U.S. Department of Health & Human Services

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Elemental Analysis Manual

for Food and Related Products

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3.3 Measurement Uncertainty

Version 3.0 (December 2021)

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Measurement uncertainties, whether stated specifically or implied, accompany elemental analysis results.

A reported result is the best estimate of the element's actual level (i.e., its true value) but its uncertainty gives additional technical insight. It provides a range within which the true value is believed to be with a stated probability (level of confidence).

As described in detail in EAM 3.2, elemental analysis involves many inter-twined terms and concepts that can be confusing, especially when people often define and use them differently. Moreover, data (known values) are used as evidence for predicting uncertainty (unknown quantities). For example, the imprecision observed during an analysis (i.e., a known quantity based on actual data) is the basis for estimating the random error uncertainty component (which is an estimate or prediction - i.e., an unknown quantity).

3.3.1 TYPES OF UNCERTAINTY

Table 3.1 shows four basic types of uncertainty discussed in the EAM.

3.3 Table 1 Types of uncertainty

type	accounts for	conf. level
component	single source of uncertainty	68%
combined	2^+ components	68%
total	"all" components	68%
expanded	total (but higher conf. level	95%, 99%

An uncertainty component (u_i) is the uncertainty attributed to an individual aspect (also called an influence factor or input quantity) of an analysis and two or more components can be combined to a single value, which is called combined uncertainty (u_c). Total combined uncertainty (u_{total}) is a comprehensive value that is supposed to account for all of the uncertainty components. However, u_{total} is more ambiguous than it would seem because there are different options for how it is calculated. An explanation on how it is calculated must therefore be either given when results are reported or made available in a laboratory's documentation.

Confidence level is a characteristic of uncertainty. Component, combined, and total uncertainties are all expressed as "standard uncertainty", corresponding to a single standard deviation of a normally distributed population which provides a ≥ 68.27% coverage probability (~68% confidence level). When uncertainty is presented in tables or given in reports of analysis, it is almost always provided as "expanded uncertainty" (U) at a relatively high confidence level with the most common being ~95% (≥ 95.45% coverage probability, corresponding to 2 standard deviations, sometimes called a 2-sigma level).

3.3.2 SAMPLING UNCERTAINTY AND HETEROGENEITY

"Sampling uncertainty" is more of a concept than a value to be determined. This term reminds decision makers that a sample is only a tiny segment of the commodity being investigated and that a contaminant level will actually vary in the marketplace. Sampling uncertainty is very important when judging compliance or developing monitoring programs and addressed in detail in a Eurochem CITAC guide[2]. However, it is outside the scope of analytical uncertainty and not discussed further in the EAM.

"Heterogeneity" will be used in the EAM to describe the variability of an analyte in a laboratory sample and is taken to be the standard deviation of the analyte in the test portions and thus a component of the total (observed) imprecision (standard deviation). The uncertainty associated with heterogeneity can therefore be estimated from the imprecision of replicate test portions, but only in relation to the total imprecision accepted for the measurement process.

Mathematically, the observed standard deviation (σ_{obs}) is accepted to be related to the measurement standard deviation (σ_{meas}) and the heterogeneity standard deviation ($\sigma_{heterog}$) according to Equation 1.

$$\sigma_{obs}^2 = \sigma_{meas}^2 + \sigma_{heterog}^2 \qquad \text{3.3 Equation 1}$$

From Equation 1, three general situations may occur. If the laboratory sample is very homogeneous, σ_{nonh} is negligible and $\sigma_{obs} \sim \sigma_{meas}$. If the laboratory sample is very nonhomogeneous, then σ_{meas} would be masked so $\sigma_{obs} \sim \sigma_{heterog}$. If there is no insight about heterogeneity, the only conclusion available is that σ_{meas} and $\sigma_{heterog}$ a are both $< \sigma_{obs}$.

Purpose designed studies to estimate homogeneity uncertainty are well defined in the context of reference material production (ISO Guide 35), but are rarely practical in routine analysis. When σ_{meas} is known, such as via a separate uncertainty budget study or a laboratory's experience, Equation 1 can also be used to calculate a value for $\sigma_{heterog}$. Although this calculation is seldom performed definitively, the essence of it is instinctively performed by sight whenever replicates are analyzed. An analyst will notice when, for example, σ_{obs} is unusually large (that is, when σ_{obs} is larger than would be expected due to analytical error only). In this case, the analyst knows heterogeneity is significant. This fact will likely not affect how the results are reported but it would be useful for deciding whether procedures could be changed for future investigations.

Rather than definitively estimate the uncertainty associated with homogeneity, the EAM considers it to be incorporated in the observed precision and expects the analyst to take reasonable steps to minimize the impact of inhomogeneity by applying homogenization as needed. Because the types of samples received at laboratories can vary greatly, analyst discretion will always be needed to address potential heterogeneity issues. An analyst needs to decide how to process samples, whether they need to be homogenized, whether single or replicate analytical portions will be appropriate, etc.

3.3.3 DETERMINING ANALYTICAL UNCERTAINTY

3.3.3.1 Approaches

Two fundamental approaches are used to estimate analytical uncertainty[3]. Elemental analysis usually involves a predictive modeling approach commonly called “bottom-up” where an “uncertainty budget” is performed (i.e., uncertainty components for the various steps, parameters, readings, etc., are combined). The other approach is a retrospective empirical approach commonly called "top-down". Top-down encompasses, for example, the data reduction work performed after a multilaboratory validation (MLV) study when performance is being studied. It is also commonly used for methods such as chromatography where individual uncertainty components can be extremely difficult to estimate. Similar to studying MLV results, results from many of a lab’s investigations are combined and performance conclusions are drawn to obtain broad uncertainty generalizations. Since elemental analysis usually involves the bottom-up approach, this is discussed below.

3.3.3.2 Uncertainty budget process

In the EAM, the procedures for choosing and calculating uncertainties follow statistical guidelines[4-6]. Per these guidelines, uncertainty estimates are based on a variety of information, such as data generated during an analysis, approximations based on previous data, experience, and scientific judgment.

Each input quantity is assigned a standard uncertainty component (u_i) which are subsequently propagated to define an interval within which subsequent measurement results are expected to lie. The basic procedure for combining uncertainties is via the root-sum-squares calculation shown in Equation 2. The order calculations are performed and ways in which components are grouped is arbitrary and will vary. The list of components to be combined will also vary because even subtle differences in analytical procedures will be reflected in the components.

$$u_{Total} = \sqrt{u_a^2 + u_b^2 + u_c^2 + \cdots} \qquad \text{3.3 Equation 2}$$

Components being combined must be expressed either all in identical units or all as relative standard uncertainties (i.e., in %). Since the units for analytical parameters depend on the method and how instruments and software are set up, unit conversions are inevitable. In practice, many of the values that need to be included are already well-established in a laboratory. Therefore, this calculation is typically relatively simple.

The error distributions for components can usually be classified as having either a normal distribution or a rectangular distribution. The variance for normally distributed components (such as imprecision for instrument alignment, plasma stability, sample introduction, etc.) are random in nature and their standard uncertainties are estimated using standard deviations. For a mean (e.g., the mean from *n* measurements of a standard solution), the uncertainty would be equal to RSD/√n (i.e., "standard deviation of the mean").

Components for which only the limit of variance is known are represented by a rectangular probability distribution and may be either random or bias in nature (e.g., standard solution accuracy, check solution control limit for long-term instrument stability, etc.). The standard uncertainty of a rectangular probability distribution is estimated by dividing the width of the interval by √3. For example, the uncertainty for a pipettor with an accuracy specification of 1% would be 1/√3=0.58%. Additional geometric probability distributions are described in guidance documents; however, they are rarely applicable and are not further discussed in the EAM.

Some components are characterized by uncertainty in only one direction (e.g., digestion losses). These components could be represented by asymmetric probability distributions. For simplicity and since these components are virtually always of minor significance, they are treated in the EAM as if they are symmetric.

For the purposes of the EAM, each of the component uncertainties are considered to be independent of one another (any potential covariances are treated as negligible).

3.3.3.3 Uncertainty Components

When uncertainty is studied in detail, the number of components can be quite large and the component breakdown will vary, not only for different methods but also according to an analyst's preference on how to combine the components. The relative magnitude of component uncertainties may play a role in which components are included in an estimation of uncertainty. As a general rule, any component which contributes less than 1/3 of the largest component may be discarded as negligible.

For elemental analysis, the following components (and combined components) will typically be the most significant:

meas--------- instrument reading and its uncertainty

std ---------- standardization parameters

blank ------- mean blank level and its standard deviation

matrix ------- maximum effect that could occur and not be noticed

misc --------- miscellaneous

other--------- digestion losses; yield; spectral issues; viscosity; surface tension; etc.

- Signal measurement uncertainty may be available directly, such as from digital peak spectral data (e.g., counts assumed to be governed by Poisson distribution) or may require replicate readings (e.g., multiple aspirations to obtain measurement standard deviation).
- Standardization can involve many details, such as standard solution accuracy, dilutions, instrument readings, etc. Since standardization is highly repeatable, it is common for uncertainty values to be pre-determined at a laboratory then checked or periodically re-established when something changes (e.g., change in instrumentation).
- Blank uncertainty is typically negligible or very low if an analyte is well above LOQ. However, it can be extremely significant when analyte levels are low. Here, the focus is on blank such as would come from reagents and containment vessels and not from spectral baselines and/or instrument characteristics.

  The critical issue for blank is the magnitude of its standard deviation. In one extreme, the blank level could be high but if it is also very stable (i.e., if its standard deviation is very small), there would be only a small contribution to uncertainty. Conversely, a blank can be low but if its standard deviation is high, uncertainty would then be high.

  When not detected (i.e., if blank is below detection), blank can be a major factor. The uncertainty associated with an unknown blank is substantial when an analyte is at trace levels.
- A matrix component is appropriate for many applications, and especially for food analysis where a wide range of foods is encountered. Unless matrix extension studies have been performed for all foods, we accept that small matrix effects could be missed. A matrix component accounts for this possibility.
- Miscellaneous is a useful component that can account for a host of minor items such as weighing, dilutions, standard accuracy, etc.
- Other components would be added, as needed, to account for special circumstances. Examples: ICP-MS ionization, viscosity, and surface tension differences; XRFS Ar trapped in sample; NAA background radiation; etc. This list can be endless.

There is no single way to account for uncertainty components. They can be estimated individually or grouped. For example, a common way to account for several components simultaneously is possible when replicate analytical portions are analyzed. The observed standard deviation (σ_{obs}) is brought into the uncertainty budget equation to simultaneously capture the errors for many of the random components (see section 3.3.3.5).

3.3.3.4 Example - Uncertainty for One Analytical Portion

The uncertainty budget process is illustrated below for a one analytical portion measurement.

> *Example:*
>
> *Zn - 0.500 mg/L (stdev = 0.0250 mg/L for n=3 aspirations)*
>
> *Printout says 5% error for peak area; n=3 aspirations*
>
> *blank - below detection, but the instrument prints out values. The long-term running laboratory mean (now up to n=492 blanks; t ~1.645) is 0.00113 mg/L with standard deviation of 0.0075 mg/L.*
>
> *Standardization - Standard deviation for 3 replicate measurements equaled 0.5%.*
>
> *Instrument drift (e.g., check solution) - In the lab, never deviates more than 3%.*
>
> *Matrix - This (food) has been analyzed many times and matrix effect has been shown to be negligible.*
>
> *Miscellaneous - For this routine procedure, the lab uses an established component (1.36%) to account for the various dilutions and mass measurements.*

The uncertainty can be calculated without blank subtraction and with blank subtraction.

Without blank subtraction

For the no blank subtraction case, Equation 3 is a logical form of the basic equation (Equation 2). Equations 4-9 show calculations for the components. Equation 10 is a repeat of Equation 3 but with numerical values and Equation 11 gives an expanded uncertainty (*U*) at ~95% level of confidence using a coverage factor of 2.

$$\mu_{Total} = \sqrt{\mu_{meas}^2 + \mu_{std}^2 + \mu_{InstDrft}^2 + \mu_{misc}^2 + \mu_{blank}^2} \qquad \text{3.3 Equation 3}$$

$$\mu_{meas} = \frac{STDEV_{meas}}{\sqrt{n_{meas}}} = \frac{0.025}{\sqrt{3}} = 0.0144\,\frac{mg}{L} \qquad \text{3.3 Equation 4}$$

$$\left(convert\ to\ percent\ \frac{0.0144}{0.0500} \times 100\% = 2.89\%\right)$$

$$\mu_{std} = \frac{STDEV_{std}}{\sqrt{n_{std}}} = \frac{0.5}{\sqrt{3}} = 0.289\% \qquad \text{3.3 Equation 5}$$

$$\mu_{InstDrft} = \frac{InstDrft}{\sqrt{3}} = \frac{3}{\sqrt{3}} = 1.73\% \qquad \text{3.3 Equation 6}$$

$$\mu_{misc} = 1.36\% \qquad \text{3.3 Equation 7}$$

Since the blank is below detection, the actual blank value could be any amount between zero and ASDL. This means ASDL (Equation 8; from 3.2 Equation 2) is the boundary for a square distribution and u_{blank} is equal to ASDL/√3 (Equation 9).

$$ASDL = 2 \times t \times s \times \sqrt{1 + 1/n} \qquad \text{3.3 Equation 8}$$

$$(= 2 \times 1.645 \times 0.0075 \times \sqrt{1 + 1/492} = 0.0247 mgL) \qquad \text{3.3 Equation 8}$$

$$\mu_{blank} = \frac{0.0247}{\sqrt{3}} = 0.01426 mg/L \qquad \text{3.3 Equation 9}$$

convert to percent $\left(= \frac{0.01426}{.0500} \times 100\% = 2.85\%\right)$

$$\mu_{total} = \sqrt{2.89^2 + 0.29^2 + 1.73^2 + 1.36^2 + 2.85^2} = 4.63\% \qquad \text{3.3 Equation 10}$$

$$U = 2 \times 4.63 = 9.3\% \qquad \text{3.3 Equation 11}$$

With blank subtraction

For the blank subtraction case, u_{net}, which captures both the signal measurement uncertainty and blank uncertainty, replaces u_{meas} and u_{blank}. Equations 12, 13, 14, and 15 present the basic equation and the calculations for u_{net}, u_{total}, and U, respectively. The values for u_{std}, $u_{InstDrft}$, and u_{misc} are the same as shown above for the no blank subtraction case.

(with blank subtraction) $$\mu_{Total} = \sqrt{\mu_{net}^2 + \mu_{std}^2 + \mu_{InstDrft}^2 + \mu_{misc}^2} \qquad \text{3.3 Equation 12}$$

$$\mu_{net} = \frac{\sqrt{\left(\frac{STDEV_{meas}}{\sqrt{n_{meas}}}\right)^2 + (STDEV_{MBK})^2}}{meas - MBK} \times 100\% \qquad \text{3.3 Equation 13}$$

$$\left(= \frac{\sqrt{\left(\frac{0.0250}{\sqrt{3}}\right)^2 + (0.0075)^2}}{0.500 - 0.00113} \times 100\% = 3.26\%\right)$$

$$\mu_{Total} = \sqrt{3.26^2 + 0.29^2 + 1.73^2 + 1.36^2} = 3.95\% \qquad \text{3.3 Equation 14}$$

$$U = 2 \times 3.95 = 7.9\% \qquad \text{3.3 Equation 15}$$

In this example, where Zn was much above ASQL and the laboratory blank was based on a large number of blanks, there was relatively little difference between the no blank subtract and blank subtract calculations. If the Zn level were lower (at ASQL) and MBK was based on only 5 blanks, *U* for the no blank subtract and blank subtract cases would have been 21% and 14%, respectively.

Note: A more rigorous treatment for setting the coverage factor may be used but the process can be very complex.

As stated in NIST Technical note 1297[3] concerning coverage factors that produce a well-defined level of confidence, "This is difficult to do in practice because it requires knowing in considerable detail the probability distribution of each quantity upon which the measurand depends and combining those distributions ..."

Such a treatment also requires knowing the number of degrees of freedom for the various aspects of the analysis and combining them using a procedure such as the Welch-Satterwaite formula, which estimates the effective number of degrees of freedom to be used in the calculations. This depth of metrological detail is beyond the scope of elemental analysis addressed in the EAM.

3.3.3.5 Example - Uncertainty for Multiple Analytical Portions

When multiple analytical portions are analyzed for a laboratory sample, additional information is available. In this case, random error is captured in the standard deviation.

Example:

Same example as above in all respects other than the following:

Zn (0.0500 mg/L) comes from three replicate analyses (0.476, 0.485, and 0.539)

Assuming the mean is given in the report of analysis, the standard deviation of the mean can be used to assign random uncertainty (u_{random}) and account for all but the potential bias components. Although this will include effects of nonhomogeneity (see section 3.3.2), we also assume the laboratory sample was prepared and the test portions were taken to make nonhomogeneity negligible. The standard deviation for the three replicate analyses is 0.0341. Equation 16 shows conversion of the standard deviation to standard deviation of the mean (division by n=3) so it can be expressed in relative form (i.e., as relative percent).

$$\mu_{random} = \frac{0.0341/\sqrt{3}}{0.0500} \times 100\% = 3.93\% \qquad \text{3.3 Equation 16}$$

Assuming the three measurements were made in rapid succession with no measurable instrument drift, the only other components to be combined with u_{random} are u_{std} and u_{blank}. This is accomplished in Equation 17. The values for u_{std} and u_{blank} were obtained from the preceding example (see Equations 5 and 9, respectively). Equation 18 shows expanded uncertainty.

$$\mu_{Total} = \sqrt{\mu_{random}^2 + \mu_{std}^2 + \mu_{blank}^2} = \sqrt{3.93^2 + 0.29^2 + 2.85^2} = 4.87\% \qquad \text{3.3 Equation 17}$$

$$U = 2 \times 4.87 = 9.74\% \qquad \text{3.3 Equation 18}$$

3.3.4 UNCERTAINTY ON A REPORT OF ANALYSIS

(To be added at a later time.)

3.3.5 UNCERTAINTY AND METHOD DEVELOPMENT - (example for Method 4.4)

In method development, control parameters minimize analytical uncertainty to the extent reasonable in a real-world laboratory setting. To determine what is 'reasonable', the uncertainty budget process is useful. As an example, the process used for EAM Method 4.4, is described where total combined uncertainty was chosen to be 10% relative at LOQ.

An uncertainty budget was set up in a spreadsheet to show total combined uncertainty while adjusting the control specifications and while discussing how these adjustments would complicate or simplify work "at the bench". Calculations without and with blank subtraction were studied.

3.3.5.1 ASDL and ASQL

Two parameters central to the calculations were ASDL (the maximum error possible when blank is below detection) and ASQL (the level defined to have 10% uncertainty).

Equation 19 shows ASDL for n=5 blanks (t = 2.132) and where s is the MBK standard deviation.

$$ASDL = 2 \times t \times s \times \sqrt{1 + 1/n} \qquad \text{3.3 Equation 19}$$

$$\left(= 2 \times 2.132 \times s \times \sqrt{1 + 1/5} = 4.67s\right)$$

When blank is below detection and analyte levels are low (~ASQL), u_{MBK} is the most significant component. As discussed above for Equation 8, if MBK is below detection, then the actual MBK value can logically be anywhere between zero and ASDL. By not subtracting blank, an error will occur up to a maximum equal to ASDL. This describes a rectangular probability distribution, which means the standard uncertainty is equal to ASDL divided by √3 (=2.7s; Equation 20).

$$\mu_{MBK} = \frac{4.67s}{\sqrt{3}} = 2.7s \qquad \text{3.3 Equation 20}$$

After choosing various control parameter options (number of blanks, maximum check solution drift, etc.), we found that ASQL would need to be in the 45s to 50s range if blank is not subtracted or 30s if subtracted. The decision was made to require blank subtraction and set ASQL equal to 30s.

3.3.5.2 Uncertainty Budget

This section shows the final calculations used for the components and their summation to obtain total combined uncertainty of 10%. According to the intent of the calculations, conservative worst-case conditions were assumed, which means variables were at control specifications, the measured level = ASQL (30s; the lowest quantitation level), and MBK=ASDL (the maximum possible undetected level, which is 4.67s per Equation 19).

- u_{net} (from Equation 13)

The control specifications for signal measurement were 7% maximum RSD and minimum of 3 repeated measurements (aspirations, etc.) which are to be averaged. For use in the equation, the 7% signal RSD needed to be converted to absolute form.

$$\mu_{net} = \frac{\sqrt{\left(\frac{STDEV_{meas}}{\sqrt{n_{meas}}}\right)^2 + (STDEV_{MBK})^2}}{meas - MBK} \times 100\% \qquad \text{3.3 Equation 21}$$

$$\left(= \frac{\sqrt{\left(\frac{\frac{7}{100\%} \times 30s}{\sqrt{3}}\right)^2 + s^2}}{30s - 4.67s} \times 100\% = 6.20\% \right)$$

- u_{std} (from Equation 5) and $u_{InstDrft}$ (from Equation 6)

Although u_{std} could have been set via a calibration curve fit, a conservative simplification was used and it was based on the individual standard control limits (5% maximum RSD and 3 aspirations). Minor standardization items, such as those associated with dilutions and mass readings, were captured in the miscellaneous component (see below).

$$\mu_{std} = \frac{5\%}{\sqrt{3}} = 2.89\% \qquad \text{3.3 Equation 22}$$

Instrument drift was purposely given a loose control limit (check solution ±10%) to facilitate high sample throughput. This value (10%) represented the bounds for a rectangular distribution. The uncertainty component was therefore equal to 10% divided by √3.

$$\mu_{InstDrft} = \frac{10\%}{\sqrt{3}} = 5.77\% \qquad \text{3.3 Equation 23}$$

- u_{matrix}

Corrections are always applied for known matrix effects but small matrix effects (such as for new matrices) might not be seen. Since effects greater than 5% would likely be noticed, this was accepted as the limit for a possible matrix-effect bias. Since this represented the bounds for a rectangular distribution, u_{matrix} was 5% divided by √3.

$$\mu_{matrix} = \frac{5\%}{\sqrt{3}} = 2.89\% \qquad \text{3.3 Equation 24}$$

- Miscellaneous Uncertainty u_{misc}

Several small uncertainty components were combined (see 3.3 Table 1). These included standard stock solution purity, reagent blank, standard curve generation, standard and unknown solution dilutions, mass measurement, and nominal digestion losses. The values were based on typical manufacturer's specifications (*e.g.*, pipet and volumetric accuracy/imprecision) or assigned according to past laboratory experiences.

3.3 Table 1. Miscellaneous Uncertainty

Dilutions	uncertainty (%)
pipettor accuracy ≤1%	0.58[a]
pipettor imprecision 0.2%	0.2
volumetric flask accuracy ≤0.1%	0.06[a]
combined (root-sum-sq)	0.61
2 dilutions	0.87
3 dilutions	1.06
Miscellaneous	**uncertainty (%)**
standard stock purity/accuracy 0.2%	0.12[a]
3 dilutions (see above)	1.06
standard blank ≤0.1%	0.0058[a]
curve generation ≤0.2%	0.2
mass measurement (RM 100±0.1 mg)	0.058[a]
digestion losses ≤0.2%	0.115[a]
2 dilutions (see above)	0.87
combined (root-sum-sq, u_{misc})	1.40

[a]Rectangular distribution

Three dilutions were assumed for standard solutions and two for unknown solutions. The digestion loss limit (<0.2%) was considered appropriate for materials posing no exceptional problems, such as routinely-used reference materials. Accuracies and limits characterized rectangular distributions whereas imprecisions characterized normal distributions.

- u_{total} (from Equation 12)

$$\mu_{Total} = \sqrt{\mu_{net}^2 + \mu_{std}^2 + \mu_{CS}^2 + \mu_{matrix}^2 + \mu_{misc}^2} \qquad \text{3.3 Equation 25}$$

$$\left(= \sqrt{6.20^2 + 2.89^2 + 5.77^2 + 2.89^2 + 1.40^2} = 9.5\%\right)$$

Rounding up gave ≤10% total combined standard uncertainty (67% confidence level), which is the assumed (or default) value that can be given with results generated using EAM Method 4.4.

3.3.6 HISTORY

EAM 3.3 Table 2. History

Version	Revisions Made	Effective Date
1.0	*Uncertainty*	June 2008
2.0	Major re-write to expand on concepts and be more general in nature instead of having strong focus on AA and ICP-OES methodology; converted to PDF for web posting.	September 2014
3.0	Updated; added *History* section.	December 2021

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