Introduction to Analytical Problem Solving

In your previous science courses you have been introduced to the scientific method. The scientific method describes the systematic way that scientists carry out their work. The scientific method breaks the process of designing, executing and interpreting the results of experiments into discrete steps based on developing and testing a hypothesis. A unique aspect of analytical chemistry is the development of new analytical methods or techniques to address scientific questions. Analytical chemistry can be defined as "the science of inventing and applying the concepts, principles, and…strategies for measuring the characteristics of chemical systems." (Murray, R. W. 1991. *Anal. Chem.*, **63**, 271A). If these new analytical methods are adopted by other scientists, they may serve as enabling technologies that can advance the work of an entire field. For example, new technologies for DNA sequencing based on capillary electrophoresis and protein analysis using mass spectrometry have had significant impact on the questions being addressed by biologists.

Analytical chemists often use a variant of the scientific method, called the *analytical approach* to problem solving (Laitinen, H.A.1966. *Anal. Chem.* **38**, 1441). This analytical approach reflects the unique role of analytical chemistry in solving complex, real world problems. A nice discussion of the field of analytical chemistry and the analytical approach can be found in Chapter 1 of David Harvey's textbook, Analytical Chemistry 2.0 (http://fs6.depauw.edu:50080/~harvey/eText%20Project/AnalyticalChemistry2.0.html). Like the scientific method, the analytical approach can be broken into several steps.

The Analytical Approach

1. Identify and define the problem
2. Design the experimental plan/procedure
3. Conduct the experiments to produce data relevant to the problem
4. Analyze the experimental data
5. Propose a solution to the problem

Many analytical problems are sufficiently complex that the scientist does not simply proceed through the steps in a linear fashion, but instead works in an iterative fashion. Once analyzed in detail, the experimental data obtained may reveal gaps or contradictory results that prompt the scientist to define new experiments to propose an alternative solution to the problem being addressed, or to address a new problem encountered in the course of data analysis and interpretation.

1. Identify and define the problem. Depending on their jobs, analytical chemists may work in two complementary modes of practice. In one mode, the analytical chemist works similarly to any other scientist involved in basic research to address a hypothesis in a scientific area by developing new measurement methods or techniques. The second aspect of analytical chemistry practice hinges on the importance of chemical measurements to address technical problems related to manufacturing and regulation. In this mode, the analytical chemist may be a member of a team addressing a particular problem and the goal may not be to answer questions to test a hypothesis, but to solve a particular practical problem. The problem may

originate outside the lab of analytical chemist, and be communicated by someone who is not an expert in chemical measurements. Therefore, the first step of the analytical process is to identify and define the problem. This is best accomplished through discussions with others involved in answering the problem; therefore, analytical chemists must be adept in communicating with other kinds of scientists, as well as people without formal scientific training. This step of the analytical process typically involves translating a larger, overarching problem into a series of specific questions that can be answered by chemical analysis.

One important aspect of the problem to consider is the nature of the chemical analysis required. The problem may require quantitative analysis, i.e. how much of a contaminant such as a pesticide is present in a water, blood or food sample. In this example, the analytical chemist knows the identity of the target analyte, but often faces the difficult challenge of obtaining accurate and precise measurements of analytes that are present only at very low levels in samples that are complex and/or are only available in limited quantities. In other cases, the problem may require qualitative analysis to determine the identity of an unknown. For example, an analytical chemist might want to determine the chemical structure of a biologically active component of an herbal medicine used by the indigenous people of a rainforest community.

2. Design the experimental plan/procedure. Once the problem has been defined, the next step is to design an experimental plan to collect data needed to address questions raised in the analysis of the problem. The experimental plan typically has several elements that will need to be considered.

Selection of the method of analysis

- What analytical methods are best suited to provide the information required?
- Of these, which techniques are available for the analysis?
- Are there cost or timing issues that will influence the choice of method?
- Do the available methods have sufficient selectivity for the type of sample that will be analyzed?
- What is the anticipated range of analyte concentrations?
- Is there a target concentration that is important for regulatory purposes?
- Is the analyte in a form (solid, liquid, gas) suitable for the analytical method selected?
- What precision is required to address the problem?
- How will the method be validated?
- What type of calibration will be used?
- Do any of the reagents used need to be standardized?
- Can a reference standard be used to ensure accuracy?

Sampling

- How will the samples be obtained and how many samples will be required?
- What physical/chemical method will be used to collect samples?
- Will the samples be acquired at discreet time points, collected over a period of time, or can the measurement be performed in real time *in situ*?
- If the object to be sampled is large, how can we ensure that the samples taken will be a good representation of the whole?
- If the object to be sampled is small, what limitations will the amount of sample available place on the analytical measurements?
- How long can the sample be considered to be stable?

Sample preparation

- Are there strategies for improving sample stability (i.e., container choice, pH adjustment, filtering, refrigeration, blocking light exposure)?
- Is the sample in the correct physical form (e.g., liquid, solid or gas) for the analytical method selected?
- Are there potential interferents that need to be removed prior to analysis?
- Does the level of the analyte need to be adjusted prior to analysis by dilution or concentration?
- If an extraction is used, how can the amount of sample recovered be determined?
- Should an internal standard and/or surrogate standard be added to aid in quantitation?

3. Perform analysis. The samples will be collected, treated and subjected to analysis according to the plan developed in step 2. The first step in performing the measurements is to verify that the instrument is working properly, i.e. it can be calibrated and gives stable results. Calibration standards, reference standards, blanks, and sample replicates will be analyzed as determined by the validation plan. When analyzing a large number of samples, it is common to intersperse standard and blank solutions regularly in the sample queue, for example after every 10 samples, to account for instrument drift that can occur during the analysis of large numbers of samples.

4. Data Analysis and Interpretation. Once the data has been acquired, it must be converted into a format that leads to meaningful interpretation. For example, the output from a GC-MS experiment will be the ion current produced at a given chromatographic retention time. Interpretation of the data begins by confirming the identity of the compound giving rise to a peak by matching the retention time and MS ions to those obtained for a standard compound. The linearity of the calibration plot is determined and the effects of drift over the course of the

experiment taken into account. Quantitative analysis typically involves comparison of the integrated ion intensity of the analyte to that of an internal standard and a surrogate standard used to account for losses during the sample preparation step. Finally, the output is converted to a mass amount or concentration unit describing the original sample.

Before data interpretation can begin, the quality of the experimental results must be evaluated. This involves examination of the precision of replicate analyses of the sample, standards and blanks, the accuracy of the results obtained for reference standards or spiked samples, and the values obtained for blanks. The method validation and experimental plans should be reexamined in light of the results obtained. Are the analyte concentrations measured in the appropriate range for the instrument and calibration procedure used? Are the accuracy and precision obtained sufficient to answer the questions raised by the problem? Were a sufficient number of samples and replicates analyzed to satisfy the quality requirements (i.e. confidence limits) for the question asked?

5. Propose Solution to the original problem. We have now reached the point in the analytical approach to problem solving where the analytical scientist, often in conjunction with others involved in the project, reflect on the results obtained. Were the data obtained sufficient to answer the questions raised by the problem? If not, do the data suggest a new problem that needs to be addressed? If a new direction is to be taken, the analytical process would then begin again with step #1, in which this problem would be clearly defined in terms of questions that could be addressed by chemical analysis. Then each of the steps in the analytical process would be followed in turn.