Ionic Contaminants (Radioactive and non-Radioactive) in Irradiated [O-18] Water. Preliminary Results of a Comparative Study.

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Introduction

Many [F-18]-containing radiopharmaceuticals are obtained by nucleophilic substitution of an appropriate substrate with resolubilized [F-18]fluoride. Typically, [F-18]fluoride is cyclotron produced by the proton irradiation of enriched [O-18]water[1]. Target water after irradiation is likely to contain a variety of ionic contaminants. In order to better understand synthesis reproducibility and reactivity of [F-18]fluoride it may well be beneficial to determine the type of contaminants present in the water and to study if these change or stay constant over a period of time. It is ultimately hoped that these data can be correlated with fluoride reactivity[2-4], and help to determine limits of acceptance for standard operating procedures (SOP) in clinical formulations.

Analytical Methods

The analysis of selected ions was accomplished with a Waters Ion Chromatography system provided with an automatic sample injector, and UV/VIS and conductivity detectors. Procedures for the analyses were those recommended by the manufacturer. Milli Q™ pure water stored under the same conditions as the samples was used as blank. Zinc is a common additive in plastic syringes and plastic bottles. To eliminate or reduce metal ion contamination all plasticware was previously soaked in ultrapure HNO_3 (6N solution). Transition metal ions (Cu, Pb, Zn, Ni, Co, Cd, Fe(II), Mn) were analyzed on a C-18 column using as eluent 2 mM octanesulfonate, 35 mM sodium tartrate, 5% acetonitrile adjusted to pH 3.65, and at a flow rate of 0.8 mL/min. Detection was done at 500 nm by post-column derivatization with 0.2 M PAR [4-(2-pyridylazo)resorcinol], 1 M acetic acid and 3 M ammonium hydroxide. The limits of detection (3 x signal-to-noise baseline) ranged from 5 to 25 ppb.

Mono and divalent cations (Li, Na, NH_4, K, Mg, Ca, Sr, Ba) were analyzed on an IC-Pak™C M/D column (Waters) with a 0.1 mM EDTA/3.0 mM nitric acid eluent at 1 mL/min and detected by conductivity. The limits of detection ranged from 1 to 100 ppb. Anions (F, Cl, NO_2, Br, NO_3, HPO_4, SO_4) were analyzed on an IC-Pak A HR column (Waters) with a borate/gluconate solvent, also at 1 mL/min and detected by conductivity. The limits of detection ranged from 1.5 to 14 ppb.

The analysis of radioactive contaminants was performed on a Canberra detector model GC 1818 provided with an integrated signal processor, and a Genie PC spectroscopy system. The detector was operated at -196 °C and shielded with 2 in of lead. Calibration for energy and efficiency was done

with an NBS-certified multinuclide source with energy peaks across the 50-2000 KeV range.

Targetry Description

Schematics of the target system for each of the two cyclotrons in use at Washington University are shown in Figure 1. The target chamber of the Japan Steel Works 16/8 (JSW) cyclotron is stainless steel with inserts and foils made out of titanium and it has a volume of 0.94 mL. The Cyclotron Corporation (CS-15) target has a stainless steel body with titanium inserts and Havar[5] foils; the target volume is 1.7 mL. Both targets are cooled with chilled water at 12-17°C. Irradiation conditions are as follows, (1.) JSW: 16 MeV protons with a 35 μA beam current; and (2.) CS-15: 15 MeV protons beam with a 20 μA beam current. Both methods will produce about 1 Ci of [^{18}F]fluoride in 90 minutes. The delivery of radioactivity from the cyclotron's targets to the hot cells is accomplished with about 25 psi of helium pressure through polyetheretherketone (PEEK) tubing (0.76 mm ID, 1.59 mm OD) in lengths varying from 20 to 63 feet.

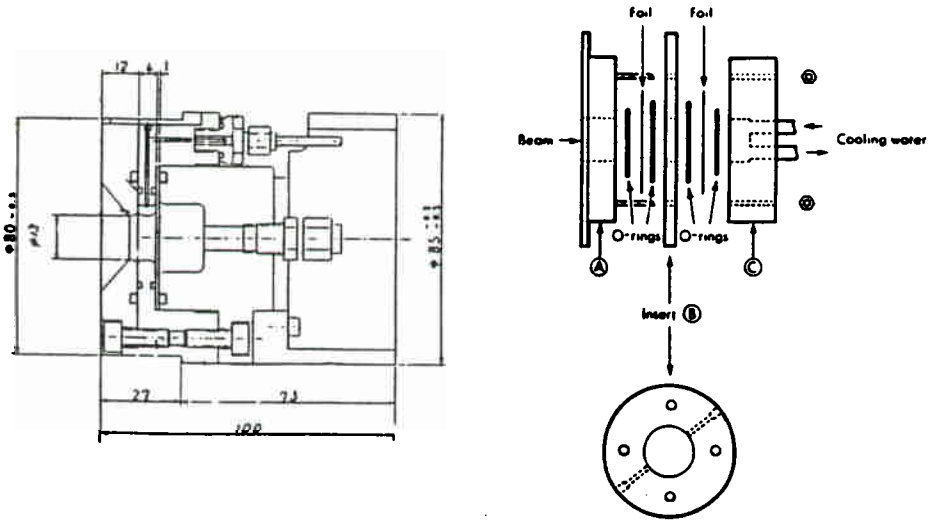

Figure 1. Diagrams showing the details of the [O-18]water targets on the JSW (left) and CS-15 (right) cyclotrons.

Results and Discussion

The ionic composition of three batches of [O-18]water before irradiation are shown in Table 1. The samples listed were analyzed for all the ions described in the analytical section; ions not listed on the table were below our detectable limits. As seen in the table, when one compares the values found for a new batch of water (Swan 989543 or Isotec RX 4536) to a reused batch after distillation (MIR 950721), the ionic composition of the three of them is within the range of 1 ppm or less for most ions investigated. A slightly higher value for sodium and potassium was found in unused water samples.

TABLE 1. [O-18]Water analysis before bombardment (n=2).

Ions Found (ppm)	MIR 950721 (Distilled)	SWAN 989543 (Unused)	Isotec RX 4536 (Unused)
Zn	0.03 ± 0.03	0.04	0.28 ± 0.26
Ni	0.01 ± 0.00	—	0.04 ± 0.04
Fe(II)	0.05 ± 0.05	0.39	0.16 ± 0.16
Na	1.04 ± 0.71	2.10	2.14 ± 1.86
NH_4	0.47 ± 0.03	0.31	1.09 ± 1.09
K	0.25 ± 0.15	0.04	1.60 ± 1.14
Mg	0.08 ± 0.06	0.13	0.03 ± 0.03
Ca	0.01 ± 0.00	0.56	0.34 ± 0.08
Cl	0.36 ± 0.17	1.22 ± 0.54	1.17 ± 0.97
NO_2	0.13 ± 0.13	0.12 ± 0.12	0.13 ± 0.13
NO_3	0.32 ± 0.43	0.38 ± 0.06	0.31 ± 0.31
SO_4	0.22 ± 0.22	0.10 ± 0.10	0.23 ± 0.23

Next, we determined the ionic composition of batches of water that were irradiated with either the JSW-168 (n=9) or the CS-15 (n=5). After a batch of water was irradiated, the target was emptied, the water was allowed to decay and IC data were collected for that batch. The results are presented in Figure 3.

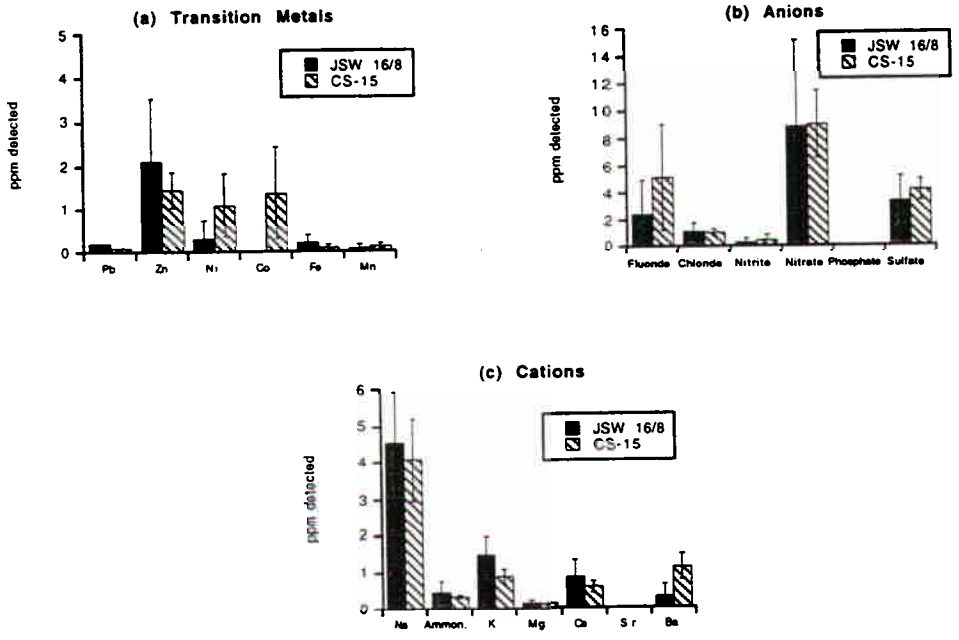

Figure 3. A comparison of ions detected in [O-18]water emerging from each of the two targets after irradiation.

We found the major metal ion contaminants to be Zn, Ni and Co. Not surprisingly, the Havar foils used in the CS-15 cyclotron target give rise to the larger amounts of Ni and Co detected. Lead, Fe and Mn were also present below 0.2 ppm. Among the cations we found similar concentrations of sodium, ammonium, potassium, magnesium, calcium and barium for both cyclotrons, with sodium being the most abundant. The largest concentrations of anions present were those of nitrate, nitrite and sulfate.

For most of the synthesis performed with [F-18]fluoride, the irradiated [O-18]water is recovered after passage through an anion exchange resin in the carbonate form[6] or a quaternary 4-aminopyridinium resin[7]. The latter forms the basis of the GE PETtrace FDG Microlab unit ("black box"). We analyzed the O-18 water emerging from both of these resins and the results are presented in Figure 4. Both resins, but especially the GE black box resin, do a good job in the removal of metal ions (Fig. 4a), below 0.1 ppm. An exception was the ion Fe(II), which was found in concentrations of 0.8 ppm after passage through the carbonate resin.

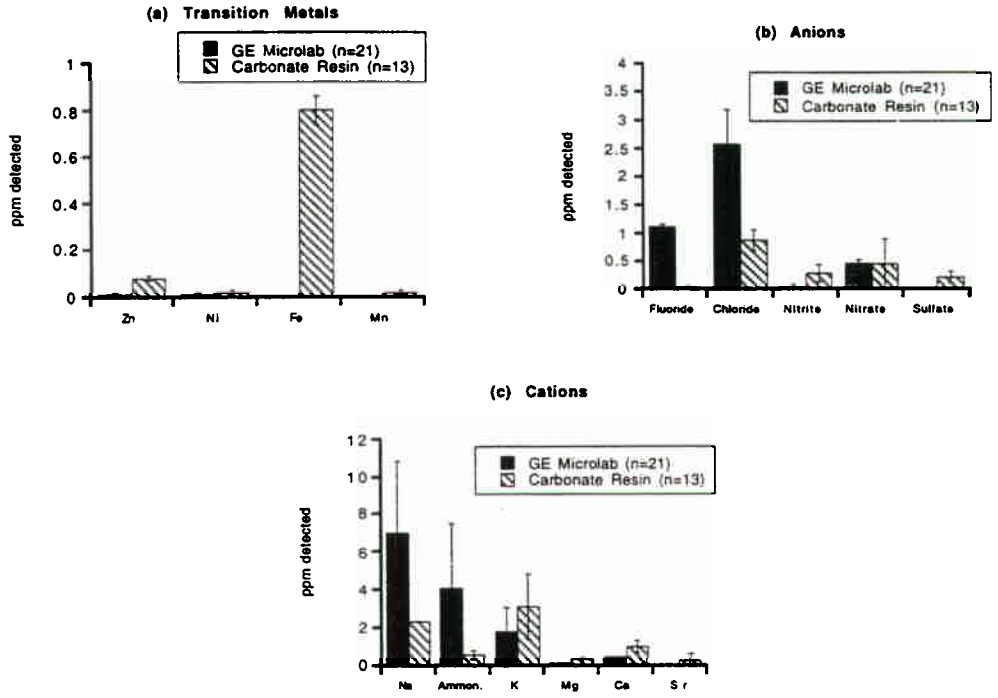

Figure 4. A comparison of the ions found in [O-18]water post-irradiation and after passing through the GE Microlab or Carbonate Resins

The analysis of anions (Fig. 4b) also shows comparable results, but in this case, the carbonate resin was more effective in removing chloride and retaining fluoride from the original irradiated water. Both resins reduced nitrite, nitrate and sulfate by 50 to 95% from the typical values found before resin treatment (see for example Fig. 3b). Very small change was observed in

the total cation composition (compare Figs. 4c and 3c), but on average, lower concentrations of sodium and ammonium ions were found in water treated with the carbonate form resin.

It is important to be aware of ionic contaminants in all reagents that come in contact with [F-18]fluoride. A case in point is the trace analysis (ICP and AA) given by the manufacturer (Aldrich) for the 99.99% potassium carbonate used to extract the radioactivity from the carbonate resin. The values reported are given in Table 2. It is important to notice the relatively large amounts of rubidium and cesium, that are present and which may detrimentally affect the course of a fluorine-18 substitution reaction, depending on the nature of the substrate and its leaving group.

TABLE 2. Trace analysis of 99.99% potassium carbonate by ICP and AA.

Ion Detected	Concentration (ppm)
Na	30
Ba	2
Zr	1
Sr	0.5
Rb	40
Cs	20

In Figure 5 we compare the effectiveness of both resins to remove radioactive trace metal contaminants from two batches of water from different vendors (Isotec and Swan). The analyses show that the [O-18] water eluted from the GE black box resin contains approximately 10 times less radioactive metal ions contaminants than that eluted from the carbonate anion exchange resin. The major trace metal contaminants found were Sc-48, V-48 and Co-56, with some traces of Mn-52, Co-57 and Ga-66.

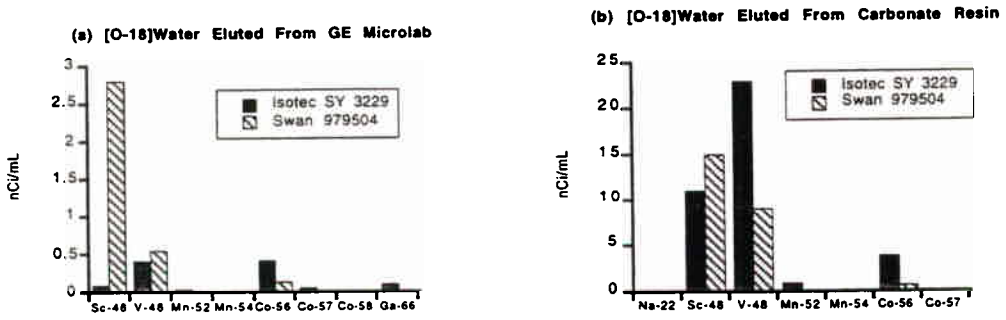

Figure 5. A comparison of the isotopes found in [O-18]water post-irradiation and after passing through the GE Microlab or carbonate resins

When two small resin columns from the GE black box were analyzed (20 mg resin/column) following the production of two batches of FDG, the removal of large amounts of V-48 (308 and 560 nCi) was reconfirmed. See the results in Table 3. Analysis of the final FDG batches (F876 and F877) was also performed and it shows no radioactive trace metal contaminants present.

TABLE 3. Analysis of resin from the GE PETtrace FDG Microlab unit after two typical FDG preparations.

Lot No.	Date	Isotope detected	Amount* (nCi)	Confid. (%)
FDG F876	7/31/95	Sc-47	0.454	99.0
		V-48	308	99.8
FDG F877	8/2/95	Sc-44x	2.79	99.2
		Sc-47	1.11	98.6
		V-48	650	99.8

*Values are decay corrected to the end of FDG synthesis.

The radiochemical analysis of the residue left on the glass vessel after distillation of previously used [O-18] water (25-50 mL batches) revealed the presence of large amounts of V-48 and Sc-48 (325 and 350 nCi respectively), followed by Co-56 (50-100 nCi) and Sc-46, Co-57, Co-58, Mn-54 (less than 25 nCi).

We have also used the HPLC anion analysis method described earlier to monitor the specific activities of [F-18]fluoride (limit of detection for fluoride ion is 1.5 ppb) produced when we suspect target problems (build-up of contaminants). Table 4 shows some values (average of two determinations) found before and after cleaning the targets.

TABLE 4. Specific activities obtained for [$^{18}F^-$] by ion chromatography.

Cyclotron	Before target cleaning (Ci/μmol)	Latest Value (Ci/μmol)
JSW-168	3.90 ± 0.71 7.85 ± 0.94	70-100
CS-15	1.06 ± 0.05	25-30

Summary

- By Ion Chromatography (IC) we analyzed series of [O-18]waters before and after irradiation.
- Compared the IC pattern of [O-18]water post-irradiation from both the JSW 16/8 and the CS-15 cyclotrons.
- Determined the specific activity of [$^{18}F^-$]fluoride by IC for both cyclotrons.

- Using a germanium detector we analyzed samples of [O-18]water for the presence of radioactive metal ions: after irradiation and after passing through the FDG resin, or, a carbonate resin.
- Determined the nature and amount of the radioactivity left on the FDG resin after a typical synthesis.
- Analyzed the final batches of FDG for the presence of radioactive metal contaminants.
- Analyzed the residues left after distillation of previously used [O-18]water for the presence of radioactive metal contaminants.

Future Work

To continue the collection of data as described above in the hope that we will be able to correlate target yields and [F-18]fluoride reactivity with contaminants that we are able to detect in the [O-18]water.

Acknowledgments

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