Memorandum

To: Savannah River Site Work Group and SEC Issues Work Group
From: SC&A, Inc.
Date: June 3, 2020
Subject: Summary Position on Trivalent Bioassay Variability

Introduction and Background

The National Institute for Occupational Safety and Health's (NIOSH's) guiding documentation for the formulation and evaluation of co-exposure modeling (formerly referred to as coworker modeling) is contained in the document, DCAS-IG-006, revision 00, "Criteria for the Evaluation and Use of Co-Exposure Datasets" (NIOSH, 2020), hereafter referred to in this memorandum as the "Coworker Criteria." One of the four tenets described in the Coworker Criteria is the concept of "data adequacy," the general evaluation of which is described as follows:

> The measurement techniques employed must be evaluated to ensure that they are capable of quantitatively measuring the exposure of interest. [NIOSH, 2020, p. 5]

The Coworker Criteria further states:

> The quality of the available data also needs to be considered. This would include a review of the appropriate collection and analysis of blank samples. When paired measurements are available, the precision between measurements should be examined. **If widely different results from the same aliquot are observed, the effect this might have on the usefulness of the data should be considered.** [NIOSH, 2020, p. 6; emphasis added]

SC&A first expressed concern about the issue of observed variability among multiple aliquots of trivalent actinide—americium/curium/californium (Am/Cm/Cf)—bioassay samples at the Savannah River Site (SRS) as far back as February 2014 (SC&A, 2014, pp. 6–31; SRS WG, 2014, pp. 186–198). Tables 1–3 of SC&A (2014) presented 188 individual examples of trivalent bioassay samples that were greater than the detection limit and contained multiple aliquot measurements that displayed significant variation among individual normalized disc results. These examples were originally taken from an electronic compilation of values produced by NIOSH at the time. Since SC&A (2014), the bioassay database has undergone revision and quality assurance tests as part of the formulation of the SRS co-exposure model (NIOSH, 2019).

Therefore, SC&A revisited the 188 samples identified in SC&A (2014) to assure the samples (1) were valid (e.g., not marked "lost in process") and (2) represent single voidings rather than multiple voidings taken throughout a given day or on multiple days. Based on this updated

dataset, SC&A identified 145 individual samples that had ranges of individual disc results that were greater than ±20 percent of the average value of the sample (i.e., one of the disc results was less than 80 percent or greater than 120 percent of the average/reported value). Of the 145 samples, 137 showed individual disc measurements that ranged greater than ±30 percent of the average value. The average of observed disc variability over the 145 identified samples was 53 percent[1] to 157 percent (or approximately ±50 percent) of the average value.

The most recent discussions concerning variability in trivalent bioassay results occurred at the joint SRS and Special Exposure Cohort (SEC) Issues Work Groups meeting on December 5, 2019 (SRS and SEC WG, 2019). Given the long time that had passed since the subject was originally broached and the lack of resolution between NIOSH and SC&A, the joint work groups tasked SC&A with consolidating its position and reviewing two references provided by NIOSH that describe the analytical chemistry process for trivalent bioassay analysis. This memo presents SC&A's consolidated position and commentary on the references provided by NIOSH.

Summary of Concerns with Analytical Method and Observed Results

In response to discussions at the December 2019 SRS-SEC work group meeting, NIOSH provided SC&A with two references that describe the analytical methods used by SRS Analytical Chemistry:

1. "Determination of Actinides in Biological Samples with Bidentate Organophosphorus Extractant" (Butler & Hall, 1970)
2. "Two Californium-252 Inhalation Cases" (Poda & Hall, 1975)

While these documents provide illustrative information on the general methods used to quantify trivalent actinides at SRS, the references do not specify actual laboratory benchtop procedures, performance indicators, or quality assurance guidelines that might explain the observed variability in a scientifically acceptable manner.

While the choice of analytical bioassay protocols is appropriate, the documentation provided regarding the bioassays performed by SRS for the determination of trivalent actinides is not adequate to support a determination of dose. The logbook and other SRS records present a number of technical questions that must be answered before deeming the results technically adequate. Unfortunately, we are unable to identify the information needed to answer these questions in the SRS logbooks. Additionally, the analytical protocols specify actions that are not documented in the logbooks, and we see documentation of actions that are not represented in the protocols and for which there is no technical justification. We have detailed the most pressing technical issue below. However, there are several other related issues that are similarly problematic. In the interest of brevity, we briefly discuss the issue of spike recoveries in this memorandum, due to its importance in establishing the technical adequacy of the laboratory data.

The records indicate multiple counts of what appear to be multiple sample preparations from separate aliquots of the same sample (discs), although we are not certain what these values represent. Some discs were counted twice, others as many as five times. The records do not

[1] This value excludes 8 samples that reported negative or zero as one of the individual disc results.

clearly provide information about them, and, in many cases, the multiple counts exhibit sufficient variability to call into question whether they represent the same sample, as discussed below. Specific questions include:

- Are they multiple aliquots from the same sample correlated with a specific void?
- Were multiple aliquots taken from what appeared to be different fractions on a sample based on observable attributes or anticipated chemical difficulties attributed to nonhomogeneous samples in the interest of representativeness?
- If multiple aliquots were taken, can we assume that they are of the same or equivalent volumes?
- What is the technical basis for this approach, and where is this aspect referenced in an analytical protocol (e.g., SRS, 1987, 1993)?
- Whatever the multiple counts represent, is this approach adequately represented in the determination of the method's measurement uncertainty?
- How much variation between discs is acceptable such that a simple average of all values is considered representative?
- Is there an acceptance criterion for the degree of variability (e.g., not to exceed 50 percent at a given disintegration rate)?

Simply put, there is a lack of clear direction or explanation of (1) why the multiple counts were made, (2) what the multiple counts represent, (3) where in the referenced analytical protocol this approach is warranted or desirable, and (4) what objective evidence indicates that the degree of variability observed is technically appropriate.

Regarding the variability mentioned above, table 1 presents results in disintegrations per minute per 1.5 liter (dpm/1.5 L) from nine discs, all of which were counted multiple times and showed reported values greater than 3 dpm/1.5 L. There are other examples with values closer to the detection limit of 0.3 dpm/1.5 L as presented in SC&A (2014). We focus on the disc results in table 1 because they all have reported values greater than 10 times the method detection limit of 0.3 dpm/1.5 L and should display precision comparable to the method's stated performance in the literature.

Table 1. Selected values from multiple counting of discs

Date	Reported value	Value 1	Value 2	Value 3	Value 4	Value 5	Value 6	SRDB reference
5/20/1986	5.7	3.66	11.18	6.04	1.79	—	—	53283, PDF pp. 288–289
5/17/1986	8.4	8.64	6.79	2.72	15.3	—	—	53283, PDF pp. 284–285
9/26/1983	3.3	2.393	4.956	2.684	-0.032	—	—	53283, PDF pp. 98–99
1/13/1984	12	4.526	15.007	15.191	—	—	—	53283, PDF pp. 118–119
6/6/1986	13.9	2.22	18.965	14.471	39.637	4.819	3.759	52022, PDF pp. 6–7

Date	Reported value	Value 1	Value 2	Value 3	Value 4	Value 5	Value 6	SRDB reference
5/21/1986	18.9	12.5	14.8	17.9	30.5	—	—	53283, PDF pp. 286–287
7/15/1986	3.5	3.54	-5.52*	3.55	0.566*	—	—	52022, PDF pp. 14–15

* It appears that these values, along with several other measurements on this logbook page, may have been crossed out at some point. However, no reason is provided (e.g., disc contaminated, lost-in-process, equipment malfunction, etc.).

On face value, these data require additional information to make them useful in supporting a valid dose assessment. There may be technically appropriate reasons for these multiple measurements and the manner in which the data have been treated, but SC&A has not found this information in source documents that have been provided to date. Based on the experience of SC&A personnel, SC&A can propose reasons why these apparent anomalies might have been reasonable approaches to address specific analytical problems. However, the records provided to date lack objective evidence that would be required to conclude that the trivalent actinide values are adequate to support a dosimetric determination. If we were able to answer the technical questions listed above, and others, we may be able to determine that these values are indeed technically adequate.

Examples of the information required to answer these questions include the following:

- example of formal SRS or laboratory calculations with all terms identified and a clear indication of the values used for volume, counting efficiency (counts per disintegration), chemical yield (target analyte percent recovery based on tracer yields or another technical reason), and measurement uncertainty

- written instructions explaining the technical basis, practice, and procedural controls regarding multiple counts

- prospectively determined acceptance criteria for the performance samples analyzed with each batch (blanks and spikes)

- objective evidence that the laboratory had predetermined acceptance criteria for the performance samples and that these criteria were technically appropriate and were, in fact, applied to routine bioassays

Absent this information, SC&A's concerns about the adequacy of the trivalent actinide data remain unresolved.

Another significant SC&A concern about the logbook evidence concerns batch spike samples. Analyzing spiked samples is a routine aspect of the analytical process and serves the important purpose of providing clear, tangible evidence of the laboratory's ability to quantify the target analyte at meaningful concentrations. Additionally, specific information on spiked samples may shed light on systematic biases in the analytical protocols. Prospectively determined acceptance criteria for spike recoveries are an integral part of this process, although we have not seen evidence of such criteria or their application in the material provided to date. SC&A noted recoveries of samples spiked with the target analyte (Am-241) that range from as low as

6 percent (SRS, 1978–1983, pp. 20–21) to 116 percent (SRS, 1981–1986, pp. 270–271), all of which SRS deemed acceptable, based on signatures of SRS personnel reviewing the data sheets. SC&A also observed situations in which the recovery was zero percent, yet SRS personnel deemed the resulting bioassay samples "OK to report" (SRS, 1981–1986, pp. 228–229). Seeing this range of values and absent evidence that the laboratory had developed and actively applied acceptance criteria for spike recoveries, it is difficult to have confidence in the technical adequacy of the bioassay values.

Standard Practices Concerning Variation of Multiple Measurements

SC&A was not able to find information on the precision of analytical methods related to trivalent actinides at SRS until a 1987 DuPont Standard Operating Procedure (DPSOL), which stated that the Am/Cm/Cf measurements in urine had a minimum sensitivity (also known as the minimum detectable activity or MDA) of 0.3 dpm/1.5 L and a precision at the 95 percent confidence level of ±19 percent at 6 picocuries per 1.5 L (~13.3 dpm/1.5 L) level (SRS 1987, PDF p. 60). This minimum sensitivity/MDA value is consistent with observed reporting levels in the captured Am/Cm/Cf bioassay records throughout the current period under evaluation (October 1, 1972–December 31, 1989). The maximum observed range of examples from SC&A (2014) that were greater than 13 dpm/1.5 L was 16–284 percent of the average/reported value.

Regarding other laboratories and standards of practice, National Council on Radiation Protection and Measurements (NCRP) Report No. 164, "Uncertainties in Internal Radiation Dose Assessment" (NCRP, 2009), provides some additional perspective. NCRP (2009) discusses the OMINEX Project, which conducted a survey of bioassay laboratories and compiled the results for 18 different laboratories included in the study. One goal of the study was to determine the optimum analytical conditions, with a focus on alpha-spectrometric measurements of actinides. The spectral measurements of actinides are considered to be among the most challenging analyses routinely conducted at radioanalytical labs. The optimum conditions determined by NCRP (2009) were based on an uncertainty of <25 percent when considering a total activity of 1 millibecquerel per day (mBq/day) sample (0.06 dpm/day) and considering an MDA of 0.1 mBq/day (0.006 dpm/day).[2] The average uncertainty reported by the participating laboratories was ±30 percent (NCRP, 2009).

The previous estimates of the generally acceptable level of precision are smaller than the average of the observed variation of trivalent actinides, which was approximately ±50 percent in the SC&A (2014) examples and revisited for this memorandum. One sample where the reported value was greater than 13 dpm/1.5 L had normalized disc results that ranged from 16 percent to 284 percent (refer to example on 6/6/1986 in table 1).

NCRP (2009) also addressed uncertainties about the effects of heterogeneity of the bioassay material (e.g., urine) and stated the following:

> In addition to the normal counting uncertainties due to counting time, detector efficiency, and counting background, the parameters influencing the uncertainty

[2] Note that the MDA/minimum sensitivity reported by SRS Analytical Chemistry was 0.3 dpm/1.5 L.

> of the results include heterogeneity of the material being analyzed, reagent blanks, and chemical yield (tracer recovery).
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> The uncertainty due to the heterogeneity of the material is calculated as SD of the results from repetitive measurements of several subsamples randomly taken from the bottle and analyzed under the same experimental conditions. It has been estimated to be equal to 5 %. [NCRP, 2009, p. 562]

Current NIOSH Response to Variability Issue

In its original response to this issue, NIOSH hypothesized that it was the administration of chelating agents (specifically, DTPA) that was the root cause of the observed variability in different aliquots of the same trivalent actinide bioassay result (SRS and SEC WG, 2017, pp. 108–119). However, in its most recent response, NIOSH has withdrawn that hypothesis (NIOSH, 2019, p. 2) and instead focused on the practical significance of the observed variation. Specifically, NIOSH (2019, p. 2) states:

> [NIOSH does] not agree that the observed variability in repeated counts prohibits use of the bioassay data for developing coworker models, primarily because:
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> - As discussed, the analytical result for a given sample can be the average of multiple counts of its planchet,
> - The bioassay results for a given person in a given year are averaged using the time-weighted one person–one statistic (TWOPOS) method,
> - The TWOPOS bioassay results for all monitored workers in a given year are averaged (via the fit of a lognormal model to the data), and
> - The 50th percentiles of the lognormal fits to the annual TWOPOS data are averaged [using the Interactive Modules for Bioassay Analysis (IMBA)] to come up with a 50th-percentile chronic intake rate over the range of years being modeled. The same process is repeated for the 84th percentile.
>
> In summary, the repeated averaging of the bioassay results before they are used in the coworker model makes the variability observed in multiple counts of a given planchet of no practical significance with respect to the final coworker model.

SC&A concedes that the statistical analysis mechanisms used on valid bioassay data during the construction of a co-exposure model may obviate the practical significance of the observed variation in the final co-exposure assignment (i.e., the intake rates assigned to an unmonitored worker). However, SC&A does not believe that this constitutes a sufficient scientific explanation of the observed variability to alleviate SC&A's concerns about the adequacy of the data for use in both individual dose reconstruction and co-exposure modeling. It is SC&A's opinion that before applying the analysis steps described in NIOSH (2019) (and shown above), the Coworker Criteria regarding the adequacy of the data must be sufficiently established. If the bioassay data are not deemed adequate prior to application of the co-exposure methodology, then the resulting co-exposure results should likewise be deemed inadequate.

Conclusion

It is SC&A's opinion that observed variability in trivalent actinide bioassay samples has not been sufficiently explained to justify use of the bioassay data in either individual dose reconstruction or co-exposure modeling. SC&A finds that the observed variability falls outside the scope of the SRS precision reported in the 1987 procedure, DPSOL 47-206, as well as the precision reported for other laboratories. Furthermore, the lack of documentation and objective evidence supporting our understanding of what exactly these data represent prevents us from accepting the results as technically adequate.

In summary, SC&A does not find that the current NIOSH position (which concludes that the multiple averaging process inherent in co-exposure modeling renders the observed variation of no practical significance) provides an adequate scientific basis to justify the use of the trivalent bioassay data under the auspices of the Energy Employees Occupational Illness Compensation Program Act. Further, SC&A believes that data adequacy should be established *before* the use of such data in co-exposure analysis; thus, NIOSH's position is of limited relevance to the questions of data adequacy. Therefore, SC&A's concerns about trivalent bioassay data variability remain unchanged, given the current state of knowledge concerning the specific operation and procedures of the SRS analytical laboratory for trivalent actinide analysis. However, additional documentation of benchtop procedures, quality assurance criteria, and/or interviews with Analytical Chemistry workers who specifically performed such work may obviate SC&A's concerns.

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