

PNL-9137-DEL

Date April 17, 1978
To H. M. Parker, Chairman
From D. R. Kalkwarf *D.R. Kalkwarf*
Subject Request to Consider the Proposed Study:
"Urinary Excretion of Metals and DTPA"

I have enclosed a copy of the 189 entitled "Urinary Excretion of Metals and DTPA", which proposes to study trace metal concentrations and chemical forms of DTPA in urine specimens obtained from ~~DELETED~~. I am submitting this proposed study for Human Subjects Committee consideration. In this connection, I understand that ~~DELETED~~ has waived certain rights of confidentiality with respect to scientific studies performed in connection with his accidental exposure and follow-up period of treatment. I will await your recommendation concerning any measures that might be required relative to human subjects consideration. If you will need any further information, please let me know.

DRK:kac

Enclosure

REPOSITORY *PNL-Engineering Services Bldg Area 3000*
COLLECTION *Urinary Excretion*
BOX No. *2951*
FOLDER *HSC 78-4*

HUMAN SUBJ.

APR 24 1978

COMMITTEE

0009199

Estimate

DEPARTMENT OF ENERGY
 ENERGY - OPERATING EXPENSES AND CAPITAL ACQUISITIONS
 SCHEDULE 159

RICHLAND OPERATIONS OFFICE
 PREPARED BY BATTTELLE-NORTHWEST

REF. NO.	21A ID PNL #34
189 NO.	
PROGRAM	Environment

1. CONTRACTOR: BATTTELLE MEMORIAL INSTITUTE - PACIFIC NORTHWEST LAB. CONTRACT NO. EY-76C-06-183D	
2. PROJECT TITLE Environment - Multi-Resource Environmental Research and Development Urinary Excretion of Metals and DTPA	
3. BUDGET ACTIVITY NO. GK-01-02-01-1	4. DATE FEBRUARY 1978
5. METHOD OF REPORTING Annual Reports and Open Literature	6. WORKING LOCATION Richland, Washington
7. PERSON IN CHARGE: S. Marks	PRINCIPAL INVESTIGATOR(S): D. R. Kalkwarf

8. PROJECT TERM:
 FROM: April 1978 TO: September 1979

	FY 1978	FY 1979	FY 1980
9. MAN YEARS DIRECTLY ASSIGNED			
(a) SCIENTIFIC	.3	.5	
(b) OTHER TECHNICAL	.1	.6	
TOTAL (NO FRACTIONS)	0	1	0
10. FUNDING (DOLLARS IN THOUSANDS)			
<u>OPERATING COSTS</u>			
(a) STAFF LABOR - DIRECT	15	34	
(b) MATERIALS, SERVICES	12	19	
SUB CONTRACTS			
(c) INDIRECT EXPENSES	13	27	
(d) _____			
TOTAL BUDGET OUTLAY	40	80	0
<u>CAPITAL EQUIPMENT NOT RELATED TO CONSTRUCTION</u>			
DELEGATION AUTHORITY	\$ 0	\$ 0	\$ 0
COSTS	\$ 0	\$ 0	\$ 0

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DEPARTMENT OF ENERC

ADDITIONAL JUSTIFICATION FOR OPERATIONAL COSTS

SCHEDULE 1 & 9

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PROJECT TITLE

Urinary Excretion of Metals and DTPA

11. Reactor Concept: Not applicable.
12. Strategic, Precious and S. F. Materials: None.
13. Publications Since January 1977 (Other than Topical or Progress Reports): None; new project.
14. Purpose, Need and Scope: The purpose of this project is to analyze ~~DELETED~~'s routine urine specimens for metals and DTPA in order to compare the relative merits of the Ca-DTPA and Zn-DTPA administration schedules used to promote his excretion of ²⁴¹Am. It will be within the scope of this project to (1) test for abnormal excretion of essential body metals, (2) determine the effectiveness of oral zinc supplements in inhibiting the excretion of these metals and (3) relate the amounts and forms of DTPA salts excreted in urine to those administered intravenously. All of the urine samples available at this time will be analyzed. This information is needed to guide physicians in regulating the dosage of DTPA salts during treatment of patients contaminated with radionuclides and to judge the adequacy of animal models for predicting the effects of DTPA salts on man.
15. Relationship to Other Projects: This project is related to the DOE-funded investigation, "Removal of Deposited Radionuclides", and would complement it by providing human excretion data for comparison with its animal excretion data.
16. Technical Progress in FY 1978: Although this is a new project, measurements to determine the feasibility of inexpensive multi-element analyses on the ~~DELETED~~ bioassay samples have already been carried out in anticipation of the need for such work. X-ray fluorescence (XRF) spectroscopy was selected as the analytical method because it was found capable of determining simultaneously the concentrations of 22 elements including all of the metabolically important trace metals. In addition, this method allows the samples to be assayed while completely sealed in Mylar film, thus minimizing the hazard of contaminating expensive analytical equipment and the laboratory area. Homogeneous aliquots of either the urine or feces specimens were dried, compressed and sealed within a Mylar envelope, and then analyzed. The sensitivity of the method was found to be at least one order of magnitude below the values actually found; and in the case of the urine samples, the sensitivity was found to be at least one order of magnitude below the lowest values found in the literature for normal individuals.

X-ray fluorescence analysis of seven ~~DELETED~~ urine samples clearly showed the increased excretion of zinc and lead following treatment by Ca-DTPA. Increased excretion of other metals was also indicated but could not be statistically verified from the few measurements made and the large range of literature values for normal individuals.
17. Expected Results in FY 1978: The first step in this project will be development of a valid assay method for total DTPA in the excreted urine of animals and man. Development will be based on methods described in the literature but would be directed toward overcoming their limitations in sensitivity and susceptibility to urinary interferences. A detection level of 10^{-5} M will be sought since the method could then

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detect anticipated urinary concentrations of DTPA for at least 16 hours after the usual 1-gram injection of Ca- or Zn-DTPA in man. This level is at least one order of magnitude less than that detected in urine by published methods, but it is still within the analytical capabilities for detecting DTPA in the absence of interfering substances and is considered an attainable goal.

Subsequently, all of the 600 currently available ~~urine~~ urine specimens will be analyzed for DTPA by the above method and for metals by XRF spectroscopy. The concentration and total content of the following elements will be determined (those considered essential for normal metabolism are underlined):

Na P S Cl K Ca Ti V Cr Mn Fe Co

Ni Cu Zn Ga As Se Br Rb Sr Hg Pb

The same samples analyzed by XRF spectroscopy would be counted for ^{241}Am content on a high-resolution spectrometer with an intrinsic germanium diode detector and optimized for low-energy photon counting. In addition, supplemental analyses for sodium and chloride ions in each urine specimen will be carried out utilizing electrodes selective for these ions.

18. Expected Results in FY 1979: Although most of the analytical work should be completed by the end of FY 1978, full exploration of the relationships between the data is expected to require time in FY 1979. Also, separation of the major metal-DTPA and Am-DTPA chelates in selected urine samples will be attempted using chromatographic techniques. If successful, the contention that some tightly bound americium complex is excreted without being chelated to DTPA will be tested by determining whether the Am-DTPA fraction accounts for all or only a portion of the urinary americium.

The analytical data will be correlated with time of sample collection, time and amount of DTPA treatment, time and amount of oral zinc administration and any available dietary data. This information will be examined statistically for possible abnormal excretion of various elements. To do this, measured data will be compared with literature values, and they will also be examined for consistently decreasing values indicative of metal depletion. As a back-up to literature values in estimating the normal range of excretion values, urine samples from a group of laboratory volunteers will be collected and assayed utilizing the same analytical equipment. The advice and aid of the Battelle-Northwest Statistics Section will be utilized in these and other comparisons to be made in this project.

The correlated data will also be examined for evidence showing the effect of oral zinc supplements on the excretion of essential metals and on ^{241}Am excretion. Relationships will be sought which suggest appropriate use of these supplements during DTPA therapy.

The variations of urinary DTPA concentrations with time after intravenous injection will be used to estimate the kinetics of DTPA release from the body. The concentration ratios of americium to DTPA in the urine samples will be analyzed in an attempt

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to identify the DTPA concentrations required for best removal of americium. Such information should be of value to physicians in establishing more effective DTPA regimens for optimal removal of radionuclides. In addition, the evolved relationships between the human data will be compared with the results of animal experiments described in the literature in order to judge the adequacy of animal models for predicting the effects of DTPA salts on man.

Finally, a comparison will be made of the relative merits in the several Ca- and Zn-DTPA administration schedules used in promoting excretion of ^{241}Am . The analytical results will include data showing the effects of daily single and multiple administrations of Ca- and Zn-DTPA, as well as the cumulative effects of protracted administration of these compounds. The excretions of ^{241}Am and essential trace metals observed after each type of administration will be correlated in order to provide a balanced view of the merits in the various schedules.

19. Description and Justification of Major Materials, Equipment, and Other Unusually Significant Cost Items: None
20. Comments: Contributing investigators: K. K. Nielson, X-ray fluorescence spectroscopy; V. H. Smith, DTPA pharmacology; and M. A. Wincek, statistical analysis.

If funded, the work proposed hereunder would be subject to approval by the PNL Human Subjects Committee.

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