

Long-lived contaminants in short-lived cyclotron-produced radiopharmaceuticals with Visual RobFit

Robert Metzger^{1,a} and George Lasche²

¹*Radiation Safety Engineering, Inc, 3245 North Washington Street, Chandler, AZ, USA*

²*Snakedance Scientific, LLC, 13509 Quaking Aspen Place NE, Albuquerque, NM, USA*

Abstract. Oxygenated target waters of cyclotron targets contain long-lived contaminants due to (p,n) reactions in the Havar target window that are spalled into the target water. These contaminants must be scrubbed out of the water as part of the drug synthesis process. Currently the USP requires that the final drug product be 99.5% pure, so the total activity of the long-lived contaminants can be no more than 0.5% of the final radiopharmaceutical product. A method of determining these long-lived contaminants with whole-spectrum non-linear shape fitting has been developed using high-resolution gamma spectroscopy. Results of whole-spectrum shape fitting are compared to results from standard software that uses results of an initial search of individual peaks. It is shown that the usual problems due to interference corrections of individually-fitted peaks are not encountered with whole-spectrum shape fitting, with improved overall analytic results.

1 Introduction

For positron-emission tomography (PET) short-lived radionuclides that emit no gamma-rays but only positrons are required. ¹⁸F is the most commonly-used for this purpose, and is commonly produced by the irradiation of oxygenated water with high-energy protons accelerated from a cyclotron through a Havar window that separates the vacuum of the cyclotron from the water target. Havar is a non-magnetic target window which must retain its strength while withstanding corrosion and the high heat loads from the transition of the proton beam. Havar is nominally composed of cobalt, chromium, nickel, tungsten, molybdenum, manganese, carbon, and iron [1]. In this process long-lived radioactive contaminants are created primarily through (p,n) reactions and are sputtered into the target water. Long-lived contaminants are also created in this process by reaction with secondary neutrons. The contaminants and this process are well-known and have been widely reported [2, 3, 4, 5, 6, 7, 8].

To meet the requirements of the USP that the final drug product be 99.5% pure, the total radioactivity can be no more than 0.5% of the final radiopharmaceutical product. Although unable to detect radionuclides such as ³H that emit no gamma rays, high resolution gamma spectroscopy is an important part of procedures commonly used to test if this requirement has been met. Among the more notable long-

lived contaminants that are evident with gamma spectroscopy are ⁵⁵Co, ⁵⁶Co, ⁵⁷Co, ⁵⁸Co, ⁵¹Cr, ⁵²Mn, ⁵⁴Mn, ⁵⁷Ni, ¹⁸³Re, ⁹⁵Tc, ^{95m}Tc, and ⁹⁶Tc. In common practice the activity concentrations of these radionuclides are determined by analysis with one of several widely-accepted commercial software applications that begin with a search of all the significant peaks in the spectrum, and then refer to a previously-determined efficiency response and to nuclear tables to try to infer the presence and activities of radionuclides evident in the spectrum. This method fails when important peaks that lie closely together are masked by interference with each other or by other, larger peaks.

The authors have applied a new method for the analysis of long-lived contaminants, using whole-spectrum non-linear shape fitting, which is implemented in an application called "Visual RobFit", or "VRF" for short. The advantage of this method, which has been described in [9] and [10], is reported in more detail in two companion papers [11] and [12]. The aim of this study is to evaluate and compare the use of VRF for analysis of cyclotron-induced long-lived contaminants in target waters with Havar foils to the results using more conventional techniques.

2 Description

A sample of target waters used in the production of ¹⁸F for PET imaging was received for analysis of long-lived

^a Corresponding author: rmetzger@radsafe.com

contaminants. The sample was taken at end of run at 10 AM, January 9, 2015, and had an activity of 19.8 GBq of ^{18}F . A spectrum was acquired at 1.42 PM, January 15, 2015, after a cool-down period of 6 days, 3 hours, and 42 minutes.

This spectrum was analyzed both with standard peak-search software and independently with Visual RobFit.

Figure 1 shows the graphical results of the fit to the spectrum using the whole-spectrum shape fitting techniques of Visual RobFit. In Figure 2, which shows detail in the region of 825 keV to 875 keV, the ability of whole-spectrum shape fitting to resolve interfering peaks is well-illustrated. Note the small peak of ^{52}Mn (at 848.18 keV, fuchsia) that is masked by two much larger interfering peaks of ^{56}Co (at 846.77 keV, dark gray) and ^{96}Tc (at 849.86 keV, lime color). With standard peak-search software, activities for both ^{95}Tc and ^{96}Tc were grouped with a suffix of "x" to include all isomers, whereas with the whole-spectrum shape fitting techniques both ^{95}Tc and ^{96}Tc were reported independently with high confidence.

Of more particular interest in Figure 2 is the resolution of two very close-lying peaks of nearly identical size, of ^{54}Mn (at 834.85 keV, orange) and of $^{95\text{m}}\text{Tc}$ (at 835.13 keV, light gray). The standard peak-search software apparently did not attempt to resolve this interfering peak as it did not report any independent presence of $^{95\text{m}}\text{Tc}$. VRF, which relies on whole-spectrum fitting, reported $^{95\text{m}}\text{Tc}$ with a confidence of 18.26 (as calculated by the activity divided by the one-standard-deviation of uncertainty in the activity), and with an activity concentration of 0.464 Bq/GBq.

A final example of the efficacy of whole-spectrum shape fitting is shown in Figure 3, where the shape of the entire group tungsten x-rays (which result from the decay of ^{183}Re) is shown in a light blue color. The standard peak-search software did not recognize tungsten x-rays, but instead incorrectly attributed two of the larger peaks to ^{232}Th and ^{241}Am , with the caution that they were "part of an undetermined solution". To illustrate why ^{241}Am might have been thought to be present by the standard peak-search software, a fictitious overlay of how the shape of a peak at 59.54 keV would have looked is shown in orange. (Note that the orange peak is of fictitious ^{241}Am and is not a fit to any real data!)

Table 1 provides a quantitative comparison of activity concentrations, and their one-standard-deviation uncertainties, as analyzed with whole-spectrum shape fitting with VRF, compared to results of analysis with standard peak-search software.

3 Method

The determination of long lived contaminants in cyclotron-produced radiopharmaceuticals is performed by taking a sample of the final drug product and recording the ^{18}F or ^{13}N activity at a specific date and time. Both the EOS and the time of expiration are commonly used. The sample is then allowed to decay for two to three days to allow the short-lived imaging product to decay away. This decay time

is optimal to ensure the analysis has sufficient sensitivity to detect the ^{55}Co ($T_{1/2}$ 17.53 hours) at the required Minimum Detectable Activity (MDA). The sample is then counted on the high resolution gamma spectrometer (P-type crystal) to identify the presence and activity of the long lived contaminants. Typically, one of two commercially-available software packages are used to analyze the resulting spectrum and the results are reported, by isotope, as Bq of contaminant per GBq of ^{18}F or ^{13}N product at the date and time submitted on the chain of custody. The method cannot detect contaminants whose half lives are too short to make it to the counting laboratory, nor pure beta emitters (i.e. ^3H).

During validation and verification testing of the new method in samples with significant breakthrough of the long-lived contaminants into the final product, it was observed that the commercial software packages could not adequately resolve and report some of the contaminants due to heavily overlapped spectra. While final products with heavy loads of the long-lived contaminants are rare, the method needs to be sufficiently robust to manage them when they do appear.

4 Conclusion

A new application of the method of non-linear fitting for nuclear spectral analysis (VRF) has been applied to the quantitative analysis of long-lived contaminants in target waters during the production of ^{18}F for PET imaging. Results of standard peak-search software were compared to results from VRF. VRF produced results that compared well with results of peak-search methods in cases where there was no interference of peaks, but performed significantly better in cases where interference was encountered.

5 References

1. Havar Technical DataSheet, Hamilton Precision Metals, Lancaster, PA, <http://www.hpmetals.com/pdfs/havar.pdf>
2. L. Bowden, L. Leon Vintro, P.I. Mitchell, R.G. O'Donnell, A.M. Seymour, G.J. Duffy, 2009, Radionuclide impurities in proton-irradiated $[\text{18O}]\text{H}_2\text{O}$ for the production of ^{18}F : activities and distribution in the $[\text{18F}]\text{FDG}$ synthesis process. *Appl. Radiat. Isot.* 67, 248–255.
3. D. Ferguson, P. Orr, J. Gillanders, G. Corrigan, C. Marshall, Measurement of long lived radioactive impurities retained in the disposable cassettes on the Tracerlab MX system during the production of $[\text{18F}]\text{FDG}$. *Appl. Radiat. Isot.* 69 (2011) 1479–1485
4. K. Gagnon, J.S. Wilson, A. McQuarrie, Comparison of Nb, Pt, Ta, Ti, Zr and ZrO_2 sputtered havar foils for the high power cyclotron production of reactive

ICRS-13 & RPSD-2016

- [18F]F₂, Proceedings of the 13th International Workshop of Targetry and Target Chemistry, Roskilde, Denmark, 2010.
- J.M. Gillies, N. Najim, J. Zweit, 2006, Analysis of metal radioisotope impurities generated in [18O]H₂O during the cyclotron production of fluorine-18. *Appl. Radiat. Isot.* 64, 431–434.
 - R.D. Hichwa, D. Kadrmas, G.L. Watkins, S.D. Wollenweber, S. Maniam, L.L. Boles Ponto, J.C.W. Richmond, J.A. Koepfel, 1995, Vanadium-48: A Renewable Source for Transmission Scanning with PET. *Nucl. Inst. Methods Phys. Res. B* 99, 804–806.
 - S. Ito, H. Sakane, S. Deji, T. Saze, K. Nishizawa, 2006. Radioactive byproducts in [18O]H₂O used to produce ¹⁸F for [18F]FDG synthesis. *Appl. Radiat. Isot.* 64, 298–305.
 - M. Marengo, F. Lodi, S. Magi, G. Cicoria, D. Pancaldi, S. Boschi, 2008, Assessment of radionuclidic impurities in 2-[18F] fluoro-2-deoxy-d-glucose ([18F]FDG) routine production. *Appl. Radiat. Isot.* 66, 295–302.
 - R.L. Coldwell, G.J. Bamford, 1991, The Theory and Operation of Spectral Analysis Using ROBFIT, American Institute of Physics, New York, 1991.
 - G.P. Lasche, R.L. Coldwell, Analysis of Nuclear Spectra with Non-Linear Techniques and its Implementation in the Cambio Application, *Journal of Radioanalytical Nuclear Chemistry* (2009) 282:211–215.
 - G.P. Lasche, R.L. Coldwell, Visual RobFit -- nuclear spectral analysis with non-linear whole-spectrum nuclide shape fitting, to be submitted for publication at the 13th International Conference on Radiation Shielding & Topical Meeting of the Radiation Shielding & Protection Division of the American Nuclear Society, Paris, France Oct 3-6, 2016.
 - R.L. Metzger, K.A. Van Riper, G.P. Lasche, Uranium and Radium in Soils by High Resolution Gamma Spectroscopy and Visual RobFit, to be submitted for publication at the 13th International Conference on Radiation Shielding & Topical Meeting of the Radiation Shielding & Protection Division of the American Nuclear Society, Paris, France Oct 3-6, 2016.

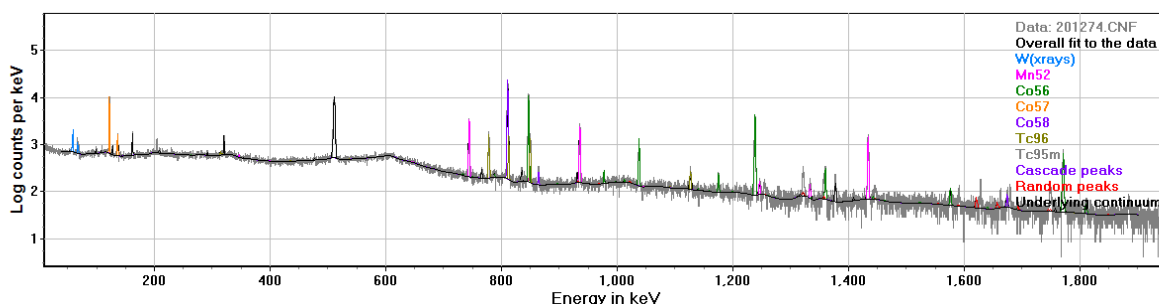


Figure 1. The analyzed spectrum of contaminants in oxygenated target water from spallation from a Havar window by protons from a cyclotron in the production of ¹⁸F for PET imaging. The sample, which had an activity of 19.8 GBq of ¹⁸F, had been aged 6 days, 3 hours, and 42 minutes prior to acquisition of this spectrum.

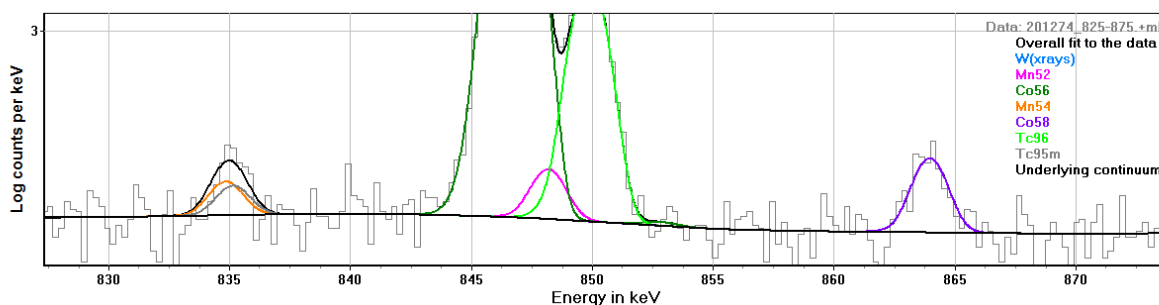


Figure 2. The region of 825 keV to 875 keV of the analyzed spectrum of contaminants, showing the resolution by VRF of the peak of ⁵²Mn at 848.18 keV (fuchsia color) that is masked by the two large peaks of ⁵⁶Co (at 846.77 keV, dark gray) and ⁹⁶Tc (at 849.86 keV, lime). Also shown is the resolution of two very close-lying peaks of nearly identical size, of ⁵⁴Mn (at 834.85 keV, orange) with the peak of ^{95m}Tc (at 835.13 keV, light gray).

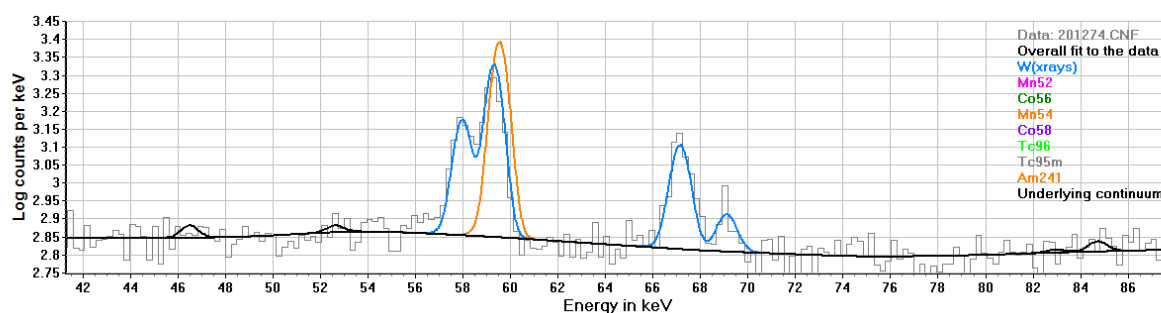


Figure 3. The analyzed spectrum of contaminants showing the whole-spectrum fit to the entire group of tungsten x-rays (light blue) compared to the shape of ^{241}Am if it had been present (orange). The standard peak-search software had suggested that the tungsten x-rays, which result from the decays of ^{183}Re , were actually due to ^{241}Am and ^{232}Th , but did flag them as "part of an undetermined solution".

Table 1. Comparison of activity concentrations (in Bq/GBq of ^{18}F) as analyzed by Visual RobFit and by standard peak-search software. The standard peak-search software results for ^{95}Tc and ^{96}Tc (in italics, gray type) were grouped with a suffix of "x" for all isomers of that nuclide. The standard peak-search software made no separate identification ("ID" in the table below) of $^{95\text{m}}\text{Tc}$, presumably due to the interference of the peak of ^{54}Mn at 834.85 keV with the peak of $^{95\text{m}}\text{Tc}$ at 835.13 keV, as shown graphically in Figure 2. The tungsten x-rays were incorrectly identified by the standard peak-search software ("SPS" in the table header below) as ^{241}Am and ^{232}Th but were flagged as "part of an undetermined solution".

Emitter	VRF	Uncert.	SPS	Uncert.
^{55}Co	119.250	14.121	133.800	0.158
^{56}Co	25.796	0.147	26.160	0.389
^{57}Co	3.630	0.037	3.545	0.116
^{58}Co	50.231	0.260	50.910	1.311
^{51}Cr	7.156	0.292	6.545	0.570
^{52}Mn	13.835	0.129	13.650	0.243
^{54}Mn	0.137	0.032	0.191	0.056
^{57}Ni	12.346	0.749	17.370	1.808
^{183}Re	1.739	0.064	1.858	0.154
^{95}Tc	44.178	5.323	<i>0.414</i>	<i>0.066</i>
$^{95\text{m}}\text{Tc}$	0.464	0.025	No ID	No ID
^{96}Tc	8.922	0.121	<i>8.365</i>	<i>0.260</i>
W x-rays	2.141	0.059	Bad ID	Bad ID