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Measurement of long lived radioactive impurities retained in the disposable cassettes on the Tracerlab MX system during the production of [^{18}F]FDG

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ABSTRACT

Using a High-Purity Germanium gamma-ray spectrometer, a number of radioisotopes have been identified within Tracerlab MX radiochemistry system cassettes used to synthesise [^{18}F]FDG. Twenty radiochemistry cassettes were measured and the average total activity of each radioisotope was determined. Using these values and decay correction, the minimum time the cassettes should be left in a decay store before the specific activity falls below 0.4B q/g, the limit for disposal alongside Clinical Waste was found to be 24 months.

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1. Introduction

^{18}F is the most widely used radionuclide in PET and is commonly produced by bombarding ^{18}O enriched water with accelerated protons. It is well established that long lived radionuclide impurities are generated using this method as a result of activation of metal atoms in the Havar foil and silver body of the Gen II targets used in the GE PETtrace cyclotron [Bowden et al., 2009; Marengo et al., 2008; Ito et al., 2006; Gillies et al., 2006; Mochizuki et al., 2006; O'Donnell et al., 2004]. Havar foil is a heat treatable, cobalt based non-magnetic alloy with a high strength and excellent corrosion resistance. Its nominal composition is cobalt (42.0%), chromium (19.5%), nickel (12.7%), tungsten (2.7%), molybdenum (2.2), manganese (1.6%), carbon (0.2%) and iron (balance) and these metals are the sources for most of the activated radioisotopes (Havar Technical Data Sheet). The radioisotopes are generated by interactions between the cyclotron target foil and the proton beam as it passes through as well as with secondary neutrons. During the interaction with the protons and neutrons, some of the activated radionuclides are knocked into the ^{18}O enriched water through the process of spallation. These long lived impurities are then transferred, along with the ^{18}F water, to the synthesis unit.

Table 1 shows the possible interactions of the incident proton beam, or secondary neutrons, within the Havar foil and silver target body by which the radioactive by-products detected may be created. [Ito et al., 2006; Marengo et al., 2008]

Since $^{18}\text{F}^-$ is produced by the $^{18}\text{O}(p,n)^{18}\text{F}$ reaction, it is necessary to remove the $^{18}\text{F}^-$ ion from its aqueous environment. On the GE Tracerlab MX system, which utilises disposable cassettes (supplied by Rotem Industries, Ltd), this is performed using a QMA Sep-Pak column (supplied as a part of ABX reagent kit, Biomedizinische Forschungsreagenzien GmbH). The $^{18}\text{F}^-$ ion is retained on the column whilst the [^{18}O]H $_2$ O passes through. In theory, the activated metal ions should pass through the column and are not retained. The ^{18}F is then eluted from the column with an Acetonitrile solution of Kryptofix and Potassium Carbonate. (Yu, 2006)

The long lived impurities are removed during synthesis enabling the final [^{18}F]FDG product to meet the requirements of the pharmacopoeias [BP, 2010; EP, 2010]. However, the long lived impurities are retained in the disposable cassette used on the Tracerlab MX radiochemistry system.

Other authors (Tables 6 and 7) have confirmed the presence of these long lived impurities in both the Havar foil and the fluorinated water. The aim of this study was to measure the levels of these long lived impurities in the disposable cassettes, and thus the levels of radioactive waste generated during synthesis, to determine the most appropriate method of disposal. The disposal of cassettes is an issue for any centre producing FDG, which applies a single-use cassette chemistry system.

2. Material and methods

2.1. ^{18}F -Fluoride production and [^{18}F]FDG synthesis

20 Production runs of ^{18}F were performed using a PETtrace 6 cyclotron (GE Healthcare). Target conditioning was undertaken

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by filling a single Gen II silver target with water ($[^{16}\text{O}]\text{H}_2\text{O}$) and irradiating for 10 min with a 16.5 MeV proton beam at 25 μA . Afterwards the same target was filled with enriched water ($[^{18}\text{O}]\text{H}_2\text{O}$; Sercon) and irradiated using a proton beam of 40 μA for 2 h. The fluoride produced was delivered to a hot cell (Gravatom) where synthesis of FDG was performed using a Tracerlab MX (GE Healthcare) radiochemistry system along with reagents, solvents and columns supplied by ABX (Advanced Biochemical Compounds, Germany). After the main production and delivery of FDG to the hot cell, the target was filled with water $[^{18}\text{O}]\text{H}_2\text{O}$ to remove any residual ^{18}F , which could potentially cause contamination and corrosion of the target. The whole procedure was finished by drying the target for 15 min to ensure that the target was ready for the next production.

Table 1
Possible nuclear reactions that create detected radioactive impurities.

| Radionuclide | Havar foil | Silver target |
|---|---|---|
| ^{51}Cr | $^{54}\text{Fe}(n,\alpha)^{51}\text{Cr}$ $^{50}\text{Cr}(n,\gamma)^{51}\text{Cr}$ $^{52}\text{Cr}(n,2n)^{51}\text{Cr}$ | |
| ^{52}Mn | $^{52}\text{Cr}(p,n)^{52}\text{Mn}$ | |
| ^{54}Mn | $^{54}\text{Cr}(p,n)^{54}\text{Mn}$ $^{54}\text{Fe}(n,p)^{54}\text{Mn}$ $^{55}\text{Mn}(n,2n)^{54}\text{Mn}$ | |
| ^{56}Co | $^{56}\text{Fe}(p,n)^{56}\text{Co}$ | |
| ^{57}Co | $^{57}\text{Fe}(p,n)^{57}\text{Co}$ $^{58}\text{Ni}(n,pn)^{57}\text{Co}$ $^{58}\text{Ni}(p,2p)^{57}\text{Co}$ $^{60}\text{Ni}(p,\alpha)^{57}\text{Co}$ | |
| ^{58}Co | $^{58}\text{Fe}(p,n)^{58}\text{Co}$ $^{58}\text{Ni}(n,p)^{58}\text{Co}$ $^{59}\text{Co}(n,2n)^{58}\text{Co}$ $^{59}\text{Co}(p,pn)^{58}\text{Co}$ | |
| ^{57}Ni | $^{58}\text{Ni}(p,d)^{57}\text{Ni}$ | |
| $^{95}\text{Tc}/^{95\text{m}}\text{Tc}$ | $^{95}\text{Mo}(p,n)^{95\text{m}}\text{Tc}$ $^{96}\text{Mo}(p,2n)^{95\text{m}}\text{Tc}$ | |
| ^{96}Tc | $^{96}\text{Mo}(p,n)^{96}\text{Tc}$ $^{97}\text{Mo}(p,2n)^{96}\text{Tc}$ | |
| ^{109}Cd | | $^{109}\text{Ag}(p,n\gamma)^{109}\text{Cd}$ |
| ^{182}Re | $^{182}\text{W}(p,n)^{182}\text{Re}$ | |
| ^{183}Re | $^{184}\text{W}(p,3n\gamma)^{183}\text{Re}$ | |
| ^{184}Re | $^{183}\text{W}(p,n)^{183}\text{Re}$ | |
| ^{184}Re | $^{184}\text{W}(p,n)^{184}\text{Re}$ | |
| ^{186}Re | $^{184}\text{W}(p,n)^{186}\text{Re}$ | |

Each cassette was removed from the Tracerlab MX 48 h after the production of FDG. This was to allow the radioactivity in the cassettes to decay to a level where it could be safely cut up and placed in a 1 lt tub. The cut up cassette was then stored for a further week to allow the activity to fall to a level that could be measured by the gamma-ray spectrometry system without large dead-time effects.

2.2. Gamma-ray spectrometry and analysis

To detect impurities in the cassette, a gamma-ray spectrometry system consisting of an ORTEC[®] GMX Series High-Purity Germanium (HPGe) Coaxial Photon Detector operated by GammaVision[®]-32 v6.08 software was used. The resolution (FWHM) of this system is 0.73 keV at 5.9 keV and 1.8 keV resolution at 1330 keV with a relative efficiency of 27%. The system has been calibrated for a range of uniform geometries, including a 1 lt tub, using a number of aliquots of CERCA LEA 9ML01ELMG05 multi-gamma reference source containing ^{241}Am , ^{109}Cd , ^{57}Co , ^{139}Ce , ^{113}Sn , ^{85}Sr , ^{137}Cs , ^{88}Y and ^{60}Co as well as a ^{152}Eu point source from Amersham for energy calibration. The operational range of the detector was set from 10–2000 keV.

Each 1 lt tub was placed directly on the detector and a spectrum captured for 8 h, which was analysed using the GammaVision[®]-32 application, with the measured activity of each detected radioisotope decay corrected back to the time of production. The GammaVision software will only decay correct the activity measured for radioisotopes if less than 12 half-lives have elapsed. For this reason, each cassette was analysed within 30 days of production to ensure that as many of the short-lived radioisotopes could still be decay corrected while taking into account the time needed for the cassette to be cool enough to prevent dead-time effects. Nuclear data for the photon energies and γ -ray emission probabilities of the radioisotopes in the GammaVision radionuclide library were obtained from the Evaluated Nuclear Structure Data File database (ENSDF).

3. Results

Fig. 1 shows a typical γ -ray spectrum obtained with the GMX-HPGe detector, labelled with the identified isotopic peaks. Eleven

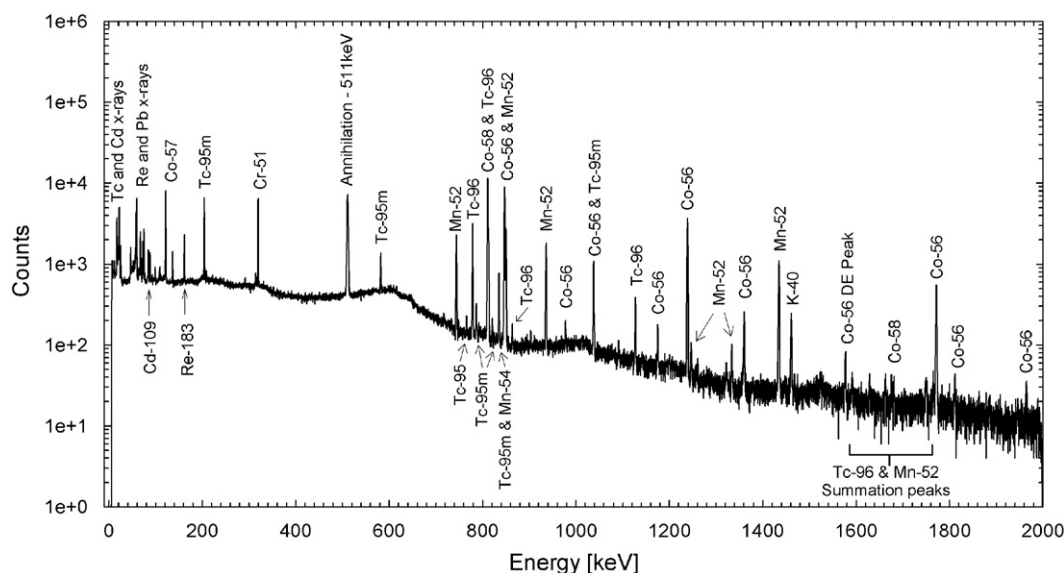


Fig. 1. Spectrum showing radioisotope photon peaks.

Table 2
Distribution of gamma-emitting radionuclide impurities in the FDG synthesis cassettes.

| Radionuclide | Half life (d) | Primary γ [keV] | Primary γ abundance [%] | Average activity (Mean \pm SEM) [Bq] | Median activity [Bq] | Range [Bq] n=20 |
|-------------------|---------------|------------------------|--------------------------------|--|----------------------|-----------------|
| ⁵¹ Cr | 27.7 | 320 | 9.86 | 373.0 \pm 81.6 | 209.2 | 87.4–1565 |
| ⁵² Mn | 5.59 | 1434 | 100.00 | 194.0 \pm 61.5 | 48.8 | 0–929.1 |
| ⁵⁴ Mn | 312 | 835 | 99.98 | 3.0 \pm 0.7 | 2.3 | 0–9.1 |
| ⁵⁶ Co | 77.2 | 847 | 99.93 | 206.6 \pm 30.3 | 144.5 | 61.6–519.4 |
| ⁵⁷ Co | 272 | 122 | 85.60 | 37.1 \pm 5.1 | 27.5 | 11.2–75.2 |
| ⁵⁸ Co | 70.9 | 811 | 99.45 | 260.1 \pm 38.2 | 182.6 | 64.4–662.5 |
| ^{95m} Tc | 61.0 | 204 | 61.92 | 58.4 \pm 9.9 | 48.6 | 6.2–180.2 |
| ⁹⁶ Tc | 4.28 | 778 | 99.76 | 846.5 \pm 147.9 | 755.5 | 0–2393.8 |
| ¹⁰⁹ Cd | 461 | 88 | 3.63 | 81.8 \pm 12.3 | 58.1 | 20–180.5 |
| ¹⁸² Re | 2.67 | 229 | 26.00 | 11.2 \pm 6.3 | 0.0 | 0–86.6 |
| ¹⁸³ Re | 70.0 | 162 | 23.36 | 22.4 \pm 5.1 | 17.0 | 0–84.3 |

Table 3
Total activity in the FDG cassettes at the end of bombardment (EOB).

| Cassette | Total activity [Bq] | Specific activity [Bq/g] | Cassette | Total activity [Bq] | Specific activity [Bq/g] |
|----------|---------------------|--------------------------|----------|---------------------|--------------------------|
| 1 | 775 | 4.1 | 11 | 3202 | 16.9 |
| 2 | 1517 | 8.0 | 12 | 5270 | 27.7 |
| 3 | 602 | 3.2 | 13 | 1541 | 8.1 |
| 4 | 721 | 3.8 | 14 | 2495 | 13.1 |
| 5 | 2266 | 11.9 | 15 | 975 | 5.1 |
| 6 | 3905 | 20.6 | 16 | 1427 | 7.5 |
| 7 | 5529 | 29.1 | 17 | 1660 | 8.7 |
| 8 | 457 | 2.4 | 18 | 1292 | 6.8 |
| 9 | 2052 | 10.8 | 19 | 3904 | 20.5 |
| 10 | 1104 | 5.8 | 20 | 1183 | 6.2 |

different radioisotopes were identified within the cassettes: ⁵¹Cr, ⁵²Mn, ⁵⁴Mn, ⁵⁶Co, ⁵⁷Co, ⁵⁸Co, ^{95m}Tc, ⁹⁶Tc, ¹⁰⁹Cd, ¹⁸²Re and ¹⁸³Re.

Table 2 shows the average activity of each of these radioisotopes detected within the cassettes along with the standard error of the mean. This table also lists the median and the range of activities for each radioisotope. The activities ranged from 0 Bq to 2.4 kBq, all of which are below exemption levels (Policy, DoH, 2007).

Table 3 shows the variation in the total activity and the total activity concentration (total activity per unit mass of the cassette) for all the cassettes measured in this study. The average total activity was found to be 2094 Bq with values ranging between 457 and 5529 Bq while the average total activity concentration was 11.0 Bq/g with values between 2.4 and 29.1 Bq/g.

The highest activity is noted for cassette no. 7. The distribution of detected long-lived isotopes is presented in Table 4.

Of the radioisotopes detected, the longest half-life is that of ¹⁰⁹Cd, and thus it is this radioisotope that is the greatest contributor to total activity over time. Table 5 shows the activities of the radioisotopes detected in the cassette with the greatest level of ¹⁰⁹Cd within this study, which represents the worst case scenarios for storage before disposal. Fig. 2 shows how the fractional contribution to the total activity of each radioisotope in this cassette varies over time, calculated by individually decay correcting each radioisotope detected and summing the resultant values at each time period. The fractional breakdown is shown at the time of production as well as 12 months and 24 months after production to give an indication of which isotopes contribute most to the need for storage before disposal.

Fig. 3 shows the variation in the total activity concentration over time, decay corrected as in Fig. 2. The threshold below which the cassette can be disposed alongside clinical waste, 0.4 Bq/g, is indicated by a dashed line in Fig. 3, which coincides with ~24 months of decay after production.

Table 4
Activity of individual isotopes within the most radioactive cassette.

| Radionuclide | Half life (d) | Activity [Bq] |
|-------------------|---------------|---------------|
| ⁵¹ Cr | 27.7 | 898 |
| ⁵² Mn | 5.59 | 929 |
| ⁵⁴ Mn | 312.3 | 5 |
| ⁵⁶ Co | 77.3 | 436 |
| ⁵⁷ Co | 271.8 | 73 |
| ⁵⁸ Co | 70.8 | 462 |
| ^{95m} Tc | 61 | 180 |
| ⁹⁶ Tc | 4.28 | 2393 |
| ¹⁰⁹ Cd | 462 | 107 |
| ¹⁸² Re | 2.7 | 0.0 |
| ¹⁸³ Re | 70 | 45 |
| Total | | 5528 |

Table 5
Activity of individual isotopes within the cassette with highest ¹⁰⁹Cd contribution.

| Radionuclide | Half life (d) | Activity [Bq] |
|-------------------|---------------|---------------|
| ⁵¹ Cr | 27.7 | 895 |
| ⁵² Mn | 5.59 | 78 |
| ⁵⁴ Mn | 312.3 | 6 |
| ⁵⁶ Co | 77.3 | 295 |
| ⁵⁷ Co | 271.8 | 67 |
| ⁵⁸ Co | 70.8 | 385 |
| ^{95m} Tc | 61 | 115 |
| ⁹⁶ Tc | 4.28 | 1826 |
| ¹⁰⁹ Cd | 462 | 180 |
| ¹⁸² Re | 2.7 | 0 |
| ¹⁸³ Re | 70 | 56 |
| Total | | 3903 |

4. Discussion

The isotopes detected by Gamma-Ray Spectroscopy (Fig. 1) during this investigation are in broad agreement with radioisotopes identified by previous authors who have looked at levels of radionuclidic impurities in the radiochemistry cassettes for FDG production [O'Donnell, Ito, Gillies, Mochizuki, Marengo and Bowden]. All authors detected ⁵²Mn, ⁵⁶Co, ⁵⁷Co and ⁵⁸Co; however, there are a number of differences between the other reported radioisotopes as shown in Table 6.

As shown in Table 1, the source of nearly all of the radioisotopes detected can be attributed to proton and neutron activation of the materials within the Havar foil. The exception to this is the ¹⁰⁹Cd generated from the ¹⁰⁹Ag(p,n)¹⁰⁹Cd interaction, which takes place when the proton beam interacts with the Gen II silver target body Table 7.

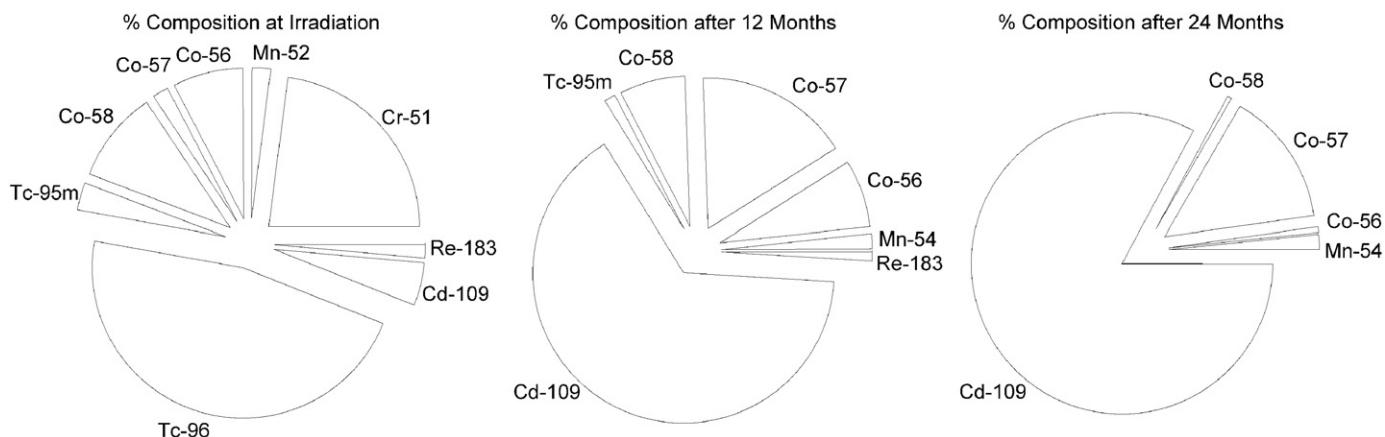


Fig. 2. Percentage composition of activity within the cassette with highest ^{109}Cd contribution at irradiation, 12 months after irradiation and 24 months after irradiation.

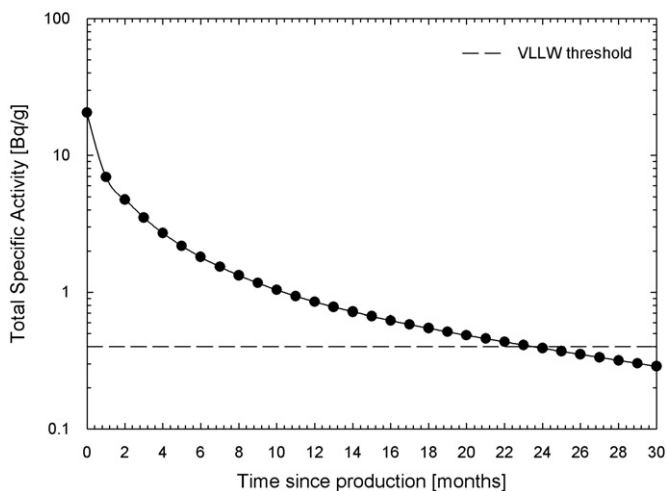


Fig. 3. Decay of total activity concentration of the cassette with highest ^{109}Cd contribution. Horizontal dashed line indicates threshold level for disposal alongside clinical waste.

Gillies et al. were the only authors to report the presence of ^7Be . ^7Be decays by electron capture or positron emission (ϵ/β^+) with a half life of 53 days and a gamma emission of 477.6 keV. The presence of ^7Be should have been detected using gamma spectroscopy by other previously mentioned authors; therefore, it is unlikely that it was present in the other authors' experiments. Proton irradiation of ^{12}C produces two reactions: $^{12}\text{C}(p,3p3n)^7\text{Be}$ and $^{12}\text{C}(p,pn)^{11}\text{C}$ (Dickson JM et al., 1951). Therefore, any carbon present in Gillies et al.'s target would have produced both ^{11}C and ^7Be . However, the short-lived nature of ^{11}C and its decay by positron emission could have prevented its detection by Gillies et al. whilst they detected ^7Be .

One potential source of Carbon is the small amount of Carbon present in the HAVAR foil. This may have been the source of the Carbon for Gillies et al. but this would have been present for all other authors and does not explain why they did not detect its presence. One possible explanation for this variation between Gillies et al. might be that the Carbon in the target foil is not the source of Carbon that produced the ^7Be for Gillies et al. One other possible source for this radionuclidic impurity may have been the presence of Carbon impurities in the target bodies used by Gillies et al. and this may have lead to the creation of ^7Be .

^{48}V was detected by Marengo et al., Gillies et al., Mochizuki et al. and O'Donnell et al. However, neither Ito et al., Bowden et al. nor ourselves detected its presence in the radiochemistry cassette. ^{48}V decays via ϵ/β^+ with a half life of 16.0 days. As Mochizuki

Table 6

Summary of reported radionuclidic impurities during routine production of ^{18}F FDG.

| | O'Donnell | Ito | Gillies | Mochizuki | Marengo | Bowden | Ferguson |
|---------------------------|-----------|-----|---------|-----------|---------|--------|----------|
| ^7Be | | | ✓ | | | | |
| ^{48}V | ✓ | | ✓ | ✓ | ✓ | | |
| ^{51}Cr | ✓ | | ✓ | ✓ | ✓ | ✓ | ✓ |
| ^{52}Mn | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ^{54}Mn | ✓ | | ✓ | ✓ | ✓ | | ✓ |
| ^{56}Mn | | | | | ✓ | | |
| ^{55}Fe | | ✓ | | | | | |
| ^{55}Co | | ✓ | | | ✓ | | |
| ^{56}Co | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ^{57}Co | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ^{58}Co | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| ^{60}Co | | | | ✓ | | | |
| ^{57}Ni | | | | | ✓ | | |
| ^{59}Ni | | ✓ | | | | | |
| ^{95}Tc | | ✓ | | | ✓ | | ✓ |
| $^{95\text{m}}\text{Tc}$ | | ✓ | | ✓ | ✓ | ✓ | ✓ |
| ^{96}Tc | | ✓ | | ✓ | ✓ | ✓ | ✓ |
| ^{98}Tc | | | | ✓ | ✓ | ✓ | ✓ |
| ^{105}Ag | | | | ✓ | ✓ | ✓ | ✓ |
| $^{106\text{m}}\text{Ag}$ | | | | ✓ | ✓ | ✓ | ✓ |
| ^{109}Cd | | ✓ | | | | ✓ | ✓ |
| ^{181}Re | | | | ✓ | ✓ | ✓ | ✓ |
| ^{182}Re | | | | ✓ | ✓ | ✓ | ✓ |
| $^{182\text{m}}\text{Re}$ | | | | ✓ | ✓ | ✓ | ✓ |
| ^{183}Re | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| ^{184}Re | ✓ | | | ✓ | ✓ | ✓ | ✓ |
| ^{186}Re | | | | ✓ | ✓ | ✓ | ✓ |

et al. used a titanium target body and coupled a titanium foil with the Havar foil, the ^{48}V detected may well have been produced by the $^{48}\text{Ti}(p,n)^{48}\text{V}$ reaction (Hichwa RD et al., 1995). However, Marengo et al. and O'Donnell et al. used a standard GE PETtrace 16.5 MeV cyclotron and standard GE silver target body sealed using a Havar foil. Ito et al., Bowden et al. and ourselves also used a silver target body and a Havar foil. This leaves the reason for this difference unclear, but it is likely that titanium was present in the target body or target foil in some centres and not others. It is worth noting that Bowden et al. and O'Donnell et al. are the same group and used the same equipment for both studies. The difference between the papers is that O'Donnell et al. studied the composition of the Havar foil after irradiation whilst Bowden et al. studied the long lived impurities at different stages in the production process. In both papers, ^{48}V was present in the Havar foil but in the Bowden et al. paper, ^{48}V was not found anywhere else in the production process. One possible explanation for this difference may be that ^{48}V is produced within the target foil but is not released into ^{18}O water undergoing proton bombardment.

Table 7

Summary of methods of investigating radionuclide impurities during routine production of ^{18}F FDG.

| | Cyclotron | Target body | Target foil | Radiochemistry rig | Point of analysis |
|------------------|-------------|-------------|-------------|--------------------|---------------------------|
| O'Donnell | PET trace | Silver | Havar | Tracer Lab | Foil |
| Ito | MINI-Trace | Silver | Havar | PET Trace | RC |
| Gillies | N/A | N/A | N/A | Tracer Lab | RC |
| Mochizuki | CYPRIS HM18 | Titanium | Ti+Havar | Home made | Foil |
| Marengo | PET trace | Silver | Havar | Tracer Lab | RC |
| Bowden | PET trace | Silver | Havar | Not stated | Havar RC Used Water Waste |
| Ferguson | PET trace | Silver | Havar | Tracer Lab | RC |

The presence of ^{51}Cr was detected by all previously mentioned authors apart from Ito et al. ^{51}Cr decays via ε/β^+ with a half life of 27.7 days. Unlike other authors, Ito et al. were using a MINItrace Cyclotron, which accelerates protons to 9.6 MeV compared to the other authors who were using higher proton energies. ^{51}Cr is generated from neutron bombardment and this would suggest that there is a difference in the secondary neutron energies between the cyclotrons used by the different authors.

^{54}Mn decays predominantly via ε/β^+ with a half life of 312.1 days. Ito et al. and Bowden et al. did not detect ^{54}Mn in the radiochemistry system although Bowden et al. did suspect detection of ^{54}Mn in their Havar foils. The presence of ^{54}Mn may not be fully evident due to the short counting period employed.

^{56}Mn was only detected by Marengo et al. Decaying via beta emission with a half-life of only 2.6 h most likely had decayed away to stable ^{56}Fe before the other authors measured the levels of radionuclidic impurities whereas Marengo et al. measured all samples within 24–72 h of EOB.

^{55}Fe and ^{59}Ni were only detected by Ito et al. Both radioisotopes decay via ε/β^+ with half-lives of 2.7 and 1.6104 years, respectively. Ito et al. were the only group to perform gamma spectroscopy using a system optimised for γ and characteristic X-rays below 30 keV and so were able to detect the characteristic X-rays emitted by ^{55}Fe (5.9 keV) and ^{59}Ni (2.4 keV). Using standard gamma-ray spectroscopy, these photons would not have been detected therefore it is unsurprising that none of the other authors detected these impurities. A possible reaction for producing ^{55}Fe is $^{55}\text{Mn}(p,n\gamma)^{55}\text{Fe}$ and for ^{59}Ni , it is $^{59}\text{Co}(p,n)^{59}\text{Ni}$. ^{55}Mn and ^{59}Co are both present in Havar foil.

^{55}Co decays via ε/β^+ with a relatively short half-life of 17.5 h. It is produced by proton bombardment of natural iron present in the Havar foil. Ito et al. and Marengo et al. performed their measurement within three and seven days from EOB, respectively. Our measurements were performed within 30 days from the EOB so the ^{55}Co may have already decayed to ^{55}Fe .

^{60}Co was detected only by Mochizuki et al. ^{60}Co decays by beta emission with a half-life of 5.27 years. Mochizuki et al. suggested that the presence of ^{60}Co in their sample could be attributed to the generation of thermal neutrons with a higher flux on their cyclotron compared to the GE PETtrace.

^{57}Ni was only detected by Marengo et al. ^{57}Ni can be a result of background neutron induced reactions. However, the same author states $^{58}\text{Ni}(p,d)^{57}\text{Ni}$ as a possible nuclear reaction for the formation of this radionuclide. It has 35.9 h half life, but it quickly decays via ε/β^+ to ^{57}Co , which was detected by all authors.

Gillies et al. did not detect any Technetium radionuclidic impurities. During their study, Gillies et al. extracted metallic impurities from the cassette before analysing the eluate with Capillary Electrophoresis. It is possible that either the Technetium impurities remained on the cassette or the Capillary Electrophoresis was not calibrated to detect Technetium.

^{95}Tc , which decays via ε/β^+ with a half life of 20 h, was only detected by Marengo et al. from selected samples measured

within three days of EOB. We detected ^{95}Tc in four cassettes that were analysed within eight days of production with activities ranging between 1000 and 6000 Bq. However, as all other cassettes were analysed at times greater than this, GammaVision will not provide a decay correction as it is over the 12 half-life limit. The number of half-lives that had passed before analysis of the four cassettes that contained ^{95}Tc would also raise doubts on the accuracy of the decay corrected values.

^{95m}Tc has a half life of 61 days and decays via ε/β^+ . As well as ourselves, Marengo et al., Bowden et al., Mochizuki et al. and Ito et al. detected ^{95m}Tc . However, Ito et al. mistakenly labelled ^{95m}Tc as ^{95}Tc in their paper. Additionally, O'Donnell et al. appear to have ^{95m}Tc peaks in their spectrum that were unidentified in their paper. Similarly, all groups except O'Donnell et al. report ^{96}Tc , which decays via ε/β^+ with a half-life of 4.3 days. Again, however, it would appear that there are ^{96}Tc peaks in their spectrum that were unidentified.

Marengo et al. were the only group to identify ^{98}Tc , which they found in their Chromatofix PS- HCO_3 column, described as a main trapping point for impurities. ^{98}Tc decays via beta emission with a half-life of 4.2×10^6 years and also emits gamma-rays at 652 keV and 745 keV. From their spectrum attained from the PS- HCO_3 column it is unclear how this isotope has been identified as the 745 keV peak would be obscured by the ^{52}Mn 744.2 keV peak while the 652 keV peak is not evident between the two ^{181}Re peaks.

Marengo et al. also detected some isotopes of silver, ^{105}Ag and ^{106m}Ag , the production of which they attributed to a (p,n) reaction with palladium present in the foils or the Helicoflex seals. They also believed other silver products may also be present but detection was limited by half-lives or low specific activity. One reason Marengo et al. identified was that more radioisotopes in general than the other groups could be the only group to use a Canberra HPGe detector with Genie 2000 software as opposed to an Ortec HPGe detector with GammaVision software. Additionally they analysed all samples within 24–72 h of EOB.

Neither O'Donnell et al., Mochizuki et al. or Gillies et al. detected the presence of ^{109}Cd in their Havar foils. ^{109}Cd is produced by the $^{109}\text{Ag}(p,n\gamma)^{109}\text{Cd}$ reaction when protons interact with the silver target body and decays with a half-life of 1.3 years via ε/β^+ to ^{109m}Ag , which further decays to ^{109}Ag via isomeric transition with a half-life of 39.7 s. As there is no silver in the Havar foil, it is unsurprising that ^{109}Cd was not detected by O'Donnell et al. or Mochizuki et al. This is supported by the paper from Bowden et al. who detected ^{109}Cd in all steps of the process but did not detect ^{109}Cd in their Havar foils. As Gillies et al. did not describe their target body or target foil, it is not possible to comment on the lack of ^{109}Cd in their results.

Rhenium isotopes are created by (p,n) interactions with isotopes of tungsten. The naturally occurring isotopes of tungsten are ^{180}W (0.1%), ^{182}W (26.5%), ^{183}W (14.3%), ^{184}W (30.6%) and ^{186}W (28.4%). The cross-sections for the production of ^{181}Re , ^{182m}Re , ^{182g}Re , ^{183}Re , ^{184}Re and ^{186}Re were investigated by other

authors using the stacked foil technique following proton bombardment of natural tungsten (Lapi et al., 2007).

^{181}Re was only detected by Marengo et al., ^{182}Re by Marengo et al. and our group, $^{182\text{m}}\text{Re}$ by Marengo et al. and Bowden et al., ^{183}Re by all but Ito et al., ^{184}Re by O'Donnell et al., Mochizuki et al. and Marengo et al. and ^{186}Re by only Marengo et al. ^{181}Re , ^{182}Re , $^{182\text{m}}\text{Re}$, ^{183}Re and ^{184}Re all decay via ϵ/β^+ with half-lives of 19.9 h, 2.7 days, 12.7 h, 70 days and 37.9 days, respectively. ^{186}Re decays via beta emission and ϵ/β^+ with a half-life of 3.75 days.

Gillies et al. did not detect any Rhenium radionuclide impurities. During their study, Gillies et al. extracted metallic impurities from the cassette before analysing the eluate with Capillary Electrophoresis. As with Technetium, it is possible that either the Rhenium impurities remained on the cassette or the Capillary Electrophoresis was not calibrated to detect Rhenium.

^{181}Re may not have been detected due to the short half-life of 19.9 h while the main gamma-ray peaks for ^{182}Re and $^{182\text{m}}\text{Re}$ are coincident so it may be difficult to keep them apart and one could be easily mistaken for the other. The most intense gamma-ray peaks of ^{186}Re (137.2 and 122.6 keV) are almost completely coincident with the two main ^{57}Co peaks (122.1 and 136.5 keV) and so it would be hard to detect the ^{186}Re beneath the ^{57}Co . Additionally, the cross section for ^{186}Re is very low; almost 40 times lower than for ^{183}Re and 10 times lower than for ^{182}Re (Lapi et al., 2007). In our investigation, we were measuring the levels in the cassettes and not the target foils, the activity of a number of the rhenium radioisotopes may have been too low for detection on our system.

Both Tables 2 and 3 demonstrate that the amount of radioactivity generated in each production run is not consistent. The total activity of each cassette varied from 456.7 to 5528.6 Bq. Similar variability in activity was seen in the individual long-lived isotopes (2.98–846.47 Bq).

Possible sources of this variability include variation in activation and leaching into the cassettes between production runs as well as variation in position of the radioactivity within the cassettes and within the 1 lt tub. To investigate the latter option, the same cassette was analysed 5 times with the 1 lt tub containing it shaken between subsequent measurements. Analysis of these results showed a maximum variation in reproducibility of 10%, which is lower than that variations observed in Tables 2 and 3. This would indicate that the variation observed is due to variation between production runs.

It should also be noted that the stated activities are most likely an overestimation due to the difference in the geometry of the uniform calibration source and the unknown distribution of activity within the cassette in a 1 lt tub.

From Tables 2 and 4 it is clear that the main contributions to the radioactivity in the cassettes we measured come from ^{51}Cr , ^{52}Mn , ^{56}Co , ^{58}Co and ^{96}Tc . Marengo et al. show ^{56}Mn , ^{58}Co , ^{181}Re and ^{95}Tc as the main contributors to the activity captured during their analysis. However, Bowden et al. present ^{58}Co , ^{56}Co and ^{96}Tc as main contributors to radiochemical parts. Gillies et al. states cobalt isotopes as main source of activity with small contribution of ^7Be and Manganese isotopes. The $[\text{18O}]\text{H}_2\text{O}$ analysed by Ito et al. showed ^{55}Fe , ^{55}Co , ^{56}Co and ^{59}Ni to have the greatest contributions.

O'Donnell et al., Mochizuki et al. and Bowden et al. also analysed Havar foil. Their findings are similar to those for the cassettes, with cobalt and manganese isotopes as well as ^{51}Cr contributing the most to the total activity in the foil.

Fig. 2 presents the percentage composition of activity within the cassette with highest ^{109}Cd contribution at irradiation; 12 months after irradiation; and 24 months after irradiation. It is noticeable that initially the main contributions to the activity in the cassettes are from ^{51}Cr , ^{56}Co , ^{58}Co , and ^{96}Tc . Over time, however, this changes until after 12 months the main

contributions are from the three Cobalt isotopes and ^{109}Cd , and after 24 months ^{109}Cd and ^{57}Co . These latter two isotopes do not initially have a large contribution but, due to their long half-lives (462 days and 271.8 days, respectively), they have a greater contribution over time to the total activity concentration used to determine if the cassette may disposed of as clinical waste.

All isotopes present in the Havar foil detected by O'Donnell et al. are relatively short-lived, with ^{54}Mn having the longest half-life of 312 days. In the samples analysed by Ito et al. most are relatively short-lived except ^{55}Fe and ^{109}Cd with half-lives of 2.7 and 1.3 years, respectively. Of the radioisotopes found by Marengo et al., only ^{109}Cd and ^{57}Co have long half-lives and so would have a large impact on the storage time and disposal.

As cadmium is the main contributor to levels of radioactivity remaining in the cassette over time, one strategy may be to replace the silver body of the target with a different material. Recently, cyclotron manufacturers have started to offer niobium target bodies rather than silver as these enable higher quantities of ^{18}F to be produced per production run. This change would remove the presence of cadmium from the long lived impurities as there would be no silver to be activated in the target body. However, it is likely that other impurities such as molybdenum, niobium, zirconium and yttrium isotopes would be generated as a result of proton bombardment of ^{93}Nb and the following isotopes may be produced: $^{93\text{m},90}\text{Mo}$, $^{92\text{m},91\text{m},90}\text{Nb}$, $^{88,89}\text{Zr}$ and ^{88}Y (Ditróí et al.). The longest lived of these impurities is ^{88}Y (106.6 days), which has a lot shorter half-life than ^{109}Cd .

Another method of reducing the long lived impurities generated in the cassettes is to coat the Havar foil in tantalum using sputtering. A recent presentation by Gagnon et al. (Gagnon et al., 2010) has demonstrated that this method provides a significant reduction in Havar associated impurities of cobalt, manganese and nickel present in the cassettes. Also Wilson et al. propose the use of Havar foils sputtered with Niobium (Wilson et al., 2008). Their research had shown decrease in long-lived impurities by ten times.

We did not investigate the level of impurities in the ^{18}O waste water, where long-lived impurities are also likely to be present. Some results for waste water are presented by other authors [Bowden et al., 2009; Marengo et al., 2008; Ito et al., 2006]

Bowden et al. and Ito et al. also measured the level of Tritium in their samples, a product of a typical run from the $\text{D}(\text{n},\gamma)\text{T}$ reaction. In our investigation the ability of Tritium formation was not assessed and the main focus was on long lived radioactive impurities.

Ito et al. conclude that isotopes found in $[\text{18O}]\text{H}_2\text{O}$ can be exempted from the limitation as radioactive materials. However, the Policy for the Long Term Management of Solid Low Level Radioactive Waste in the UK states that the limit below which any radioactive waste can be disposed of alongside clinical waste is 0.4 Bq/g. Fig. 3 shows the variation of the total activity concentration over time for the cassette with the highest ^{109}Cd contribution within this study. It is obvious that the cassette must be treated as radioactive waste and stored for a period of time prior to disposal. As it is not practical to assay each cassette prior to disposal, a solution is to determine the period of storage required for the cassette encountered during this study that takes the longest time to decay below the 0.4B q/g limit and use this as the storage time of all cassettes before disposal alongside clinical waste. Fig. 3 shows this storage time should be 24 months prior to disposal. As discussed, due to difference in geometry of the calibration source and the cassettes, this storage time will be an over-estimate, however, it will ensure that levels drop below the Low Level Limit.

However, disposable cassettes consist of three parts, which can be easily separated. As the activity in the cassette is not distributed

evenly, it may be necessary to identify the parts of the cassette, which are in the direct contact with the activity. That would improve waste management and help to minimise storage area for radioactive waste, but requires additional study in this area.

5. Conclusion

To assess the presence and activity of long-lived gamma-ray emitting impurities in the routine production process of FDG, 20 cassettes were measured using a high-resolution gamma-ray spectrometer. Eleven radionuclides, ^{51}Cr , ^{52}Mn , ^{55}Fe , ^{56}Co , ^{57}Co , ^{58}Co , $^{95\text{m}}\text{Tc}$, ^{96}Tc , ^{109}Cd , ^{182}Re and ^{183}Re , were detected experimentally in the FDG cassettes after the synthesis process identified by photon peaks within the energy range of 10–2000 keV. The average activities of these radionuclides ranged between 2.98 and 846.47 Bq with an average total activity in the cassette of 2094 Bq. There could be two reasons for such a variability of measured activities. One is the position of the radiation within the cassettes and the variation of the position of the cassettes within the tub. The other is that the amount of activity released from the foil varies between production runs.

The greatest contribution to the total activity over time was from ^{109}Cd , which determines the length of time the cassettes need stored before disposal. For the cassettes to be disposed alongside clinical waste, they must be stored until they decay below the specific activity concentration limit of 0.4 Becquerels per gram. Based on the cassette with the largest ^{109}Cd contribution, an appropriate storage time would be 24 months before disposal should ensure that the cassettes can be classified and disposed of as clinical waste. This is a conservative storage time due to the overestimation of activity from variation in geometry to that of the calibration source, however, it will ensure that the cassettes can be safely classified and disposed of as clinical waste after this period.

References

- Bowden, L., León Vintrolé, L., Mitchell, P.I., O'Donnell, R.G., Seymour, A.M., Duffy, G.J., 2009. Radionuclide impurities in proton-irradiated ^{18}O H_2O for the production of ^{18}F –: activities and distribution in the ^{18}F FDG synthesis process. *Appl. Radiat. Isot.* 67, 248–255.
- BP, 2010. Monographs: radiopharmaceutical preparation, fluorodeoxyglucose [^{18}F] injection. In: British Pharmacopoeia 2010, British Pharmacopoeia Commission, London.
- Dickson, J.M., Randle, T.C., 1951. The excitation function for the production of ^{7}Be by the bombardment of ^{12}C by protons. In: *Proceedings of the Physical Society Section A*, vol. 64, p. 902.
- Ditrói, F., Hermanne, A., Corniani, E., Takacs, S., Tarkanyi, F., Csikai, J., Shubin, Y.N., 2009. Investigation of proton induced reactions on niobium at low and medium energies. *Nucl. Inst. Methods Phys. Res. B* 267 (19), 3364–3374.
- Department of Health, 2007. Policy for the Long Term Management of Solid Low Level Radioactive Waste in the United Kingdom.
- EP, 2010. Fluorodeoxyglucose [^{18}F] injection. European Pharmacopoeia, European Directorate for the Quality of Medicines, Strasbourg, France.
- Gagnon, K., Wilson, J.S., McQuarrie, A., Comparison of Nb, Pt, Ta, Ti, Zr and ZrO_2 sputtered Havar foils for the high power cyclotron production of reactive [^{18}F]F–. In: *Proceedings of the 13th International Workshop of Targetry and Target Chemistry*, Roskilde, Denmark, 2010.
- Gillies, J.M., Najim, N., Zweit, J., 2006. Analysis of metal radioisotope impurities generated in ^{18}O H_2O during the cyclotron production of fluorine-18. *Appl. Radiat. Isot.* 64, 431–434.
- Havar Technical Data Sheet, Hamilton Precision Metals, Lancaster, PA, <<http://www.hpmetals.com/pdfs/havar.pdf>>.
- Hichwa, R.D., Kadrmas, D., Watkins, G.L., Wollenweber, S.D., Maniam, S., Boles Ponto, L.L., Richmond, J.C.W., Koepfel, J.A., 1995. Vanadium-48: A Renewable Source for Transmission Scanning with PET. *Nucl. Inst. Methods Phys. Res. B* 99, 804–806.
- Ito, S., Sakane, H., Deji, S., Saze, T., Nishizawa, K., 2006. Radioactive byproducts in ^{18}O H_2O used to produce ^{18}F for [^{18}F]FDG synthesis. *Appl. Radiat. Isot.* 64, 298–305.
- Lapi, S., Mills, W.J., Wilson, J., McQuarrie, S., Publicover, J., Schueller, M., Schyler, D., Ressler, J.J., Ruth, T.J., 2007. Production cross-sections of 181–186Re isotopes from proton bombardment of natural tungsten. *Appl. Radiat. Isot.* 65, 345–349.
- Marengo, M., Lodi, F., Magi, S., Cicoria, G., Pancaldi, D., Boschi, S., 2008. Assessment of radionuclidic impurities in 2- ^{18}F fluoro-2-deoxy-d-glucose ([^{18}F]FDG) routine production. *Appl. Radiat. Isot.* 66, 295–302.
- Mochizuki, S., Ogata, Y., Hatano, K., Abe, J., Ito, K., et al., 2006. Measurement of the Induced Radionuclides in Production of Radiopharmaceuticals for Positron Emission Tomography. *J. Nucl. Sci. Technol.* 43, 348–353.
- O'Donnell, R.G., León Vintrolé, L., Duffy, G.J., Mitchell, P.I., 2004. Measurement of the residual radioactivity induced in the front foil of a target assembly in a modern medical cyclotron. *Appl. Radiat. Isot.* 60, 539–542.
- Wilson, J.S., Avila-Rodriguez, M.A., Johnson, R.R., Zyuzin, A., McQuarrie, S.A., 2008. Niobium sputtered Havar foils for the high-power production of reactive [^{18}F]fluoride by proton irradiation of ^{18}O H_2O targets. *Appl. Radiat. Isot.* 66, 565–570.
- Yu, S., 2006. Review of ^{18}F -FDG synthesis and quality control. *Biomed. Imaging Interv. J.* 2, 4.