Appendix C

Summary of TRS Audit Procedure

The following text was excerpted from the TRS QA/QC Audit Report for the Greer study. For complete details of the procedures and results, the reader is referred to the actual TRS audit report and DOD consultative letter which can be found on EPA's data CD as document ID# 98977.

TRS was contracted by *TERA*, on behalf of the Perchlorate Study Group (PSG) to audit the documentation for protocol/study conduct and the accuracy and reliability of the thyroid function data, and the serum and urine iodine measurements of the subject study, in support of a PB/PK model that is to be submitted to the U.S. EPA. In addition, the serum chemistry, hematology (CBC), drug testing, and preliminary urinalysis data were evaluated. TRS was free of any conflict of interest. They had not previously conducted any work or audits for *TERA*, the PSG, or the Oregon Health Sciences University.

The results of the audit were summarized into five tables:

- Protocol Requirements and Study Documentation Review
- Thyroid Function (Serum) Data
- Serum Iodine Data
- Urinary Iodine Data
- Serum Chemistry, Hematology (CBC), Drug Test and Preliminary Urinalysis

Some data were reviewed in a previous QA/QC audit by M. G. Schneider, which is documented separately. These data included the RAIU results, perchlorate dosing, and serum and urine perchlorate analyses. The TRS audit report and DOD consultative letter can be found on EPA's data CD as document ID# 98977.

I. Specific QA/QC Procedures

The following outline documents the specific procedures that were followed for the QA/QC review of the data supplied to TRS for adherence to protocol, and the results of the thyroid function tests and serum and urinary iodine measurements.

A. Protocol requirements (Table 1)

A review of the study documentation was conducted to determine that the protocol was followed as written. In addition, the auditor was looking for documentation that the blood and urine samples required by protocol were collected. The following documentation found in each subject's folder was reviewed:

1. OHSU subject record (which was sanitized to provide only subject ID, body weight and dose calculation, and to exclude several preliminary protocol required elements, such as physical examination, thyroid palpation and drug screen results);

2. OHSU Consent Form;

3. Subject Study Log Forms documenting perchlorate ingestion and urine collections;

4. OHSU printout documenting administration of the ^{123}I.

5. OHSU Nursing Flow Sheet (NFS) - , a form that identified the protocol-required elements by "x" in each pertinent box, and which documented that the protocol element was followed by the nurse placing a handwritten "3" next to the "x"). The nurses also used this form to record body weights and other study notations, including the initials and/or signatures of the nurses completing the form; and

   Because the NFS were never intended to be the raw data documentation of sample collection, additional documentation was provided to the auditor in the form of Excel spreadsheets. These spreadsheets contain the transcribed information from the lab slips and sample labels. To verify that the required samples were collected when this information could not be located in the subjects' folders, these spreadsheets were used. No attempt was made to audit all of the entries recorded in the spreadsheets. However, two subjects from the main study and two subjects from the uptake only (short) study were randomly selected for review of all their data points entered in the spreadsheets. This additional review was included to verify that this database accurately documented the sample collection.

B. Thyroid function (serum) data (Table 2)

TRS conducted a complete review of the thyroid function data for each subject. The thyroid function analyses data were provided in each subject's folder and in the USAF.XLS Excel Spreadsheet made available by the OHSU laboratory. The date and time of blood collection were verified against the specified date and time that the blood collection required by the protocol.

Table 2 of the audit identifies the thyroid function parameters that wer ruquired by the protocol for each interval and indicates what parameters were available in the raw data. Discrepancies are noted.

C. Serum and urinary iodine measurements (Tables 3 and 4)

In the initial review of these data, TRS identified that the data were collected and analyzed using two different methods. Some of the data were recorded manually and calculations were performed using Excel spreadsheets prepared by the laboratory. TRS has a standard policy to audit 100% of all manually collected data; however, due to the large volume of manually collected data and the time constraint for completion of the audit, it was determined that at least 20% of the data would be audited. The results of the audit of 20% of the data would determine if a full audit of these data were necessary.

Therefore, TRS chose nine subjects (approximately 20% of the population) for whom all of the data would be checked for accuracy of the manual transcriptions into the spreadsheet and accuracy of the manual calculations. The formulas used were also confirmed visually in the Excel spreadsheet. In order to check the accuracy of the calculations, TRS requested electronic copies of the Excel spreadsheets and copies of the hand-generated standard curves for the serum and urine iodine measurements for the following nine subjects:

1. General procedures for evaluation of serum iodine data (all subjects):

a. Performed QA/QC for all serum iodine data using the hand-recorded raw data sheets, including the standard curves and the Excel spreadsheets as appropriate.

b. Verified that all protocol-required samples were analyzed in duplicate.

c. Verified that all analyses required to be repeated as noted on hand-recorded raw data sheets or Iodine Calculations Excel spreadsheets were performed.

d. Utilized provided spreadsheet, where possible, to verify sample collection for missing data analyses or to clarify discrepancies found in the raw data documentation.

2. Procedures for evaluation of serum iodine data from the nine subjects (20%) noted above:

a. Checked all %T values for the standards of 0, 0.02, 0.04, and 0.06 µg I against the hand-recorded raw data sheets and the hand-recorded standard curve sheets.

b. Verified all µg I values recorded on the hand-recorded raw data sheets against the hand-recorded standard curves.

c. Verified all manually calculated Total I ug/dL values (µg I/sample size).

d. Verified the Iodine Calculations Excel spreadsheets for the one subject where the results were analyzed using Excel, as described for the urine analysis data (see below).

3. General procedures for evaluation of urinary iodine data (all subjects):

a. Performed QA/QC for all urinary iodine data using the electronic copy of the spreadsheets and the hand-recorded raw data.

b. Verified that all protocol-required samples were analyzed in duplicate.

c. Verified that all required repeat analyses, as noted on the Iodine Calculations Excel spreadsheets or the hand-recorded sheets. were performed.

d. Checked the subjects' folder for documentation that the urine samples were collected, and confirmed that the dates and times corresponded to the entries on the Iodine Calculations Excel spreadsheets and hand-recorded raw data sheets.

4. General procedures for evaluation of urinary iodine data from the nine subjects identified above:

a. Checked all entries on the Iodine Calculations Excel spreadsheet for set, date, tube #, date, time, %T, amt (mL) and all %T for standards of 0, 0.02, 0.04, and 0.06 µg I against the hand-recorded data.

b. Verified Total I ug/dL

c. Verified µg I values

d. Verified values in the Results and final Results tables

D. Serum chemistry, hematology (CBC), drug test, preliminary urinalysis (Table 5)

Verified the presence of these data points as per protocol. The protocol specified that thyroxine-binding globulin was a test required for the serum chemistry profile. Since this parameter was routinely analyzed separately from the other serum chemistry parameters, the presence of this analysis was also documented.

TRS compiled the results of their audit into 5 tables.