Application Note

Radionuclidic Impurity Analysis with Apex-Guard™ Software

Purpose

Apex-Guard V1.2 introduces a statistically defensible impurity analysis algorithm for radionuclidic purity (RNP) measurements of radiopharmaceutical samples using gamma spectroscopy. This application note is targeted for users and reviewers of the impurity analysis results. In this document, understand how the algorithm works and learn considerations when deploying the radionuclidic impurity measurement approach.

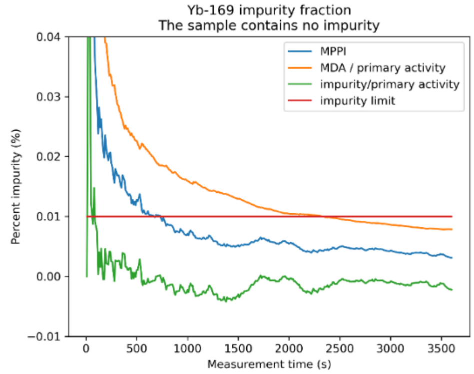

Figure 1 *Evaluation of an Lu-177 spectrum for a non-present Yb-169 impurity at various count times using different evaluation metrics.*

Executive Summary

Apex-Guard implements an integrated impurity analysis algorithm for the purpose of reporting sample radionuclidic purity.

- The algorithm is applicable both for detected levels of impurities and for evaluating measurements where the impurity is not detected in the sample.
- The algorithm takes into account measurement uncertainties and provides a statistically defensible approach by calculating the upper limit of the activity ratio of the impurity radionuclide activity to the activity of a primary radionuclide or the total sample.
- Apex-Guard provides a concise report, enabling an easy-to-decipher comparison to user-defined percent limits for individual radionuclides and the total radionuclide impurity in the sample.
- A discussion of the Apex-Guard methodology versus the minimum detectable activity (MDA) for use in impurity analysis shows that the MDA provides an overly conservative estimate of the activity ratio.

Several other topics are explored in this note, including spectral features that may complicate the analysis, counting functionality improvements, use of external reference activities, and an example with Lu-177.

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Problem Statement

In the production of radioisotopes for radiopharmaceutical applications, it is required to demonstrate that radionuclidic impurity percentages of the sample are below required limits. High-resolution gamma spectroscopy is an attractive measurement technique that can be used for this purpose, as it is non-destructive and allows for quantification of many radionuclides in a single measurement. However, interpretation of gamma spectroscopy introduces many challenges and quantification of impurities is not always straightforward. This is further complicated by the high activity of a primary radionuclide present in the sample, introducing high Compton continuums and random summing features in the spectrum.

Another important challenge is to understand that the absence of a measurable signal in the spectrum does not imply that the radioactive impurity is not present, and even when the signal is present it may be weak and with a large relative uncertainty that may impact the confidence of the result. It is worthwhile to note that approaches to verifying radioactivity of non-detected radionuclides below certain values (i.e., the minimum detectable activities) solves a slightly different problem than introduced by radionuclidic impurity concerns, where one must verify the radioactivity of a non-detected radionuclide is below a certain percentage of the total sample activity.

Finally, many users today rely on manual calculations in spreadsheets, introducing opportunities for human error and limited traceability.

Background and Terminology

Radioisotope production for use in radio-imaging and radio-therapy pharmaceuticals is an important and growing application of radionuclides. Production of these radioisotopes varies and can use techniques spanning from milking of other radionuclides to bombardment of target radionuclides in cyclotrons and linear accelerators to neutron irradiation in nuclear reactors. During the production process, it is possible that other radionuclides or radioisotopes are produced together with the desired radionuclide. These are considered impurities and often can be chemically separated from the sample. The activity of the impurities that remains after the separation can be expressed as a percentage or fraction of the total activity of the sample, which we call the percent impurity. It is typically required to perform quality assurance measurements to verify that this percentage is below a required limit. Conversely, it is also common to report the Radionuclidic Purity (RNP), which is the percentage of the primary radionuclide activity to the total sample activity, and which often must equal or exceed a required limit.

Often the activity of the sample is almost entirely made of the activity of the primary radioisotope, and so in practice users may report the radionuclide impurity as a percentage of the primary radioisotope activity rather than total sample activity. To be more general in our discussion, we simply term the total sample activity as the “reference activity”.

Note: Radioisotope production for radiopharmaceutical applications spans multiple different disciplines, and as such multiple terms are colloquially used. While radioisotope, radionuclide, and nuclide have subtlety different technical meanings, in this application note we treat them interchangeably.

Introduction of Mirion’s Radionuclidic Impurity Evaluation

The Mirion Apex-Guard software is a commercially available gamma spectroscopy solution for radioisotope producers, which Mirion continues to evolve to meet the dynamic needs of these users. The initial release of Apex-Guard built on the established Apex-Gamma Application for high productivity gamma spectroscopy to address GMP and FDA-regulated data integrity requirements. Apex-Guard V1.2 addresses the need to have a generalized, robust, and scientifically defensible radionuclidic purity

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calculation and reporting for gamma spectroscopy. The algorithm calculates a probability density of the ratio of the measured radionuclidic impurity activity to the reference activity, and then determines an upper limit of the true impurity percentage at a defined confidence. This value, called the maximum potential percent impurity, can be used to report if the impurity activity in the sample is lower than the required impurity percentage limit. This approach works for all cases expected in gamma spectroscopy: no signal, weak signal, and large signal.

Theory

This section gives an overview of the theory of the calculation of the MPPI, more details can be found in the Apex-Gamma Lab Productivity Software User's Manual [2]. Consider two measured radionuclides X and Y, with their true activities not correlated and their activity probability normally distributed in the following way: $N_X(\mu_x, \sigma_x)$ and $N_Y(\mu_y, \sigma_y)$ where μ is the measured activites and σ the measured activity uncertainty. The probability density of the ratio Z of the two radionuclides is then

$$Z = \frac{X}{Y} = \frac{N_X\left(\mu_x, \sigma_{u_x}\right)}{N_Y\left(\mu_y, \sigma_{\mu_y}\right)}$$

Equation 1 *Probability density of the activity ratio*

The full expression of the probability density is complicated, but Simon and Ftorek [4] have shown that there is a simpler expression of the probability density. This leads to an expression for the cumulative distribution [Equation 1 below] that is applicable to most practical applications. The Apex-Guard Impurity Algorithm uses the cumulative distribution function whenever appropriate. In two cases the full function is used. The approximation will be used whenever the relative uncertainty of the reference activity is less than 20% and the reference activity is non-zero.

$$F_Z^{\dagger}\left(z_0 \middle| \mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}\right) = \frac{1}{2} + \frac{\mathbf{erf}\left(\frac{p\left(\frac{z_0}{r} - 1\right)}{\sqrt{1 + \frac{p^2}{q^2}\frac{z_0^2}{r^2}}}\right)}{2 * \mathbf{erf}\,(q)}$$

where z_0 is the activity ratio and **erf** is the error function:

$$p = \frac{\mu_X}{\sqrt{2}\sigma_{\mu_X}}; \quad q = \frac{\mu_Y}{\sqrt{2}\sigma_{\mu_y}}; \quad r = \frac{\mu_x}{\mu_y}$$

Equation 2 *Simplified cumulative distribution function of the activity ratio*

For radionuclidic purity quality assurance measurements, it is typical for the impurity radionuclide (defined as radionuclide X above) to have very low activity in the sample or to not be present at all. In this situation, the ratio of the impurity radionuclide to the primary radionuclide activity sample can be evaluated by forcing a calculation of an activity of the impurity radionuclide, for example by calculating gross signal in a region of interest (ROI) and subtracting the continuum. This may result in a measured activity value with a very large relative uncertainty or even a negative activity value. However, when the measured activity value is negative, this result should still be consistent with a zero or positive activity by considering also the measurement uncertainty. Figure 2 shows a spectrum ROI where the calculation of net peak area is negative but with an uncertainty that makes the net peak area, and hence radionuclide activity, consistent with zero or positive.

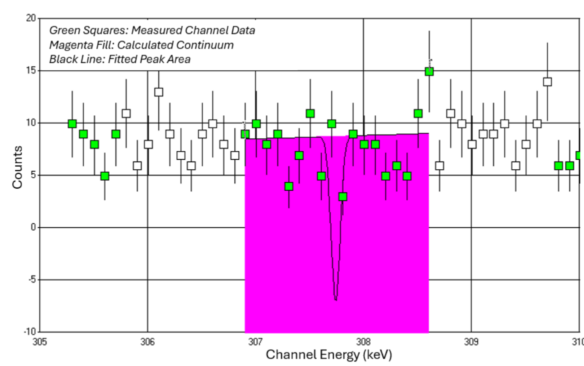

Figure 2 *Calculation of the peak area at the location of a peak from a possible impurity*

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We know that it is not physically possible for the true activity of a radionuclide to be negative; therefore, the ratio of two radionuclide activities also cannot be negative. Unphysical negative activities in mathematical modeling can be addressed by following the recommendations in ISO11929 [5,6].

Therefore, in the Apex-Guard impurity analysis algorithm, the probability density for a negative activity ratio is set to zero and then renormalized such that the total probability is 1. For evaluation of the probability density for the ratio of the activities, one can consider three metrics:

- z is any evaluated ratio, in percent, of the impurity activity to reference activity. The integral from 0 to z is the probability that the true ratio is less than z.
- The confidence limit α, with typical values of 1% or 5%. The confidence limit represents the probability that the algorithm will falsely report an activity ratio that is lower than the true activity ratio, when the true activity is at the limit.
- A new parameter is introduced called the Maximum Potential Percent Impurity, or MPPI, which is the value of the activity ratio z where the probability that the true activity ratio is less than or equal to this value is 1-α. For an α value of 5 or 1 %, a user can be 95 or 99 % confident, respectively, that the true activity ratio is below the MPPI.

To illustrate the effectiveness of this approach, Figure 3 shows an example of a probability density as a function of activity ratio for an impurity with a measured activity of 1 +- 0.7 Bq and primary radionuclide with a measured activity of 1000 +- 20 Bq. One can observe that the most likely true activity ratio value is 0.1% (where the probability density is at a maximum); however, the probability density extends to about 0.35 %. The MPPI marks an activity ratio value where the probability that the true activity ratio is below this value is 95%. In this case it is about 0.22 %. If one would have simply divided the two measured activities and disregarded their uncertainties, one may have reported an activity ratio of 0.1 %. By including the activity uncertainties and the prior knowledge that the activity ratio cannot be negative, we can now say with 95% certainty that the true activity ratio is less than 0.22 %. Taking the uncertainty into account significantly reduces the risk of drawing the conclusion that the activity ratio is less than a desired limit when the measured activity ratio is close to the limit.

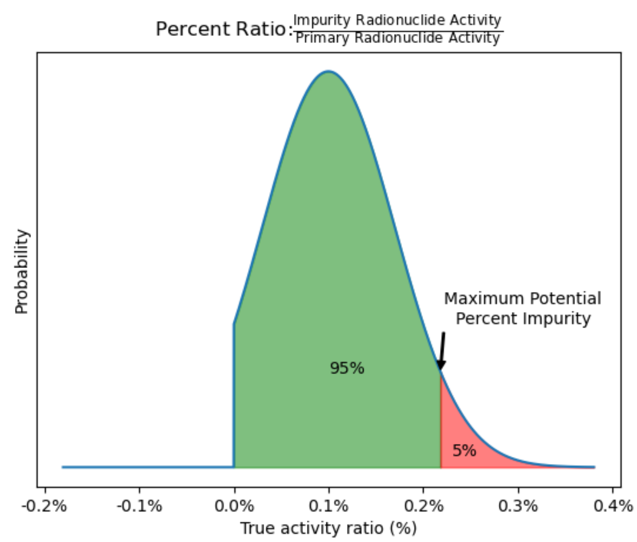

***Figure 3** Probability density for the activity ratio for the example measurement including the prior that the activity ratio is non-negative.*

The Apex-Guard Radionuclide Impurity Summary Report

A key requirement of the Apex-Guard Radionuclidic Impurity methodology is to have a concise, easy-to-interpret, and meaningful radionuclidic purity analysis report. This is shown in Figure 4. While typically integrated into a larger report, the Radionuclide Impurity Summary report section can also stand alone.

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In the following sections, we discuss the key information communicated by this report.

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Analysis Report for Sample ID 12345

QA Measurement of Lu-177 Production

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/4/2024 4:16:03PM

Radionuclide	Impurity Analysis Category	Activity (kBq/units)	Activity Uncertainty at 1.0 sigma	MDA / Reference Activity	Maximum Potential Percent Impurity	Percent Impurity Limit
Lu-177	Primary	4.547E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.012%	0.005%	0.010%
Yb-175	Impurity	---------	---------	0.002%	0.001%	0.100%
Sum of Impurities :					0.006%	0.100%

>> Sample analysis results are below the specified radionuclide impurity limits at reference time 10/4/2024 4:16:03PM.

>> Minimum Radionuclidic Purity : 99.994%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

***Figure 3** Example of an Apex-Guard Radionuclide Impurity Summary Report*

Header Information and Analysis Parameters

For sample identification and analysis traceability, key information is included in the header of the report. Identifying information such as the report generation date/time, the sample ID, and the sample description are in the header of each page. Information about the analysis settings (MPPI Activity Reference, Alpha Confidence, and Nuclide Library) are in the header of the report section.

The **MPPI Activity Reference** can be configured in the analysis sequence setup screen. The activity reference is the “Y” in the denominator of the activity impurity ratio and can be the total activity of the sample (including or excluding the daughters of the primary radionuclide), the activity of the primary radionuclide only or its surrogate, or an activity provided by the user external of the gamma spectroscopy measurement. This option might be used when the activity of the primary radionuclide cannot be measured, for instance when it has already decayed away or when the activity measurement from another system must be used for regulatory reasons. Please note, as the application does not know the details on the radionuclide, it cannot decay correct to the reference date and so the activity must be entered at the time indicated on the reporting.

The **Alpha Confidence** is configured in the analysis sequence setup screen, indicating the probability that the true value of the activity ratio is larger than the MPPI value. Typical alpha confidence values are 1% or 5%.

The **Reference Date** is indicated above the report data and provides the date and time that all the Activity, MDA, and MPPI values are determined for. These may be decay-corrected forward or backward in time from the actual measurement of the sample. In one option of the report, a user can select to have two reference dates presented for a single measurement.

Radionuclide Library and Impurity Analysis Category

To keep the report concise, only radionuclides defined and assigned an impurity analysis category in the nuclide library are listed in the Radionuclide Impurity Summary report. The following impurity analysis categories are available:

- The **Primary Radionuclide** is the pharmaceutical radionuclide of interest. A primary radionuclide or primary radionuclide surrogate must be present in any Apex-Guard Impurity Analysis, unless the “user-defined reference activity” option is used in the analysis setup.
- The **Primary Surrogate** is a useful option when the primary radionuclide is hard to measure. In this case, a daughter radionuclide may be used as the surrogate for the primary radionuclide, such that the radionuclide activity of the daughter is used as the reference activity. This might be done when the daughter is in equilibrium with the primary radionuclide, such as Fr-221 or Bi-213 for Ac-225.

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- **Daughter Radionuclide:** In some instances, it may be necessary to identify a radionuclide as a daughter of the primary radionuclide and ensure its emission lines are not flagged as unidentified peaks in the spectrum. For example, one application is when the daughter is shorter lived and will grow in from the primary radionuclide. This selection will result in the MPPI not being calculated for the radionuclide, but the measured activity may be part of the reference activity if a corresponding option is selected for the impurity analysis setup.
- The **Impurity Radionuclide** category will result in an MPPI being calculated for each emission line of the radionuclide, and then the lowest MPPI for all the lines will be reported for the radionuclide MPPI.

Percent Limit and Report Evaluations

The MPPI of each impurity radionuclide can be compared to a percent limit of the reference activity. This is specified by the user in the Nuclide Library Editor and is displayed next to the MPPI for each nuclide. If the calculated radionuclide MPPI is higher than the percent limit, the entire row in the report is highlighted in yellow to easily flag the result.

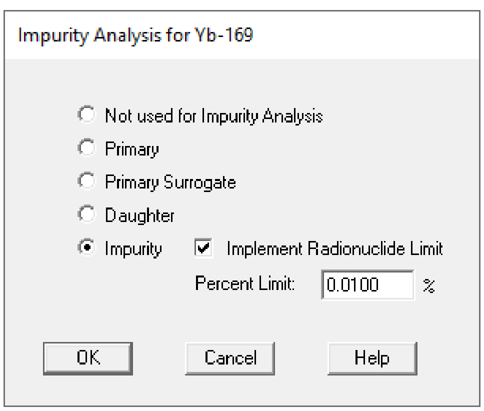
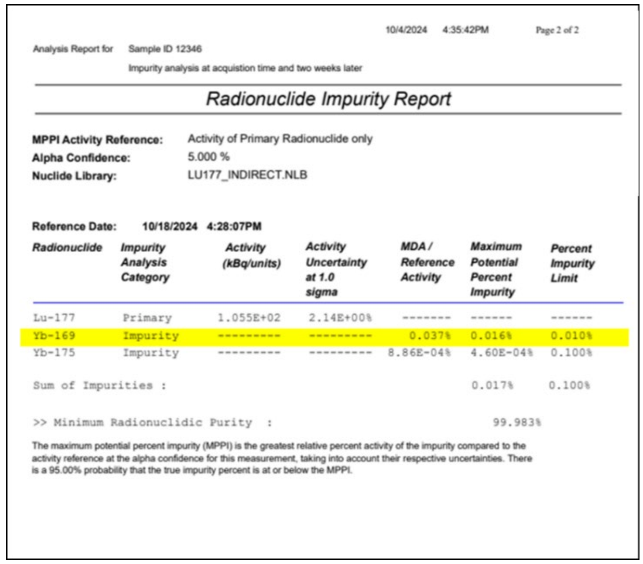


***Figure 4** Nuclide Library Configuration screen for radionuclide impurity limits*



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Analysis Report for Sample ID 12346

Impurity analysis at acquistion time and two weeks later

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: **10/18/2024 4:28:07PM**

Radionuclide	*Impurity Analysis Category*	*Activity (kBq/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Lu-177	Primary	1.055E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.037%	0.016%	0.010%
Yb-175	Impurity	---------	---------	8.86E-04%	4.60E-04%	0.100%
Sum of Impurities :					0.017%	0.100%

>> Minimum Radionuclidic Purity : 99.983%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

Figure 5 Radionuclide Impurity Summary report demonstrating an MPPI value exceeding an impurity limit

Sum of Impurities and Minimum Radionuclidic Purity

In addition to an impurity limit for each radionuclide, it may be required to report the total radionuclidic purity of a sample. In Apex-Guard, we define a term “minimum radionuclidic purity” as 100% minus the linear sum of all the impurity radionuclide MPPI’s defined for the sample:

$$RNP_{Min} = 100\% - \sum MPPI_X$$

***Equation 3** Minimum Radionuclidic Purity implementation in Apex-Guard*

The sum of each of the radionuclide MPPI’s, labeled “Sum of Impurities”, is displayed on the report and can be evaluated against a total impurity percent limit. The “Total Radionuclidic Impurity” limit is specified by users at the procedure level for standard counts, although it can be modified in data review for a re-analysis using the Analysis Sequence Setting.

Like the radionuclide MPPI, the Sum of Impurities line is highlighted in yellow if it exceeds the total percent limit. It is useful to note that taking the sum of the radionuclide MPPIs is a conservative

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approach because it is not likely that the true activity ratio for all impurity radionuclides is at their respective MPPI values.

If all radionuclide MPPI values are below the defined limits and the Sum of Impurity MPPIs are below the total radionuclidic impurity percent limit, then the report will generate the following statement: “Sample analysis results are below the specified radionuclide impurity limits at reference time.” If there are unidentified peaks in the spectrum, this will be indicated with a footnote following the statement. Unidentified peaks can be reviewed in the “NID Interf Wt. Mean & Unident” or “Unknown Line Report” report sections.

Reported Activities and Minimum Detectable Activities

The Radionuclidic Impurity Summary Report also has columns for the activity, activity uncertainty, and MDA divided by reference activity for each of the radionuclide categories. The activity and activity uncertainty are only displayed if the radionuclide is identified in the spectrum. Typically, this is the weighted mean activity. Conversely, the MDA / Reference Activity is only displayed if the radionuclide is not identified in the spectrum. In this case, the MDA is determined either by the Currie MDA or ISO11929 MDA calculation and then is divided by the reference activity defined for the spectrum. The MDA / Reference Activity is displayed on the report to assist users in understanding how the MPPI compares to the MDA, and more discussion is provided on this topic later in this application note. If one does not require display of the MDA / Reference Activity on the Radionuclide Impurity Summary report, it is a minor modification of the Apex-Guard report template to remove this column.

Additional Features and Discussion

Spectral Analysis Challenges and the Radionuclide Impurity Detail Report

Evaluation of radionuclide impurities in a gamma spectroscopy spectrum is based on observing regions of interest at the energies of emission lines associated with the radionuclide impurity. A maximum potential percent impurity is calculated for each emission line, and then the lowest line MPPI value is reported for the radionuclide MPPI. Line MPPI values for a given impurity radionuclide may vary due to the emission line intensity, the detection efficiency at that energy, and the number of other counts in that region. A particular challenge is if the counts are present from other spectral interferences. The Apex-Guard Radionuclide Impurity Detail Report is available to help users interpret the individual emission line MPPI contributions to the reported radionuclide MPPIs and diagnose challenges for specific emission lines.

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Analysis Report for Sample ID 12345
Test

Radionuclide Impurity Detail Report

MPPI Activity Reference : Activity of Primary Radionuclide only
Alpha Confidence : 5.000 %
Nuclide Library : LU177_INDIRECT.NLB

Reference Date: **10/23/2024 8:57:43PM**

Radionuclide	*Energy (keV)*	*Line Activity (Bq/units)*	*Activity Uncertainty at 1.0 sigma*	*Line MDA / Reference Activity*	*Line MPPI*	*Percent Impurity Limit*
Yb-169	177.21 @	3.886E+00	1.54E+03%	0.023%	0.020%	0.010%
	197.96 @	3.691E+01	1.15E+02%	0.016%	0.019%	0.010%
	307.74 !	-2.782E+01	9.30E+01%	0.010%	0.006%	0.010%
Yb-175	282.52	-3.657E+01	1.01E+02%	0.014%	0.009%	0.100%
	396.33 !	-5.311E+00	1.28E+02%	0.003%	0.002%	0.100%

The Line Maximum Potential Percent Impurity (Line MPPI) is the greatest relative percent line activity for the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. The reported MPPI for the radionuclide is the lowest of the Line MPPIs, excluding those marked as "Do not use in weighted mean/MPPI."

Flags
! = Used for radionuclide MPPI
@ = Marked as "Do Not Use in Weighted Mean/MPPI" in nuclide library
# = Could not calculate MPPI because the line activity uncertainty is zero
$ = Could not calculate MPPI because the line activity is more than three sigma below zero

Figure 6 *Example of a Radionuclide Impurity Detail Report in Apex-Guard*

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There are many spectroscopy features that can contribute counts in the region of interest being used for a line MPPI. Additional peaks may form in the spectrum due to true coincidence summing, random summing, escape peaks, and backscatter peaks, or may be present due to observable low intensity lines of the primary high activity radionuclide. Many of these events may also shift counts from other regions of the spectrum and increase the continuum in the region of interest. Occasionally it might be necessary to omit an impurity emission line for consideration in use of the radionuclide MPPI. When the “No Wt Mean or MDA” flag is set in the nuclide library editor, the emission line is excluded from any MPPI calculation. The following described various spectroscopy phenomena to be aware of and possible mitigation strategies:

- True Coincidence Summing (TCS): Many radionuclides may emit multiple photons in a single decay. When the sample is in a close geometry to the detector, these photons may be detected as one event, shifting counts and forming additional peaks in the spectrum. This can especially be of concern if the TCS peak forms at the same energy as the emission line of the impurity of interest. While deploying true coincidence summing correction algorithms are recommended to correct the summing radionuclide activity for loss of counts in the peaks of interest, true coincidence summing corrections will not remove the extra counts in the region being evaluated for an impurity. Therefore, the only way to reduce the impact of TCS for a line MPPI is to reduce the detection efficiency. If the TCS is the result of low energy photons, this may be achieved with a copper or other attenuator between the sample and detector. Otherwise, increasing the source-to-detector beyond ~10 cm will mitigate TCS.
- Random Summing: Random summing occurs when photons from different decays are detected as one event in the spectrum, which is more likely to occur with the higher count rates often experiences with high activity samples. Similar to TCS, random summing causes shifting counts and forming of additional peaks in the spectrum. To reduce the impact of random summing, the count rate needs to be reduced either through lower detection efficiency or by reducing the primary source activity in the count.
- Escape Peaks: There are a couple of unique spectral features that may be observable in some situations. Pair production will create annihilation photons, resulting in peaks at 511 keV and 1022 keV less than the emission energy, and Ge escape peaks occur when X-rays escape from the HPGe detector; these are observable at an energy 10 keV less than the energy of a very strong emission. If this overlaps with an emission line from your impurity, it is recommended to not use the emission line of the impurity for MPPI analysis.
- Backscatter Peaks: Gamma rays emitted from the sample interacts with all material surrounding the crystal and they can Compton scatter before entering the active crystal, resulting in a characteristic broad peak that may be misidentified by the peak search algorithm. If this is done, these peaks need to be identified as backscatter peaks and not as peaks from an impurity.

Using the “User-Entered Reference Activity (Measured Externally)” Option

In many cases, it is not possible or desired to use the activity measured from the impurity sample count for the primary radionuclide reference. This could be because the sample activity has already decayed away and the activity is being used from

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an earlier count, or the activity measurement must be from another system for regulatory reasons.

To support these scenarios, the Apex-Guard Impurity algorithm has an option to use a user-entered reference activity. This is configured by selecting the option in the ASF's MPPI analysis setup and the corresponding sample script in the procedure setup. The sample entry screen is modified to have fields for entering the reference activity, reference activity uncertainty, the activity and sample units, and an optional text field to provide identifying information about the reference activity. Because the software is not knowledgeable on the decay data of this reference activity, it is required to provide the activity at the impurity calculation reference date. This will be used for reporting all MPPI values with the count.

It is also required to enter a non-zero uncertainty for the reference activity, as the MPPI algorithm determines probability densities based on this information. If not readily available, it may be challenging to determine the uncertainty of the reference activity; however, it is useful to consider instrument nominal uncertainties, measurement statistics, and other contributions to develop an understanding of the measurement uncertainty.

For example, a dose calibrator can be very accurate (+/-2%) if used properly and with precision. However, studies have shown that incorrect calibration factors, human error, and decay factors may result in an uncertainty of +/-20% [5].

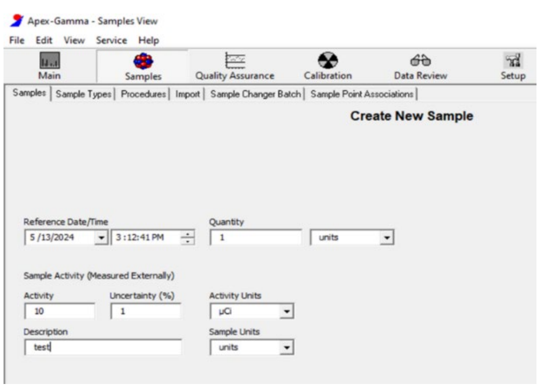

Figure 8: *Sample Entry screen for providing user-entered reference activity*

How is MPPI different from MDA divided by the reference activity?

A few common questions that are asked include how the Minimum Detectable Activity (MDA) is different from the Maximum Potential Percent Impurity, and what are the implications of using each. The MDA as defined by Currie [1] and in ISO11929 [5,6] address the question how much activity is required to determine if a radionuclide is present in the sample. Specifically, the MDA is defined as the activity that 95% of the time will produce a response in the detector that with 95% certainty is larger than the response without the radionuclide present. It is common to use an MDA value to report that a non-detected impurity is below the activity ratio limit of the impurity to the primary radionuclide or total sample activity.

However, for radionuclidic purity QA measurements, the objective is slightly different than reported by the MDA; it is to prove that the activity of the impurity is less than or equal to a percentage of the reference activity, where the reference activity may be the activity of the primary radionuclide or the total sample activity. Let's look at two scenarios when considering the MDA and the MPPI: when the impurity is not detectable in the sample, and when the impurity is detected and quantified.

When the impurity is not detected in the sample, the MDA will use the continuum in the region of interest to calculate and uncertainty and then uses this to calculate an activity per the MDA methodology. Meanwhile, the MPPI will estimate the peak area of the region of interest using continuum to either side of the ROI and force an estimation of the activity for use in the probability density of the activity ratio. A key point here is that the forced estimate of activity per the MPPI method will always be much lower than the calculated MDA, and that use of the MDA in the activity ratio of an impurity analysis will result in an overly conservative value.

When the impurity is detected, the same method is used by the MPPI algorithm as described above. Meanwhile, use of the MDA is no longer appropriate and instead the user should be using

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the activity of the identified nuclide to report the activity ratio. The drawback of providing a direct ratio of the activities is that if the true impurity activity ratio is close to maximum value, an incorrect assessment of the impurity activity ratio could occur if the uncertainties are not considered. When the impurity radionuclide is present and quantified, the MPPI method automatically uses the quantified impurity activity and its uncertainty, and as before, the probability of drawing the incorrect conclusion is determined by the α confidence.

The "Count to MPPI" Feature

Apex-Guard includes a feature to count to MPPI. When it is used, the measurement will proceed to the minimum count time and then calculate the MPPI for each impurity radionuclide and check if they and the sum of impurities are below the desired limit. If they are, the measurement will stop. If they are above the desired limit, Apex-Guard will extend the count time using an estimate of when the MPPI will be reached. The process will be repeated until the desired limit has been reached or the maximum count time has been reached. When the impurity is not present the MPPI is expected to decrease with time. However, when the spectrum contains low statistics, the MPPI can fluctuate with additional counts in the spectrum, and it is challenging to estimate the additional count time to reach the desired MPPI. When this is the case, it is possible that the MPPI will be significantly below the desired limit. Therefore, it is recommended to set the minimum count time to a time that will give sufficient statistics to limit the fluctuations of the MPPI. If an impurity radionuclide is present in the sample with an activity ratio above the desired limit, the MPPI will never be reached. Setting a reasonable maximum count time is crucial to prevent the count to run for an excessive amount of time.

Practical Examples: Lu-177 Evaluation and Ac-225 Evaluation

The MPPI algorithm has been applied to Monte-Carlo simulations of a Lu-177 sample without any impurities and a Lu-177 sample with Yb-169 and Yb-175 impurities at 0.01% and 0.1% respectively. The impurity activities in the second case are at the desired limits. The Monte-Carlo simulations simulated 360 10-second measurements that were summed to give the time evolution of the spectrum from 10 seconds to 1 hour measurement. This shows how the algorithm performs over time and how the results improve with increasing measurement time and statistics. Together with the MPPI, two other common metrics are also calculated, MDA/reference activity and the activity ratio not taking uncertainties into account. The software was forced to calculate an activity for Yb-169 in the first case. When the impurity is not present the MPPI is always below the MDA/reference activity, and it goes below the desired impurity limit at around 600 seconds while the MDA/reference activity around 2250 seconds. This means that it is possible to draw the correct conclusion that the activity ratio is below the desired ratio with measurement time that are more than a factor of 3 shorter than using MDA/reference activity.

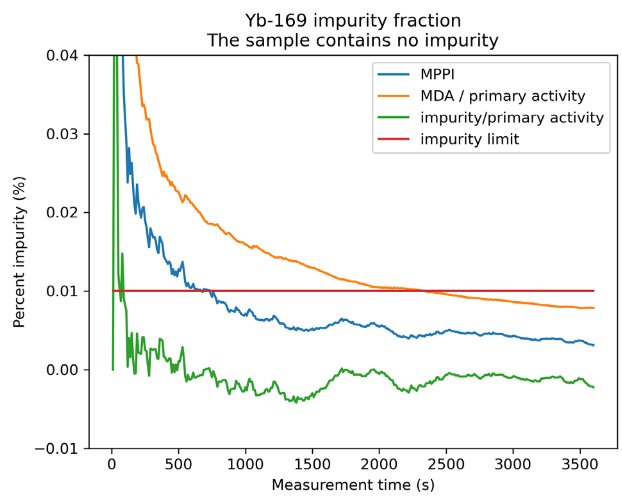

***Figure 9** The MPPI, MDA/reference activity, activity ratio, and the desired impurity limit for a Lu-177 sample without Yb-169 present*

The second example, Figure 11, demonstrates the performance when the impurity radionuclide is present and at the desired limit. The MPPI value initially decreases as the statistics increases, but at around 600 seconds measurement time it stops to decrease and stays constant; most importantly, it stays above the true ratio and the desired limit.

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This means that by using the MPPI as the metric one would always draw the correct conclusion that the activity ratio is not below the desired limit. MDA/reference activity is always decreasing and as we can see, it eventually goes below the MPPI and it will go below the desired limit. This means that just using the MDA/reference activity with long enough measurement time one will make the incorrect decision that the activity ratio is below the desired limit. This also means that one would have to eventually change the metric used for determination if the activity ratio is below the desired limit.

If we look at the ratio of the measured impurity activity to the measured primary activity without taking uncertainties into account, it is below the desired limit. In Figure 9, the impurity/primary activity is plotted as zero when the peak locate algorithm doesn't identify a peak at the emission energy and once the peak is found it is plotted as the ratio. If this metric is used one can see that for the entire measurement time one would draw the incorrect conclusion that the activity is below the desired limit.

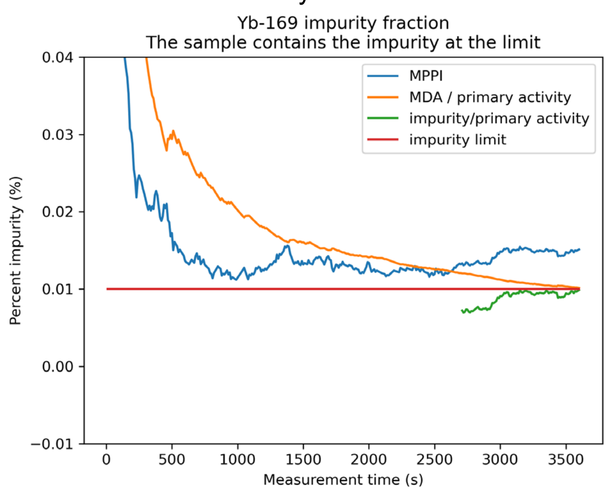

Figure 10 *The MPPI, MDA/reference activity, activity ratio, and the desired impurity limit for a Lu-177 sample with Yb-169 present at the desired limit of 0.01%.*

The third example shows Monte-Carlo simulations of a sample in the same geometry as the previous examples but with Ac-225 in equilibrium with its daughters and without any impurities. The simulated activity of Ac-225 was about 1.2 MBq. The simulations were again performed in 360 10 second measurements and summed and analyzed to get the time evolution of the MPPI and the MDA/reference activity. The MPPI and MDA/reference activity was calculated for Ra-225 which have a single gamma ray emission at 40 keV. The time evolution of the MPPI and MDA/reference activity is shown in Figure 11. MPPI is again always below the MDA/reference activity for all measurement times, and it goes below 0.01% after about 700 seconds. MPPI stays below 0.01% except for two short intervals of measurement times around 1500 seconds.

While the general trend of the MPPI is to decrease with time if the impurity is not present, it can fluctuate with statistics of the measurement. With increased measurement time the measured activity of the impurity will go toward the true value and the uncertainty will decrease, the MPPI can increase with increased measurement time if the measured activity increases faster then the uncertainty is reduced but eventually it will reduce again as the measured activity will move towards the true activity. This is what happens at around 1500 seconds and after that we can see that the MPPI will again reduce with increased measurement time. MDA/reference activity goes below the 0.01% limit at around 3000 seconds a factor of 4 longer measurement time than the MPPI and almost a factor of 2 longer measurement time than the longest measurement time gives an MPPI that is above the limit. Again, demonstrating that using the MPPI can significantly shorten the measurement times when the impurity radionuclide is not present in the sample.

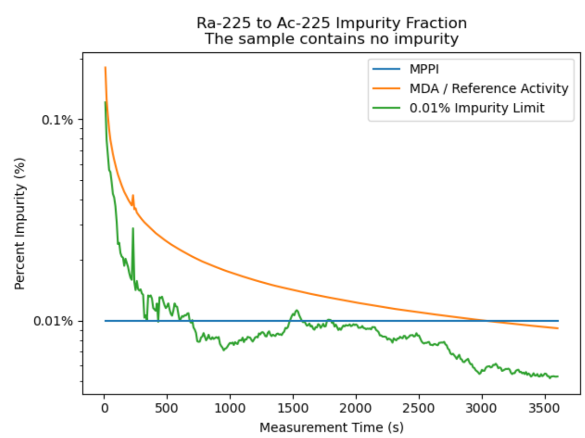

Figure 11 *The MPPI, MDA/reference activity, activity ratio, and the desired impurity limit for a Lu-177 sample with Yb-169 present at the desired limit of 0.01%.*

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