization mass spectrometry. Some degree of chemical isolation of the uranium is necessary before it can be observed. The extent of th chemical isolation required is, however, not known. We therefore began this investigation in a conservative manner by making a preliminary separation of uranium from urine by adsorbing the uranium on an anionic resin column, washing most of the other constituents from the column and then eluting the adsorbed uranium from the column. Using this preliminary separation, we obtained a small volume of solution relatively free of other inorganic materials that can then be used to load resin beads with uranium for mass spectrometry measurements. The merits of this procedure, which is the first step in what we refer to as the normal method, is that it isolates the uranium from a relatively large volume and concentrates it into a small volume.

Partway into this study, it appeared that such an extensive preliminary isolation of uranium might be unnecessary. In fact, since the most abundant cations in urine do not adsorb on anion resin from highly acidic solutions, it seemed possible that the final loading of the resin beads might be done directly from urine acidified to 8M with hydrochloric acid. We refer to this procedure as a direct bead-loading method. Although we were unable to study this method extensively we did manage to analyze two human urine samples and the spiked synthetic urine described in Section 3.5. The measured uranium concentrations are given in Table 4.7. For comparison, concentrations observed in these samples by the normal method are also presented along with mean values obtained by each method. Also given are the differences, in percent, between the results found by the two methods. (The two urine samples had been analyzed by independent methods prior to these measurements, and although the levels of uranium were known only roughly, they were expected to be elevated above normal levels.) As can be seen in Table 4.7, the uranium concentrations found by the direct-loading method differed from those observed by the normal method

Table 4.7 Comparisons of Uranium Concentrations Measured by Direct Bead Loading and Normal Method

Sample	Method	Volume Analyzed (mL)	Net Concentration (µg/L)[b]
Spiked Synthetic[a]	Normal	1.00	7.19[c]
Spiked Synthetic[a]	Direct Loading	0.500	7.04[c]
		0.500	7.13[c]
		Mean	7.09
		Difference(%)[d]	-1.3
		Bias(%)[e]	-1.9
Urine A	Normal	1.00	2.86
		1.00	2.81
		1.00	2.78
		Mean	2.82
Urine A	Direct Loading	0.500	2.81
		0.500	2.68
		Mean	2.74
		Difference(%)[d]	-2.8
Urine B	Normal	1.00	8.25
		1.00	8.31
		1.00	8.30
		Mean	8.29
Urine B	Direct Loading	1.00	8.09
		0.500	8.13
		Mean	8.11
		Difference(%)[d]	-2.2

[a]Specified concentration is 7.23 µg/L.
[b]Values tabulated have been corrected for blank of 0.15 µg.
[c]Values reported in Table 4.5
[d]Difference computed by expression: 100 (Normal Method Value-Direct Method Value)/Normal Method Value.
[e]Bias applies to direct-loading method value.

by only about 1-3 percent. For the spiked synthetic urine, specified to contain 7.23 µg/L on a volume basis, the concentration observed by the direct loading method was 7.09 µg/L - a bias of 1.9 percent. It should be noted that the procedural blank for the direct-loading method was assumed to be the same as the small sample blank of the normal method, 0.15 µg/L, given in Section 4.2.

Based on the rather good agreement of the results of the direct-loading method with the specified concentration of the synthetic urine and with the results of the normal method, it appears that the direct-loading method offers considerable promise for the measurement of uranium in urine. The direct-loading method has several significant advantages over methods in which the uranium is isolated before the beads are loaded. Because no preseparation of the uranium is made, the direct-loading method is very simple to use and can be applied much more efficiently and economically. Since the sample is contacted by only one small container, and only a small amount of high-purity hydrochloric acid and two or three resin beads are added to the sample, it may be possible to significantly lower the procedural blank. In addition, it may be possible to carry out analyses by the direct loading method in normal laboratory environments, without the use of clean rooms, and still maintain very low procedural blanks.

A possible disadvantage of the method is that it may not have sufficient sensitivity for determining uranium at sufficiently low concentrations. Since the amount of uranium that is adsorbed on two or three resin beads is governed by a dynamic chemical equilibrium, as discussed in Section 4.3, and depends on the ratio of the volumes of the resin beads and the aqueous phase, very little increase in adsorption would be expected when sample volumes in excess of 0.1 mL were employed. The preseparation method does not have this limitation because the uranium in large volumes of urine can be isolated and concentrated into a small volume for bead loading. Since it has been shown that detection limits of about 0.02 µg/L can be attained when the uranium in 10 mL samples is isolated and concentrated into a fraction of one milliliter, it seems reasonable to assume that detection limits of about 10 times this level, i.e., 0.2 µg/L, could be easily attained by the direct loading method. The intrinsic sensitivity of IDMS is quite adequate to measure levels of uranium much lower than 0.2 µg/L by the direct bead loading method if the uranium background can be reduced sufficiently. Further study of this method seems highly desirable.

4.8 Measurement of Thorium and Plutonium in Human Urine

Although most of the effort in this study was devoted to the development and evaluation of the IDMS method for the determination of uranium in urine, sufficient experimental work was also conducted with thorium and plutonium to gain a reasonable understanding of the capability of IDMS for measuring these elements. Experimental accomplishments include measurements of indigenous thorium in urine and in a

corresponding procedural blank and measurements of plutonium in urine to which known amounts of Pu-239 had been added. Approximate limits of detection that were derived from these measurements will be discussed below. Although the chemical yield was not determined for plutonium, the mass spectrometer ion currents (counts) obtained for the Pu-242 mass tracer were high when plutonium was eluted from the ion exchange column with HCl containing small amounts of HF. The ion counts obtained indicate that the yields were comparable to those of U and Th discussed in Section 4.3. This separation scheme for Pu(IV), which is outlined in Section 3.3.2, was adapted from well known procedures reviewed by Coleman (Co65). As stated previously in this report, both the Pu-242 and Pu-239 used in this study were added to samples and maintained in the +4 oxidation state. Known separations procedures for Pu(IV) were therefore followed. Indigenous plutonium was not measured in urine. If indigenous plutonium were to be measured by this or similar IDMS methods, chemical treatment would be necessary to ensure that the indigenous and added mass tracer were in the same oxidation states prior to the chemical separations. Suitable procedures for this purpose are given by Coleman (Co65). The necessity of such treatment to obtain isotope exchange was discussed in Section 4.4.

Thorium was determined in three samples of human urine and in three procedural blanks. These analyses were made by combining 10 mL of Ultrex nitric acid with 10 mL of urine (or triply-distilled water for the blank) and following the procedure outlined in Section 3.3.3. A mean of 0.077 µg/L and a standard deviation of 0.011 µg/L were found for the urine sample. The procedural blank had a mean concentration of 0.036 µg/L and a standard deviation of 0.0075 µg/L. When the blank value was subtracted from the mean value for the urine, a net concentration of 0.041 µg/L was obtained. The reader may note that the procedural blank value given above for thorium is very similar to that given in Table 4.1 for uranium. The urine sample analyzed for thorium was the same as the one analyzed for uranium and discussed in Section 4.6. The net thorium concentration, given above, also appears to be similar to the net uranium concentration which was estimated to be 0.032 µg/L.

Samples of urine were prepared for plutonium determinations by adding Pu-239 to urine to obtain the following concentrations: 0.493, 2.46, 49.3, 493. picograms per liter. Ten milliliter aliquots of these samples were analyzed according to the plutonium procedure given in Section 3.3.2. The plutonium concentrations observed in the samples are listed in Table 4.8

Although the data are limited, we can use the results given above for thorium and those of Table 4.8 to roughly estimate the detection limits and analysis sensitivity for thorium and plutonium. In the case of thorium, we have used the data for the urine sample and the procedural blank to estimate a pooled standard deviation from the six observations. The resulting standard deviation was estimated to be

Table 4.8 Observed Plutonium-239 Concentrations in Urine Spiked with Pu-239

Sample	Observed Plutonium Concentrations, pg/L			
	Level 1 (0.49 pg/L)	Level 2 (2.46 pg/L)	Level 3 (49.3 pg/L)	Level 4[c] (493 pg/L)
1	a	b	48	494
2	a	2.7	47	485
3	a	3.2	47	
Mean		2.9	47.3	489
RSD(%)		12.	1.2	1.3

[a] Ion counts for these samples were too low to quantify the data.
[b] Experimental difficulties invalidated measurement.
[c] Only two samples were analyzed.

0.009 µg/L. Multiplying this standard deviation by 4.65 (as was done for uranium in Section 4.6) we obtain a rough estimate of the net detection limit for thorium to be about 0.04 µg/L. This concentration is about the same as the net concentration observed for the urine sample that was measured. The level at which the relative standard deviation would be 10 percent is about 0.1 µg/L. Thus, the capability of IDMS to measure thorium in urine is about the same as for uranium in urine. In the case of plutonium, the minimum amount that can be measured is not regulated by a procedural blank but is determined by the total volume of sample processed, the chemical yield for the recovery of plutonium from the sample, and the intrinsic sensitivity of the mass spectrometry. Thus it is evident from the data in Table 4.8 that the determination limit (level at which the relative standard deviation is 10 percent) is about 3 µg/L.

5. SUMMARY AND EVALUATION

5.1 Introduction

This chapter presents the main conclusions from experimental studies on the possible use of isotope dilution mass spectrometry (IDMS) and the resin bead methodology for high sensitivity analysis of uranium, plutonium, and thorium in human urine. Practical and economic considerations are discussed, and the technique is compared with other methodologies that are now in use or have promise for use in bioassay measurements to define occupational exposure.

5.2 Conclusions from Experimental Studies

The primary objective of this study was to evaluate IDMS for bioassay measurements of uranium, plutonium, and thorium. Major emphasis was given to measurement of uranium in urine because of the widespread potential for occupational exposure in the uranium mining and milling industry and because of the accepted practice of assessing occupational exposure by urine analysis. Lesser emphasis was given to measurements of plutonium and thorium because of the more limited occupational exposure and the resulting less common use of bioassay monitoring for these elements. For uranium, a major consideration in this study was to establish the lowest practical detection limit for the element in urine, and experimental studies were conducted to emphasize sensitivity considerations.

The question of what limit of detection is required for uranium, plutonium, and thorium in urine was addressed early in this study. Stated another way, if there were no limitations in measurement methodology, what is the lowest detection limits that would be beneficial in assessing occupational exposure? We have concluded that this lowest detection limit for uranium in urine should be such that the indigenous, background uranium concentration in nonoccupationally exposed population groups can be reliably measured. With analysis methodology capable of measurements at the background level, any occupational exposure could be identified, monitored, and controlled. There are a number of studies which have dealt with the indigenous level of uranium in urine (see section 1.3 of this report). These studies indicate that the lowest concentration range of uranium in the urine of population groups not subject to occupational exposure is of the order of 0.01 to 0.1 µg/L. This level was therefore chosen as the desired detection limit for our efforts. Since plutonium does not occur naturally in human urine, the detection limit that is needed cannot be established in this manner. With thorium (Th-232), there is little information currently available in the literature on the background levels in urine. Because of the difficulty in specifying needed lower detection limits for plutonium and thorium, the objective of our studies for these elements was to establish the experimental detection limit of IDMS using procedures which

give acceptable detection limits for uranium.

This study has shown that IDMS combined with the resin bead technique can measure uranium in urine at a concentration of 0.06 µg/L (0.04 pCi/L natural uranium) with an uncertainty of about 10% (RSD) using 10 mL of sample. Plutonium can be determined at a level of 3 picograms/L (0.2 pCi/L Pu-239), and thorium, at a level of 0.1 µg/L (0.01 pCi/L Th-232). These limits are determination limits as defined by Currie (Cu68). The detection limits, also as defined by Currie, are approximately 0.02 µg/L for uranium (0.01 pCi/L), 1 picogram/L (0.06 pCi/L) for plutonium, and 0.04 µg/L (0.004 pCi/L) for thorium for sample volumes of 10 mL. At levels above the determination level, all the elements can be measured with excellent precision (typically 1%, RSD), and the isotopic composition for major isotopes can be reliably established. The lower limit of detection for uranium and thorium is set by the variability of the procedural blank and not by instrumental sensitivity factors. The procedural blank for uranium found in this study was 0.030 $\pm$ 0.005 µg/L. The blank value is highly dependent on the laboratory conditions in which the chemical procedures were performed. Pickup of uranium contamination from laboratory air, labware, and chemical reagents is a problem at these exceedingly low-concentration levels. The detection limit for uranium is, therefore, limited by the care and attention given to contamination control. In these studies, a moderate level of contamination control was maintained; conventional chemical laboratories with laminar-flow hoods, limited personnel access, and careful sample screening were routinely used. It is our opinion that more stringent measures for contamination control may be too impractical and costly for routine use in bioassay monitoring programs. With moderate efforts to control contamination, we have been able to attain a detection limit for uranium that is in the range of the lowest indigenous levels of uranium reported in the urine of nonoccupationally exposed human population groups.

Even though the main emphasis of this study has been to maximize sensitivity in the measurement of uranium in urine, it is apparent that contamination in the collection of urine samples may be an additional problem. To obtain limits of detection approaching the indigenous, background level, one must use extreme care to prevent contamination of the urine in the sample collection process.

The precision of the IDMS technique is excellent for uranium at concentration levels at which variations in the procedural blank are insignificant. At concentrations above 1 µg/L, precision of the measurements are of the order of 1% (RSD). At concentrations approaching the detection limit (<0.1 µg/L), precision becomes poorer because of variations due to inadvertent contamination from a number of sources.

Assesssment of accuracy of the IDMS method for uranium is more difficult because of the unavailability of standard reference urine with well-defined uranium concentration or of a reliable alternative method for measuring the exceedingly low-concentration levels for comparison

with IDMS. Based on analysis of a synthetic urine sample, accuracy is excellent at the 7 µg/L level. There is no indication of any significant bias in the method.

Direct bead loading is a viable alternative to the ion exchange concentration procedure for uranium. The direct bead-loading technique works well, is simplier to perform, but may suffer from insufficient sensitivity. The minimum detectable concentration using the direct bead-loading technique is believed to be as low as 0.2 µg/L (0.1 pCi/L natural uranium) - about ten times higher then the detection limit of the ion exchange concentration procedure. Probably, further efforts to reduce contamination would improve the sensitivity of this method.

There are, so far as we know, no chemical interferences in the IDMS method for the determination of uranium, plutonium, or thorium in urine. The chemical separation followed by highly specific mass spectrometric analysis makes direct interferences unlikely. Likewise, the effects of secondary chemical interferences which would cause poor yields in the procedure are minimized because the isotope dilution methodology very accurately corrects for chemical losses in the separation procedure. The only requirement is that enough of the element is adsorbed on the ion exchange beads to allow an accurate measurement of the isotopic mass ratios.

5.3 Practical and Economic Factors in the Use of Isotope Dilution Mass Spectrometry

The practicality of a measurement technique is an important consideration in assessment of the technique for general usage. Experimental studies in this report have demonstrated that IDMS combined with the resin bead methodology satisfies most requirements of sensitivity, precision, and accuracy for bioassay measurements. IDMS is, however, a nonconventional bioassay measurement methodology, and the practicality of the method and economic consideration are important factors in assessment of the method.

The basic technique for measurement of uranium, plutonium, and thorium in urine by IDMS is simple and well understood. The ion exchange concentration procedure isolates the elements from a small sample of urine. Well documented procedures for loading the elements of interest onto resin beads are published, and the mass spectrometric analysis is available at many laboratories. The procedure is simple to perform and could be routinely executed with minimally trained staff. The mass spectrometric measurements, while requiring comparatively complex instrumentation and knowledgeable staff, could be routinely performed. In most respects, the methodology is amenable to routine application in large-scale bioassay monitoring programs.

There are two factors relating to practicality that are of concern, however. First, our studies have shown that the most important factor

for high sensitivity analysis of urine is the avoidance of contamination in the handling and processing of samples. Precautions are necessary to prevent sample contamination. For this reason, we believe that any methodology for analysis of uranium in urine that approaches the 0.01-0.1 µg/L level must be performed in special laboratories that are maintained to minimize sample contamination. The second factor related to the practicality of the method is the complexity of operating and maintaining mass spectrometry equipment. Mass spectrometers can be run routinely by trained staff but successful operation depends on the availability of technical staff with knowledge to set up methods, to diagnosis problems with the instrument, and to make repairs. For these reasons, and also because of the high capital costs for mass spectrometers, we do not believe that the IDMS technique is a practical methodology for a small laboratory, particularly one associated with and near a uranium milling or mining operation. There are, however, a number of high quality commercial analysis laboratories in this country that would be capable of establishing the IDMS capability for bioassay measurements. Lists of such laboratories can be found in such publications as the Annual Buyers Guide issue of Nuclear News published by the American Nuclear Society or the Annual Labguide issue of Analytical Chemistry, published by the American Chemical Society. For these laboratories, the main requirement would be that the number of samples analyzed (sample load) would be sufficient to justify the capital expenditures needed to purchase instrumentation and provide special laboratories for chemical processing in a low uranium background area.

With these thoughts in mind, we have attempted to provide an estimate of costs for high sensitivity analysis of uranium, plutonium, and thorium in urine for bioassay purposes. We have assumed in obtaining this estimate that the analyses would be performed by a capable commercial analysis laboratory with staff having expertise in chemical separations, mass spectrometry, and contamination control. We have also assumed that a moderate level of laboratory efficiency is achieved. Table 5.1 shows a breakdown of costs for a hypothetical commercial laboratory to analyze urine for uranium, plutonium, or thorium by the IDMS-resin-bead technique. The elements would be determined in 10-mL aliquots of urine by procedures described in this report with a determination limit for uranium of about 0.06 µg/L (±10% RSD).

The major equipment costs to perform the analyses would be to purchase a high resolution mass spectrometer and to set up laboratories for chemical processing and mass spectrometer operations. An automated mass spectrometer (such as a Finnigan MAT 261 (A183)) could be used to analyze about 24 samples per day. The cost of the mass spectrometer including setup and checkout would be approximately 350k$. Laboratory setup would include equipment for fabricating and cleaning filaments, laminar flow hoods, etc., and would cost approximately 150k$. The total setup cost would be approximately 500k$. If it is assumed that the useful lifetime of the equipment and laboratory facilities is 15 years, the annual cost would be approximately 33k$ per mass spectrometer system. A facility with one mass spectrometer should be able to analyze up to 6200 samples per year, assuming only one analysis per sample.

Table 5.1 Estimates of Costs for Determination of Uranium, Plutonium, or Thorium by Isotope Dilution Mass Spectrometry

Cost Elements	Annual Cost (k$) for Various Sample Loads (samples/day)			
	12	24	36	48
1. Chemical isolation and bead loading (technician labor)	60	100	130	160
2. Mass Spectrometer operation (technician labor)	90	120	150	180
3. Technical and administrative support (professional labor)	50	50	100	100
4. Supplies and maintenance	56	87	144	175
5. Annualized costs for mass spectrometer and lab facilities	33	33	66	66
6. Downtime and quality control	30	50	60	70
TOTAL ANNUAL COST	319k$	440k$	650k$	751k$
ANNUAL SAMPLE LOAD	3,100	6,200	9,400	12,500
COST PER SAMPLE	$102	71	69	60

Higher sample loads would require duplication of the mass spectrometer unless the throughput could be increased.

Costs for preparing and analyzing samples would be primarily for support of technicians for chemical separations and bead loading (item 1, Table 5.1) and mass spectrometer operations (item 2). Mass spectrometer operators would also perform routine activities associated with preparing and cleaning filaments and maintenance of the mass spectrometer. Professional staff assistance (item 3) would be required for technical support, supervision, and administration. In Table 5.1, we have assumed that the annual labor costs are 60k$ per technician and 100K$ per professional person (overhead and profit included). Costs of maintenance of the mass spectrometer is estimated at 25k$ per year per instrument, and supplies are estimated at $10 per sample.

Table 5.1 shows that the analysis cost is approximately $102 per sample for a sample load of approximately 3100 samples/year (12 samples/day). One mass spectrometer would be required for sample loads up to about 24 samples/day, and for larger sample loads, additional mass spectrometers would be required. The large drop in analysis costs (per sample) as the sample load increases is due to an expected increase in efficiency of personnel and full use of the mass spectrometer. If personnel and/or the mass spectrometer(s) are used for other work, a portion of the operating costs could be allocated to this work, reducing costs for sample loads of 12 samples/day and 36 samples/day. The mass spectrometer(s) would be fully allocated for bioassay measurements at sample loads of 24 and 48 samples/day, and no significant cost savings would results from performing other work on the mass spectrometer.

If the measurement sensitivity requirements were lowered somewhat to a determination limit of 1 μg of uranium per liter (10% RSD), then the direct bead-loading technique described in Section 4.7 would be applicable for uranium analysis of urine. Cost reductions would result mainly in items 1, 3, and 4 on Table 5.1. A cost reduction of $10-$15 per sample could be realized, giving a cost range of $85 to $50 per sample for sample loads of 12 to 48 samples/day, respectively.

It should be emphasized that this cost analysis is very preliminary and is only a guide for comparison of IDMS with other methods for bioassay measurements. We have attempted to be realistic in the estimates and have not taken account possible developments that could occur in maximizing efficiency in the chemical processing of samples or in improving the thoroughput of thermal ionization mass spectrometers.

5.4 Comparison of Bioassay Measurement Methodologies

There are several techniques that have been proposed for high sensitivity analysis of uranium, plutonium, and thorium for bioassay measurements. A review of these methods is presented in the appendix of this report. Experimental studies have shown that some of the

methods are capable of measuring the elements in urine at exceedingly low levels. Other methods, because of their inherent sensitivity, have been proposed but have not been experimentally demonstrated. Table 5.2 summarizes important factors related to methodologies currently in use or proposed for use for high sensitivity measurement of the elements in urine. Two methodologies, fluorometry and low-level alpha counting, are in routine use at this time for bioassay measurements; one method, neutron activation analysis with delayed neutron counting, is used routinely to a limited extent at laboratories with neutron irradiation facilities. The remaining methods listed in Table 5.2 have not been utilized to any significant extent for routine bioassay measurements.

Fluorometry and radiochemical determinations with alpha counting are accepted methods for urine bioassay measurements and are used at a number of industrial, commercial, and governmental laboratories. Fluorometric methods that analyze 0.1-mL samples directly have the advantages of simplicity, low cost (~$20 per analysis), and moderate sensitivity. The method is nearly ideal for levels of uranium in urine above about 10 µg/L. Published fluorometric methods that analyze urine directly do not, however, measure uranium reliably below about 5 µg/L, do not give isotopic information, and can not be used for plutonium and thorium analyses. If, however, uranium is separated from volumes of urine of 10 mL or more as was done by Dupzyk and Dupzyk (Du79), the sensitivity of the resulting analyses approaches the levels that have been obtained by IDMS. However, because of the additional labor required for the chemical separations, the cost for the fluorometry would be increased. The cost for equipment to perform conventional fluorometric analysis is relatively low (<50k$).

Radiochemical separation followed by low-level alpha spectroscopy is also an excellent method for bioassay measurements. Its main advantages over conventional fluorometric methods are higher sensitivity and its applicability to determination of uranium, plutonium, thorium, and isotopic composition. High sensitivity is achieved by concentrating the elements from a large volume of urine (usually 1 liter) and by using low-background alpha detectors. Concentration of the elements by chemical methods increases the possibility for contamination of samples and raises the analysis cost. Typical costs for routine uranium analysis of urine for a detection limit of 0.1 µg/L is in the range of $50-$100 per sample. Costs for plutonium and thorium analyses are similar but at different sensitivity levels (Table 5.2).

In recent years, neutron activation analysis with delayed neutron counting has been used at U. S. Department of Energy laboratories for routine analysis of uranium in urine. The methods are highly automated and do not require chemical processing. No cost information is available, but for large numbers of samples, it is expected that the cost would be low (<$10 per analysis). The sensitivity of the method (1 µg/L) is better than fluorometry but is not as good as alpha counting methods. The main disadvantage of the method is that a reactor facility with a sample transfer system is required. The sample transfer system must rapidly remove samples from the reactor after neutron irradiation.

Table 5.2 Factors for Comparison of Bioassay Measurement Methodologies*

	Fluorometry	Alpha Counting**	Laser Fluorometry	IDMS***
In routine use	Yes	Yes	No	No
Experimentally demonstrated for bioassay measurements	Yes	Yes	Yes	Yes
Elements determined	U	U, Pu, Th	U	U, Pu, Th
Provides isotopic composition	No	Yes	No	Yes
Chemical processing required for urine analysis	No	Extensive	(Minimal)	Minimal
Equipment Costs	Low	Low	(Medium)	High
Analysis Cost	Low	Medium	(Low)	Medium
Reported limit of detection, µg/L				
a. Uranium	1-10	0.03	(1)	0.02
b. Plutonium	ND	2×10^{-7}	ND	1×10^{-6}
c. Thorium	ND	0.08	ND	0.04
Volume of sample needed to attain lower limit of detection, mL	0.1	1000	(0.2)	10

*Parentheses around table entries indicate uncertainty because of lack of pertinent research and development on method. ND indicates that the element can not be determined by the method.

**Following radiochemical separation. Limits of detection for natural uranium, ^{235}Pu, or ^{232}Th are based on counting sensitivity of 0.01 pCi.

***Isotope dilution mass spectrometry (thermal ionization).

Table 5.2 (cont.) Factors for Comparison of Bioassay Measurement Methodologies*

	Delayed Neutron Counting	Neutron Activation Analysis	Fission Track Counting	RIMS**
In routine use	Limited	No	No	No
Experimentally demonstrated for bioassay measurements	Yes	Yes	No	No
Elements determined	U	U, Th	U	(U, Pu, Th)
Provides isotopic compostion	U-235	Yes	U-235	Yes
Chemical processing required for urine analysis	No	Minimal	Not Known	(Minimal)
Equipment Costs	High	High	High	High
Analysis Cost	(Low)	(High)	(Low)	(Low)
Reported lower limit of detection, µg/L				
a. Uranium	1	0.001	0.01	(0.05)
b. Plutonium	ND	ND	ND	Not Known
c. Thorium	ND	10	ND	Not Known
Volume of sample needed to attain lower limit of detection, mL	25	U:25, Th:1	0.05	(10)

*Parentheses around table entries indicate uncertainty because of lack of pertinent research and development on method. ND indicates that the element can not be determined by the method.

**Resonance ionization mass spectrometry.

Facilities of this type are available at several laboratories (mainly governmental) in the U. S., but a facility of this type would be difficult to justify solely for urine bioassay measurements.

Neutron activation analysis (NAA) with gamma-ray spectrometry and fission track methods have been investigated for bioassay measurements but have not been used routinely to any extent. The techniques have good sensitivity, may be performed at low cost, but, like NAA with delayed neutron counting, require a source of neutrons from a nuclear reactor. Unlike the delayed neutron method, however, rapid transfer of samples from the reactor is not necessary. Large numbers of samples can be simultaneously irradiated and then transferred to a distant laboratory for gamma-ray spectroscopy or fission track counting measurements.

Resonance ionization mass spectrometry (RIMS) and laser fluorometry are techniques that are currently under development and have potential for high sensitivity measurements of uranium, plutonium, or thorium in urine. A recent report by Hinton (Hi81) indicates that laser fluorometry can measure uranium in urine down to a detection limit of about 1 µg/L (0.2 mL of sample). Reports of sensitivities approaching 0.001 µg/L of uranium in water samples (Bu83) suggest that higher sensitivities for urine analysis may be possible by laser fluorometry. The laser fluorometric method has essentially the same desirable features as the fused-salt fluorometric method. Equipment costs will probably be moderate (50-100k$), extensive chemical processing may not be required for urine, and analysis costs could be low.

The RIMS technique is under active development at this time for bioassay measurements. A recent report by Parks (Pa83a) examines the feasibility of determining uranium, plutonium, and thorium at low levels in urine. Based on this report, sensitivity for uranium should be of the order of 0.05 µg/L in urine, minimal chemical processing would be required, and analysis costs could be low ($10-$30 per sample). Although equipment costs would be high, sample analysis costs could be low because of high sample throughput.

The experimental studies described in this report and other studies (Fa83, Du79) have demonstrated that isotope dilution mass spectrometry can be used for high sensitivity analysis of urine. The intrinsic or instrumental sensitivity of mass spectrometry is very high; femtogram quantities of the elements can be detected by the mass spectrometer. This high intrinsic sensitivity is evident in the determination of plutonium in urine. Plutonium at a concentration of 2 picograms/L can be easily measured in a 10 mL sample by the technique. For uranium and thorium, however, the intrinsic sensitivity is not so important, because sensitivity is limited by the procedural blank for these elements. Therefore, in comparisons of IDMS with other methodologies, one must be aware of the differences in intrinsic sensitivity and the actual sensitivity that can be obtained by a workable procedure. Actual sensitivity may be affected more by the chemical procedure used to

prepare samples for analysis than by the intrinsic instrumental sensitivity.

Comparison of IDMS methods with the currently used methods for bioassay measurements of uranium indicates that it is about two orders of magnitude more sensitive than classical fluorometric methods. Costs per analysis by IDMS ($60-$100) are considerably higher than for fluorometric analysis (<$20) but IDMS can be used to determine all three elements and provides isotopic composition whereas fluorometry determines only elemental uranium. The sensitivity of the IDMS method is comparable with the intrinsic sensitivity of alpha radioactive measurement techniques for uranium, plutonium, and thorium. Likewise, costs for analysis are very similar ($50-$100). Even though the sensitivity for the alpha-counting method is comparable with IDMS, a large volume of urine (1 liter) is required for the alpha-counting method whereas only 10 mL of urine is required for IDMS. Also, the detection limit for alpha-counting methods can not be greatly improved by reduction of contamination, whereas improvements in contamination control can greatly improve the sensitivity of the IDMS method.

Objective comparison of IDMS with RIMS and laser fluorometric methods is not yet possible because the latter techniques are not experimentally demonstrated for high sensitivity urine analysis. Based on information available at this time, both techniques may offer significant advantages over thermal ionization mass spectrometry; lower costs per analysis at equal sensitivity may be possible with RIMS, while both cost and sensitivity advantages may be possible with laser fluorometry. Both of these methods should be further evaluated to establish if the techniques are indeed applicable for high sensitivity bioassay measurements of urine at low cost.

The main disadvantages of IDMS for urine bioassay measurements are the high cost required for the purchase of mass spectrometers and the limited throughput of samples caused by the time consuming procedures necessary for thermal ionization of the elements. These factors make the analysis costs higher than may be desirable for large-scale bioassay monitoring efforts. Automated instruments are now available for thermal ionization mass spectrometry that can easily handle up to 24 samples per day. Increases in sample throughput above this level may be possible through future instrumental developments. (The sputtering technique being developed by Parks (Pa83b) is one possible approach to increasing sample throughput.) At this time, we believe that the IDMS - resin bead technique, except for costs considerations, has many desirable features for high sensitivity analysis of uranium, plutonium, and thorium in urine. Future developments in mass spectrometry instrumentation may make the technique cost competitive with other methods.

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7. APPENDIX

REVIEW OF HIGH SENSITIVITY MEASUREMENT METHODOLOGY FOR URANIUM, PLUTONIUM, AND THORIUM IN URINE

This appendix is a review of methodologies currently in use or under development for high sensitivity measurement of uranium, plutonium and thorium in human urine. The review is selective rather than comprehensive, drawing primarily on the recent scientific literature describing new developments and methodologies for high sensitivity measurements The following methodologies are reviewed: fluorometry and phosphorometry (including laser methods), natural radioactivity, radioactivity induced by neutron irradiation (neutron activation analysis), fission track counting methods, and resonance ionization mass spectrometry. A review of thermal ionization mass spectrometry is presented in Chapter 2 of this report.

7.1 Fluorometry and Phosphorometry*

Fluorometry is a widely used, high sensitivity method for the determination of uranium in a variety of sample types. It is a generally accepted method for analysis of uranium in urine but cannot be used fo analysis of plutonium or thorium.

Fluorometric analysis of uranium is based on the excitation of the uranyl ion by absorption of ultraviolet light. The excited uranyl ion decays spontaneously back to the ground electronic state and in the process emits light. The intensity of the emitted light is proportional to the number of excited ions that were formed in the excitation process. In the absence of secondary reactions (quenching), the lifetime of the excited uranyl ion is of the order of a few microseconds, so there is a finite time delay in the excitation/emission process. Because of energy losses due to radiationless processes within the excited uranyl ion, the energy of the emitted light quanta is less than the energy of the absorbed light quanta; therefore, the wavelength of the emitted fluorescent light is higher than the wavelength of the excitation source.

The terms "fluorometry" and "phosphorometry" are both used to describe methodologies for determination of uranium. The techniques differ in the manner in which the light emission measurements are made. In a fluorometric analysis, the intensity of the emitted light is measured simultaneously with the excitation process. In phosphorometry, the emission intensity measurements are made at a short time interval

*The terms "fluorimetry" and "phosphorimetry" are occasionally used for "fluorometry" and "phosphorometry".

(few microseconds) after a pulsed light source excites the uranyl ion.

Numerous methods are described in the literature for analysis of uranium by fluorometry. Variations on the classical methods of Price et al., (Pr53) and Centanni et al., (Ce56) are commonly used. In the method, a small sample (usually an aqueous solution) is added to solid sodium fluoride or a mixture of sodium fluoride and lithium fluoride. The fluoride salt(s) is fused by heating, incorporating the uranium uniformly in the fluoride melt and eliminating water, organic matter, and volatile inorganic matter. After cooling, the solid fluoride melt is subjected to a fluorometric analysis using a fluorometer. The specimen is irradiated with ultraviolet light at about 320 to 370 nm, and the fluorescent intensity is measured at about 530 to 570 nm at a 45-90° angle to the incident excitation light beam. Standards and blanks are treated in a similar manner to establish a calibration curve and to correct for background fluorescence. In case of quenching* by impurities in the sample or the fluoride salt, a chemical separation prior to the analysis is performed to isolate uranium, and/or standard addition techniques are employed.

Improvements and modifications of the basic fluoride salt/fusion method for fluorometric uranium analysis include the use of gold dishes and fluxes which are dominately carbonate (EP80), automated apparatus for fusion of the fluoride salts (St79), a furnance-sintering method rather than a flame fusion method (Ca78), chemical separations to minimize interference by quenching (Ca78, AS83, Pa70), and the use of radioactive U-232 to establish recovery of uranium in separation procedures (Ha79). Instrumentation for making fluorometric intensity measurements is available commercially, but some laboratories design instrumentation for their specific needs. One such instrument is an automated fluorometer ideally suited for routine analysis of hundreds of samples per week (Ca78). This instrument consists of a combination mercury arc lamp (for excitation) and photomultiplier detector (for emission intensity measurements) with a light interference filter to isolate the 550-nm fluorescence of uranium. The amplified fluorescence intensity is fed to an on-line calculator for standards calibration and sample calculation.

Several procedures for the fluorometric determinations of uranium in urine have been recently published (Gr75, Ba80, Vo82). In these procedures, a dried 0.1-mL urine sample is fused with sodium fluoride or

*Quenching is the name given to any reduction in the intensity of fluorescence due to specific effects of constituents of the sample matrix. Quenching may occur as a result of partial absorption of the fluorescent light by some component of the sample matrix, or it may occur because of energy transfer from the excited uranyl ion to some chemical species in the fluoride salt matrix.

sodium fluoride (98%) - lithium fluoride (2%), and the fluorescent intensity of the uranium in the fluoride salt matrix is measured. No chemical isolation of uranium prior to the fusion is required. Apparently, because of the small volume of sample taken, elements and organic compounds are not present in sufficient quantity to cause interference by quenching. The sensitivity of these fluorometric methods are of the order of 1 µg/L of uranium (Vo82). The 1982 Procedures Manual of the Environmental Measurements Laboratory states that concentrations of uranium of 1-1000 µg/L can be measured directly without problems due to quenching. Background fluorescence reduces the accuracy of the method in the concentration range 1-10 µg/L.

Further information regarding the sensitivity of the fluorometric method can be gleaned from an ASTM procedure (AS83). This procedure provides an empirical equation for estimating the overall precision (standard deviation), SD, for the direct measurement of uranium in water, viz.,

$$SD=0.0024 + 0.2001\ U^{1.5293}$$

where U denotes the uranium concentation in mg/L. From this relation one can deduce that the relative standard deviation (RSD) would be ±10% for samples of 30 µg/L; at concentrations of 5 µg/L the RSD is ±50%. It should be noted that since only 0.1 mL is used for a measurement, the quantity of uranium on the fused disk that is required to provide a RSD of ±10% is 3 ng. Thus if an easily used chemical method provided the capability of isolating all the uranium from one liter of urine without contamination, fairly accurate analyses should be possible at levels of 0.003 µg/L. Dupzyk and Dupzyk (Du79) reported on the use of an ion exchange separation scheme in which the uranium was separated from 10 mL of urine. The limit of detection was reported to be 0.1 ± 0.1 µg/L.

Within the last 3-4 years, several interesting new developments have been made that have considerable promise for significantly improving methodology for fluorometric analysis of uranium in urine. These new developments involve the use of lasers to excite phosphorescence in solutions derived from urine (Hi81) and water (Wh80, Zo81, Ka81). The laser light has a wavelength of 337 nm and the phosphorescence is measured at 516 nm. The laser is pulsed about 16 times per second, and the detector response is delayed so that fluorescence measurements do not begin after each pulse until organic fluorescence with lifetimes of 4-10 nanoseconds have decayed; the uranium phosphorescence with lifetimes of 100 to 500 µs is then measured. Using the equivalent of 0.2 mL of urine, Hinton (Hi81) reported that 1.0 µg/L could be detected, but no estimate of the uncertainty at this level was given.

Perry et al., (Pe81) measured uranium in aqueous solutions by coprecipitating uranium on calcium fluoride and then measuring laser-induced phosphorescence in the precipitate after it was fused at 800°C.

It was reported that the luminescence intensity is linear over the concentration range of 0.002 to 0.02 µg/L and that uranium at the level of 10^{-5} µg/L could be detected.

Recent work by Bushaw (Bu83) utilizes pulsed dye-laser excitation to induce phosphorescence in solutions of uranyl phosphate. A multichannel scaler photon counting system was used to obtain time resolved emission spectra of the uranyl ion. Kinetic analysis of the resulting data allowed correction for matrix quenching and temperature effects which reduce the quantum yield of the uranyl ion fluorescence. Detection limits of the order of nanograms per liter were demonstrated for ground water samples. Application of the method to synthetic urine samples showed that the method is capable of highly precise analysis at the 7 µg/L concentration level. Urine sample pre-treatment before analysis was minimal; samples were wet ashed with nitric and perchloric acid and dissolved in phosphoric acid for measurements.

7.2 Methods Based on Measurement of Alpha Radioactivity

The measurement of alpha activity is a commonly used method for the determination of uranium, thorium, and plutonium in human excreta. Both gross alpha counting methods and alpha spectroscopy are employed. Like mass spectroscopy and neutron activation methods, alpha spectroscopy is capable of measuring individual isotopes and thus provides more information about internal dose than just elemental concentration. Although alpha spectroscopy can be accomplished with several types of detectors, the silicon semiconductor surface-barrier detector is now the one usually-preferred, principally because of its high energy resolution (Ei79). The energy resolution of present detectors, expressed as the full width at half maximum height (FWHM) of peaks in pulse height spectra, is typically 20-40 keV, depending mainly on the detector size. This resolution is small compared to the differences among the principal alpha energies of several thorium, uranium, and plutonium isotopes that are listed in Table 1.

Alpha counting or alpha spectroscopic counting measurements are normally accomplished by chemical isolation of the radionuclides from the sample and by mounting the separated product in a nearly massless form on an alpha counting disc or plate. Methods of depositing the thin source include electrodeposition (Ha79), evaporation of aqueous and non-aqueous solutions (EP80, Gr62), and coprecipitation in a thin calcium fluoride precipate (Si81). Liquid scintillation spectroscopy methods, described below, uses altogether different techniques.

The detection limit for alpha radioactive measurements is mainly of a practical or economic nature and depends on the amount of sample analyzed and the time interval that can be devoted to counting. The counting efficiency for alpha spectroscopy, i.e., the fraction of alpha particles generated on a counting disc that produces pulses in full energy peaks, is typically 0.2-0.3. Neglecting the effects of background contamination, the detection limit can be taken as the count that will yield a relative standard deviation of 30%. (This limit is consistent with

Table 1. Nuclear Data Pertinent to Alpha Activity Measurements

Nuclide	Half Life (y)	Alpha Energy (MeV)	Alpha per Decay	Specific Activity (dpm/µg)	Approximate Measurement Sensitivity (µg/L)
Th-230	7.7×10^{4}	4.69	0.76	4.48×10^{4}	4.46×10^{-7}
Th-232	1.40×10^{10}	4.02	0.77	0.244	0.08i
U-232	72	5.32	0.69	4.75×10^{7}	4.21×10^{-10}
U-233	1.59×10^{5}	4.82	0.84	2.14×10^{4}	9.33×10^{-7}
U-234	2.44×10^{5}	4.77	0.72	1.39×10^{4}	1.43×10^{-6}
U-235	7.04×10^{8}	4.40	0.57	4.79	0.0042
U-238	4.47×10^{9}	4.19	0.77	0.746	0.026
Pu-239	2.41×10^{4}	5.15	0.73	1.38×10^{5}	1.45×10^{-7}
Pu-242	3.76×10^{5}	4.90	0.74	8.72×10^{3}	2.29×10^{-6}

*Assumes an alpha counting sensitivity of 0.01 pCi/L (EP79).

principles given by Currie (Cu68) that are discussed in Section 4.3 of this report.) This relative standard deviation implies a count of about 10 in the full-energy peaks of the pulse height spectrum. Since one liter samples of urine and a 24-hour counting period are reasonable practical limits, then one can estimate that the detection limit for alpha emitters on an activity concentration basis is about 0.02 dpm/mL or approximately 0.01 pCi/L (EP79). This limit of detection on a weight concentration basis is listed in Table 1 for several isotopes of thorium, uranium, and plutonium. Because of their long halflives, Th-232 and U-238 are measured with the least sensitivity, having detection limits near 0.05 µg/L whereas the short-lived Pu-239 has a limit of about 10^{-7} µg/L. Aside from the possibility that the measurement sensitivity may not be entirely adequate for some applications, the principal limitation on the use of alpha counting methods is the effort and cost required to isolate the alpha emitters for counting. For urine bioassay, the cost of high-purity reagents necessary to analyze liter quantities of urine is also significant.

Many chemical separation procedures and alpha counting methods have been described in the literature for determination of uranium, plutonium, and thorium, and only pointers to some of the more important literature will be given here. Drury et al., (Dr81) gave a brief summary of the literature for uranium measurements in water. Typical of the widely accepted methods for the separation and measurement of uranium and plutonium in urine are those published by the Environmental Measurements Laboratory (Vo82). Methods for the determination of the actinides in water and much of the literature on this subject have been summarized by the Environmental Protection Agency (EP80). Many papers have dealt specifically with the separation and determination of uranium and plutonium in urine (St74, Ve78, Ho79). Although intense study of the separation of actinides dates from before the Manhattan Project, the continued need for faster and better methods is attested to by a recent publication (Be83).

An alternative to the method of counting alpha emitters on thin alpha mounts is liquid scintillation counting (Ho74, Mc80). The rather elaborate electronic counting circuits can reject pulses due to beta-gamma sources, and background count rates are of the order of 0.01 counts/ minute. The energy resolution for alpha spectroscopy is in the range of 200-300 keV(FWHM). Chemical separations of alpha emitters are required, and it is common to extract the radionuclides directly into the liquid scintillator. The advantages and disadvantages of the method, which perhaps is slightly more sensitive than other alpha counting methods, have been summarized by McDowell (Mc80). The method was used by Ryan et al., (Ry82) to determine plutonium in 1-liter samples of urine at the 0.09 dpm/mL (0.04 pCi/L) level.

7.3 Neutron Irradiation Methods

Neutron methods for determination of uranium, plutonium, and thorium,

are based on nuclear reactions that take place when the elements are irradiated with neutrons. The source of these neutrons is usually a nuclear reactor, but other sources such as neutron generators or isotopic neutron sources can also be used. There are basically two types of neutron methods applicable to the determination of these elements in urine. Neutron activation analysis can be used for determination of uranium and thorium. Fission track counting following neutron irradiation is applicable to the determination of uranium. (In principle, plutonium can be determined by fission track or neutron activation methods, but because of practical considerations, other methods are preferred.)

Neutron activation analysis for uranium and thorium is based on the following nuclear reactions:

$$\text{U-238}\ (n,\gamma)\ \text{U-239} \longrightarrow \text{Np-239}$$
$$\text{Th-232}\ (n,\gamma)\ \text{Th-233} \longrightarrow \text{Pa-233}$$

In these reactions, the U-238 isotope of uranium or the Th-232 isotope of thorium captures a neutron and is transformed to U-239 or Th-233. These activation products beta decay to Np-239 or Pa-233. The quantity of U-239 or Th-233 produced in an irradiation is proportional to the amount of uranium or thorium in the sample. Gamma-ray spectroscopy is used to measure either U-239 or Np-239 for uranium analysis, or Th-233 or Pa-233 can be measured to determine thorium.

Delayed neutron counting is an alternative method for the determination of uranium. In this method, uranium is irradiated with thermal neutrons, and the U-235 isotope undergoes fission. About 1.6% of the fission events give rise to fission products which beta decay to other nuclides which emit neutrons. The half-lives of these beta emitting radionuclides range from about 2 to 55 s, and the neutrons emitted by the beta decay products are called delayed neutrons. Measurement of these delayed neutrons forms the basis for the determination of uranium by the delayed neutron counting method.

Fission track counting is one of the most sensitive neutron methods for the determination of uranium. Uranium-235 fissions when exposed to thermal neutrons, and the very energetic fragments formed in the fission process can produce tracks in an adjacent track recorder. The track recorder is etched with a suitable solvent, and the tracks are visible when magnified 50-400 times under a microscope and can be counted. Similar irradiations of known quantities of U-235 provides a means to relate track density to uranium content.

7.3.1 Neutron Activation Analysis

Delayed neutron counting is probably the most useful, although not the most sensitive neutron activation analysis method for determining uranium. The method is one of the simpliest procedures in analytical measurements.

The sample is packaged in a suitable container, irradiated for about one minute in a high neutron flux in a nuclear reactor, and returned to a neutron counter where delayed neutrons are counted. Irradiations can be made in a pneumatic transfer system for about one minute. A known amount of U-235 is similarly measured to quantify the counts obtained for the unknown sample. This method has been described by several authors (Dy62, Am62). A recent paper describes an automated delayed neutron measuring system (Pa81). If a neutron flux of about $3x10^{13}$ neutrons/cm^2·s is employed, the method permits detection of about 10^{-4} µg of U-235 (0.014 µg natural U), and one can accurately measure about ten times this quantity. Essentially no interferences are present for uranium in most materials.

Delayed neutron counting has been applied to the determination of uranium in urine in several studies. Kramer et al., (Kr67) compared delayed neutron counting with a neutron activation analysis method based on the measurement of U-239. A sensitivity of about 0.1 µg/L for U-235 was obtained when 0.5 mL of urine was irradiated. Brits and Holemans (Br79) used delayed neutron counting to determine uranium in 100-mL aliquots of urine. The uranium was complexed with thiocyanate and then adsorbed on an anion exchange resin which was irradiated and counted. A sensitivity of a few tenths of a µg/L was apparently obtained. Ide et al., (Id79) reported on the use of delayed neutron counting at Los Alamos National Laboratory where the method has been used to screen several thousand urine samples for uranium. In the LASL method, 25 mL of urine is irradiated and counted without any sample processing. The sensitivity for U-235 was reported to be 1.5 pCi/L (0.0069 µg/L). For natural uranium the sensitivity was 1 µg/L, and for depleted uranium containing 0.18% U-235, the sensitivity was given as 4 µg/L.

Natural uranium can be determined at much lower levels by neutron activation analysis of U-238 than by delayed neutron counting of U-235. Natural uranium as well as Th-232 has been determined in sub-gram samples of high-purity silicon at the 0.01 ppb level without chemical separations (Dy82). Gamma-ray spectroscopy was used to measure Np-239 and Pa-233 induced activities. The analysis of urine for uranium and/or thorium by this method is complicated due to the large amounts of sodium, potassium and other trace elements that form highly radioactive samples when urine is irradiated directly. Chemical separations must be performed either to isolate the uranium and thorium before irradiation or to isolate the activation products after irradiation. Each alternative has disadvantages. If preirradiation separations are employed, then the usual care in bioassay measurements must be exercised to prevent contamination of the sample with ambient uranium and thorium. If postirradiation separations are used, then work with highly radioactive samples is necessary.

Several studies of the activation analysis of uranium in urine via U-238 activation have been reported. Kramer et al., (Kr67) determined uranium in urine by measuring the neutron induced U-239 following its separation by a solvent extraction process. It was reported that 0.001

µg/L of U-238 could be accurately measured. Manchuk et al., (Ma79) studied the determination of both U-238 and Th-232 in urine by neutron activation analysis. Samples of one mL were irradiated and the induced Np-239 and Pa-233 were separated on anion exchange resins which were then measured by gamma-ray spectroscopy to yield detection limits of 5 µg/L for uranium and 10 µg/L for thorium. Other chemical separation methods for reducing interfering radionuclides were studied but found to be inferior to anion exchange. Holzbecher and Ryan (Ho80) determined U-238 in urine by complexing the uranium with oxime and absorbing the complex on activated carbon. The carbon was irradiated, and the induced U-239 was measured to yield a sensitivity of about 5 µg/L.

Thorium-230, a long-lived alpha-emitting member of the decay chain of U-238 can be activated to Th-231 by thermal neutrons and determined by gamma spectral measurements of the short-lived Th-231. Kathren et al., (Ka80) studied neutron activation analysis of Th-230 and stated that it should be possible to measure 10^{-5} µg.

Plutonium-239, like U-235, fissions when exposed to thermal neutrons, but the very low levels present in biological materials coupled with the need to chemically separate U-235 to levels below that of plutonium before neutron irradiation probably rules out neutron methods for plutonium for bioassay purposes.

7.3.2 Fission Track Counting Methods

Fission track counting is an extremely sensitive method for determination of uranium. The fission tracks produced in a track recorder during the irradiation of U-235 are a sensitive indicator of the quantity of U-235 that is adjacent to the recorder.

Polycarbonate films (Lexan), mica, and fused silica are the most used track recorders. Enge (En80) has given a very comprehensive introduction to this method. A book by Fleischer, Price and Walker (Fl 75) reviews the findings of more than 1300 papers on nuclear track counting. A journal "Nuclear Tracks" was begun in 1975. The method is simple to use and many samples can be irradiated simultaneously. Manual track counting is somewhat time consuming, but automated track counters have been developed (Ma81). A recent study of uranium in ceramic semiconductor packages reported a detection limit of less than 0.04 ppb for natural uranium (Ri81). Only one published study has applied fission track counting to the determination of uranium in urine. Chakarvarti et al., (Ch80) dried 0.05 mL of urine on Lexan films, irradiated to a neutron fluence of 10^{17} n/cm^2, and counted the total number of tracks produced. Uranium levels of (1.2-1.7) x 10^{-3} µg/L were reported. However, our calculations and a subsequent paper by Lal et al., (La82) in which the fission track method was used to measure uranium in milk indicates that the level of uranium in urine that were reported were in error by a factor of 100 and should have been given as 0.12-0.71 µg/L. The total number of

tracks per sample measured by Chakarvarti ranged from about 7,000 to 40,000. From these results, it seems likely that uranium in urine at the 0.01 µg/L level could easily be measured using sample volumes of only 0.05 mL.

7.4 Resonance Ionization Spectroscopy

Resonance ionization spectroscopy (RIS) is a recently developed technique that has considerable potential for high sensitivity analysis of most elements. The RIS technique is based on the photoionization of gaseous atoms by absorption of photons that energetically match quantum-selected states of the atoms (Yo79, Hu79, Hu77). The most simple RIS scheme involves a two photon process that first excites the atom to an intermediate state that is energetically more than halfway to the ionization potential of the atom. Absorption of a second photon then leads to ionization. The result of this photoionization process is a positively charged ion and an electron. Detection of the electron has been shown to be an extremely sensitive analytical tool (Hu77). The ion generated can also be used for analysis by extraction into the ion source of a mass spectrometer for mass analysis. This latter technique is called resonance ionization mass spectrometry (RIMS). Development of RIMS is now underway at a number of laboratories.

In RIMS, gaseous neutral atoms of an element can be produced in several ways including vaporization by thermal heating of a sample with an electrical filament or a high-powered laser (Do82) or by sputtering the sample with charged ions (Pa83a). Atoms in the vapor state are then photoionized using one or more tunable lasers to excite the electron resonance transition. Ions produced in the process are collected and analyzed by a mass spectrometer. Most often, a high power pulsed laser is used for photoionization, and almost all atoms in the laser beam are excited and photoionized. A number of recent papers describe the methodology for performing RIMS (Pa83b, Ki83, No83, Fa83, Yo83).

RIMS is an important new development in the mass spectrometry field because of the extremely high elemental selectivity possible with the technique. Selection of the laser excitation wavelength and/or the use of multiple photon excitation processes, makes it possible in principle to photoionize a single element. The selectivity of the technique is most important for minimizing isobaric (same mass) interferences in mass spectrometric analysis. The sensitivity of RIMS is presently not well defined but is at least comparable with conventional thermal ionization mass spectrometry. At present, sensitivity is limited by the low-duty cycle of high-powered pulse lasers used for photoionization (Do82) and by difficulties in containment of the atomic vapor cloud within the laser beam (No83).

There is at this time no reports of the use of RIMS (or RIS) for bioassay measurement of uranium, plutonium, or thorium in human excre-

ta. A recent report (Pa83a), however, examines the possible use of RIMS for analysis of these elements in urine, blood, and feces. Based on this report, the method appears capable of performing uranium analyses on urine down to levels of 0.05 µg/L with reasonable cost and with good accuracy. Recent papers (Do83) describe the use of RIMS for isotopic measurements of uranium and plutonium without isobaric interferences.

The RIMS technique is in a rapid stage of development at this time. Indicators are that the technique may be of considerable value for bioassay measurements in the future.

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16. ABSTRACT (200 words or less)

A study was made to evaluate the sensitivity, precision and accuracy, and practicality of isotope dilution mass spectrometry (IDMS) for bioassay of uranium, plutonium, and thorium in human urine. The study showed that uranium at a concentration of 0.06 µg/L (0.04 pCi/L natural uranium), plutonium at 3 pg/L (0.2 p Ci/L Pu-239, and thorium at 0.1 µg/L (0.01 pCi/L Th-232) could be measured with an uncertainty (RSD) of ten percent using 10 ml samples. The lower limits of detection for uranium and thorium were set by background contamination, whereas the detection limit for plutonium was determined by chemical yield and intrinsic instrumental sensitivity factors. Precision and accuracy is excellent (∿1-3%, RSD) at concentration levels where background contamination is insignificant and instrumental sensitivity is adequate.

Comparison of IDMS with other methods shows the technique is more sensitive than conventional fluorometric methods but is similar in sensitivity to alpha-radioactivity measurement methods that utilize large sample volumes (1 L). Costs for urine analysis by IDMS ($60-$100 per sample) are estimated to be considerably higher than cost for fluorometric analysis and approximately the same as the cost for alpha-radioactivity methods. Other methods that have been used or are currently under development are discussed.

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