Title
TELLURIUM--118/ANTIMONY-118 GENERATOR

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Tellurium-118/Antimony-118 Generator

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DISCLAIMER

Tellurium-118 /Antimony-118 Generator

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Abstract

The purpose of this research was to develop a radioisotope generator to obtain ^{118}Sb (3.5 m half-life, 75% positrons) from the 6.0 d ^{118}Te parent, which was produced by the irradiation of an Sb target with 67 Mev protons. About 2 mCi of ^{118}Te was produced per run.Gamma ray analysis with a GeLi detector indicated the production of $^{118}Te/^{118}Sb$, ^{120}Sb, ^{122}Sb, $^{119}Te/^{119}Sb$, $^{119m}Te/^{119}Sb$, ^{121}Te, and ^{121m}Te. The Sb target was brought into solution with HCl and HNO_3 acid. Six % sodium tartrate was added to the target solution to form the Sb-tartrate complex for loading onto an inorganic ion exchange column of neutal alumina (Al_2O_3), stannic oxide (SnO_2), or a combination of Al_2O_3 and SnO_2. Six % sodium tartrate at various pH's ranging from 2 to 8 were used as the eluent solutions. Elution yields of ^{118}Sb and breakthroughs of Te radioisotopes were determined by dose calibrator measurements and GeLi analysis.

Results indicate that the ^{118}Sb yield at pH 7.0 from the SnO_2 was twice the yield from Al_2O_3 with 6% tartrate.while the breakthroughs of Te radioactivity were nearly comparable for the two columns. However, elutions with 6% tartrate at pH 3.5 doubled the yield of ^{118}Sb from Al_2O_3 while elutions at pH 3.5 from SnO_2 increased the ^{118}Sb yield about 28%. Cumlative elution volumes of 6% tartrate at pH 7.0 from either Al_2O_3 or SnO_2 led to a gradual reduction in ^{118}Sb yield from about 25% down to 5-6%. Elutions at pH 3.5, however, led to a higher yield without a gradual reduction in yield with cumulative elution volumes of 6% tartrate. A pH of 5.0 was finally chosen as the best compromise between sustained levels of ^{118}Sb yield and the biological and chemical advantages of working at a pH higher than 3.5.

Exchange labeling was used to label thio compounds with the ^{118}Sb-tartrate from the generator. HPLC analysis and positron camera images of the in vivo distribution of the exchange labeled compounds were used to assess the exchange labeling method.

Introduction

For positron emission tomography (PET), relatively short half life positron emitters are desirable to permit the administration of adequate doses of radioactivity to provide good statisitical sampling in the regions of interest for the quantitation of metabolic and flow processes with PET. Radioisotope generators are a convenient and economical method for obtaining the needed short lived positron emitter without the need for an on-site dedicated cyclotron [1-4]. This report describes the methods and results from the work on developing the Tellurium-118/Antimony-118 (^{118}Te / ^{118}Sb) Generator. This was a collaborative research effort between Lawrence Berkeley Laboratory (LBL) and Crocker Nuclear Laboratory (CNL), U.C. Davis. The targetry and cyclotron irradiation parameters for the production of the 6.0 d ^{118}Te parent were developed at CNL,while the chemistry for working up the Sb metal target, inorganic column chromatograpy for the separation of the 3.5 m ^{118}Sb from the 6.0 ^{118}Te parent, the exchange labeling of ^{118}Sb to

other compounds, and the in vivo distribution of the ^{118}Sb-compounds in rats by positron imaging were done at LBL. The decay scheme for ^{118}Te / ^{118}Sb is shown in Figure 1.

Methods

Antimony metal was used as the target material and irradiated with protons at the CNL 76-inch cyclotron to produce the ^{118}Te parent radioisotope by the ^{121}Sb (p,4n) ^{118}Te nuclear reaction. This method is similar to that reported by Mausner, etal [5]. The maximum crosssection for this nuclear reaction is about 670 mb at 47-48 Mev. The proton energy was 67 Mev for an irradiation of 2.5 g of Sb metal. The yield was about 2 mCi / uAh.

The irradiated Sb metal target was brought into solution with 10 ml of 12 M HCl and 2.5 ml of 15 M HNO_3 acid. The target solution was diluted tenfold with 6% sodium tartrate at pH 3.5 or 7.0. The Sb-tartrate solution was then allowed to drip slowly through an ion exchange column 1 cm i.d. x 25 cm high. Ion exchange beds were 4 cm high and contained either neuteral Al_2O_3 or SnO_2 (H^+). A combination column containing 1 cm of neutral grade Al_2O_3, 100-200 mesh, and 4 cm of SnO_2 (H^+) was evaluated as the column of choice for this generator. Rapid bolus elutions were done with 4 ml volumns of 6% tartrate at pHs' ranging from 2.0 to 8.0. The yield of ^{118}Sb was determined by reading the radioactivity in a dose cailbrator, corrected for decay to determine the yield of the ^{118}Sb at the time of elution and dividing this value by the radioactivity on the column (also read on the calibrator). Breakthrough of the Te radioactivity was determined on the elution volume by waiting 45-50 m for the ^{118}Sb to decay away and reading the residual radioactivity on the dose calibrator and dividing by the total radioactivity on the column. Elution yields and breakthroughs were determined for Al_2O_3, SnO_2, and a combination column containing both adsorbers. The effects of pH, cumulative elution volumes, and length of time between elutions were determined on the yield and breakthrough of ^{118}Sb and ^{118}Te respectively.

Exchange labeling was attempted with ^{118}Sb-tartrate eluates from the generator, which were incubated with various ligands such as diethyldithiocarbamate (DEDTC), dimethlyl dithiocarbamate (DMDTC), pyrollidinedithiocarbamate (PDTC), D-penicillamine (PA), and dimercaptothiadiazole (DMTD). HPLC analysis was used to determine the efficiency of the exchange labeling chemistry. Animal experiments were conducted in rats with intravenous injection of the ^{118}Sb-tartrate or exchange labeled thio compounds and imaging the uptake and clearence of the radiotracer with time using the Anger Positron Camera. These thio compounds were selected for exchange labeling with ^{118}Sb-tartrate because of their potential as antidotal chelates in acute antimony intoxication [6].

Results

The radionuclides produced in the irradiated Sb target are shown in Table 1 with the relative abundace of the principal radioisotopes. ^{118}Te and ^{119m}Te are produced in nearly equal amounts of 0.75 and 0.81 nCi respectively in an aliquot of the target solution analyzed with a GeLi detector. Furthermore, because of the nearly similar half lives of 6.0 and 4.68 d respectively, the radioactivity measured on the dose calibrator for ^{118}Te also includes ^{119m}Te for nearly the life of the generator. Thus the yields of ^{118}Sb calculated by dividing the decay corrected ^{118}Sb by the total Te activity on the column will give an apparent yield which is low by a factor of nearly 2 from the true yield because the ^{119m}Te decays to the 1.58 d ^{119}Sb, which cannot grow back into equilibrium amounts in the short 20-25 m alloted for the in-growth of 3.5 m ^{118}Sb. The elution yields of ^{118}Sb shown in Table 2 reflects the apparent yield with the true yield higher by about a factor of 2. These values compare the apparent elution yields of ^{118}Sb-tartrate as well as the breakthroughs of ^{118}Te and ^{119m}Te from an Al_2O_3 column with that from a SnO_2 column. The

yield of ^{118}Sb-tartrate from the Al_2O_3 column with 6% tartrate at pH 7.0 was 5.4±1.04% and the Te breakthrough was 0.27 ± 0.17 %. For the SnO_2 column, the yield was 10.3 ± 0.38 % and the breakthrough was 0.32 ± 0.15 %. When the pH of the 6 % tartrate eluent was lowered to 3.5, the yield of the ^{118}Sb-tartrate increased twofold to 10.3 ± 0.69 % from the Al_2O_3 column. For the SnO_2 column the yield increased 28 % to 12.9 ± 0.55 % with the pH 3.5 eluent. The breakthroughs of Te radioisotopes were nearly comparable for the Al_2O_3 and SnO_2 columns at 0.27 ± 0.17 % and 0.32 ± 0.15 % respectively with the pH 7.0 tartrate eluent. With the pH 3.5 eluent, the breakthroughs were 0.63 ± 0.43 % for the Al_2O_3 and 0.46 ± 0.14 % for the SnO_2 columns.

The results shown in Figure 2 are from a combination column containing 1 cm of neutral grade alumina (on the bottom) and 4 cm of $SnO_2[H^+]$ (above) eluted with 4 ml of 6 % sodium tartrate in a rapid bolus elution. The effect of pH on the apparent yield of ^{118}Sb shows that at pH 7.0 there is an initial high yield of about 25%, which rapdily decreases to about 14 % and then slowly decreases to about 6.5 % with cumulative elution volumes. The apparent yield can be increased to about 15 % by using pH 3.5 eluent. To find a more physiological pH and still maintain a useful and continued ^{118}Sb-tartrate yield of about 12 %, pH 5.0 appears to be the most useful. These apparent yields can be increased by factor 2 or to about 24 % true yield at pH 5.0.

Figure 3 shows the apparent breakthrough of ^{118}Te, this also includes the breakthrough of ^{119m}Te. These breakthrough numbers include ^{118}Te, ^{119m}Te, and in the first elution of the day or after a time greater than the usual 20-30 m between elutions, the ingrowth of ^{119}Sb. The breakthrough decreases by a factor of 10 or more after the first elution of the day and stabilizes at about 0.08 %.

The effect of pH alone on the apparent yield of ^{118}Sb and on the apparent breakthrough of ^{118}Te are shown in Figures 4 and 5 respectively. The yield of ^{118}Sb-tartrate is highest at pH 3.5 at about 12.5 %, and decreases to 8.5 to 9.0 % between pH 2.0 to 5.0. At higher pH there is a gradual loss in elution yield down to about 5.0 % at pH 8.0. The maximum yield at pH 3.5 is very likely related to the pKa_1 2.93 and pKa_2 4.23 of the tartaric acid.

Exchange labeling studies indicated some success by HPLC analysis and by uptake and distrilbution with time in rats imaged under the Anger positron camera. Figure 6 shows the difference in uptake and clearence in rats of ^{118}Sb-tartrate compared to ^{118}Sb-DEDTC. The former compound was seen in the blood pool early with relatively rapid clearaence by the kidneys into the bladder, while the latter compound was retained in the liver with little or no clearence by the kidneys. HPLC analysis showed three U.V. peaks with corresponding radioactive peaks indicating three species of radiolabeled DEDTC containing about 60 % of the radioactivity. The ^{118}Sb-tartrate came off early in the void volume and contained about 40 % of the radioactivity.

Discussion and Conclusions

Cyclotron irradiations with 25-30 μA of 67 Mev protons will easily produce several hundred mCi of ^{118}Te which is adequate for patient studies with 10-15 mCi of ^{118} Sb. After initial washing of the generator column, the generator eluate provides essentially carrier-free ^{118}Sb-tartrate, which has an LD_{50} of about 60 mg/kg in rats. There was no visible toxic response to repeated injections of 1 ml of ^{118}Sb-tartrate over a period of several days. The true elution yield with 6 % sodium tartrate at pH 5.0 is about 24 %, while the breakthrough of ^{118}Te is about 0.05-0.10 %. The elution yield and breakthrough can be stabilized at optimum levels over cumulative elutions of several hundred ml in 4 ml elution volumes with pH 5.0 tartrate. Exchange labeling of

thio compounds was moderately successful as indicated by HPLC analysis and animal imaging studies.

Future directions for research include the investigation of ^{118}Te production by the irradiation of enriched ^{116}Sn (95 %) with alpha particles. This would eliminate the presence of carrier Sb which creates probelms in the chemistry and separation and eliminate the need for tartrate to complex the Sb. Once carrier free ^{118}Sb and ^{118}Te are available, it would be possible to elute the ^{118}Sb with H_2O from a column of activated charcoal or graphite, which retains the ^{118}Te, as reported by Ambe [7]. Further studies are needed to develop a suitable compound labeled with ^{118}Sb for PET studies.

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REFERENCES

[1] YANO, Y., BUDINGER, T. F., CHU, P., GRANT, P. M.,OGARD, A. E., O'BRIEN, H.S., HOOP, B. Evaluation of rubidium-82 generators for imaging studies, J. Nucl. Med. 17: (1976), 536.

[2] YANO, Y., BUDINGER, T. F., EBBE, S. N., MATHIS, C.A., SINGH,M., BRENNAN, K. M., MOYER, B. R. Gallium-68 lipophilic complexes for labeling platelets. J. Nucl. Med. 26: (1985), 1429.

[3] YANO, Y. Essentials of a rubidium-82 generator for nuclear medicine.

[4] YANO, Y. Radioisotope generators for short-lived positron emitters applicable to positron emission tomography. Bull. Am. Physical Soc. 33: (1988), 1748.

[5] MAUSNER, L. F., PRACH, T., RICHARDS, P. Production of radionuclides for generator systems. In: Radionuclide Generators, F.F. Knapp and T. A. Butler, editors, Washington, D. C., American Chemical Society, (1984), 77.

[6] Basinger, M. A., Jones, M. M. Structural requirements for chelate antidotal efficacy in acute antimony (III) intoxication. Research Comm. in Chem. Path. and Pharm. 32: (1981), 355.

[7] Ambe, S. Separation of trace metals, In (III), Sn (IV), Sb (V), and Te (IV) by adsorption on activated carbon and graphite. J. Radioanalyt. and Nucl. Chem. 81/1: (1984), 77.

FIGURE CAPTIONS

Fig. 1. Decay scheme for $^{118}Te/^{118}Sb$.

Fig. 2. Apparent yields of ^{118}Sb-tartrate from a combination column containing SnO_2 and Al_2O_3 and as a function of eluent pH and cumulative elution volume.

Fig. 3. The apparent breakdthrough of ^{118}Te (also contains ^{119m}Te and ^{119}Sb) as function of cumulative elution volume and time between elutions.

Fig. 4. Apparent ^{118}Sb-tartrate yield as a function of pH alone.

Fig. 5. Breakthrough of $^{118/119}Te$ as a function of pH alone.

Fig. 6. ^{118}Sb-tartrate and ^{118}Sb-diethlydithiocarbamate in rat 5 m post IV injection as shown by positron camera imaging.

Table 1

GeLi Analysis of Antimony Target

Isotope	t 1/2	γ's MeV	Decay	nCi Target Solution
Sb-120	5.76 d	1.17 (100%)	EC	0.37
Sb-122	2.70 d	0.564 (71%)	β- (98%) β+ (2%)	0.42
Te-118	6.0 d	no γ's	EC (100%)	0.75
Sb-118	3.6 m	0.511 (150%) 1.229 (2.5%)	β+(75%)	
Te-119m	4.68 d	1.221 (67%)	EC (100%)	0.81
Sb-119	1.58 d	0.024 (16%)	EC	

Table 2

^{118}Sb Elutions from ^{118}Te

Column	Eluent	^{118}Sb Yield (%)*	^{118}Te Breakthrough (%)*
$SnO_2[H^+]$	6 % Tartrate pH 7.0	10.3 ± 0.38 n=7	0.32 ± 0.15 n=7
$SnO_2[H^+]$	6 % Tartrate pH 3.5	12.9 ± 0.55 n=5	0.46 ± 0.14 n=5
Al_2O_3	6 % Tartrate pH 7.0	5.4 ± 1.04 n=6	0.27 ± 0.17 n=6
Al_2O_3	6 % Tartrate pH 3.5	10.3 ± 0.69 n=7	0.63 ± 0.43 n=7

* Mean ± Standard Deviation

Te-118 / Sb-118 Decay

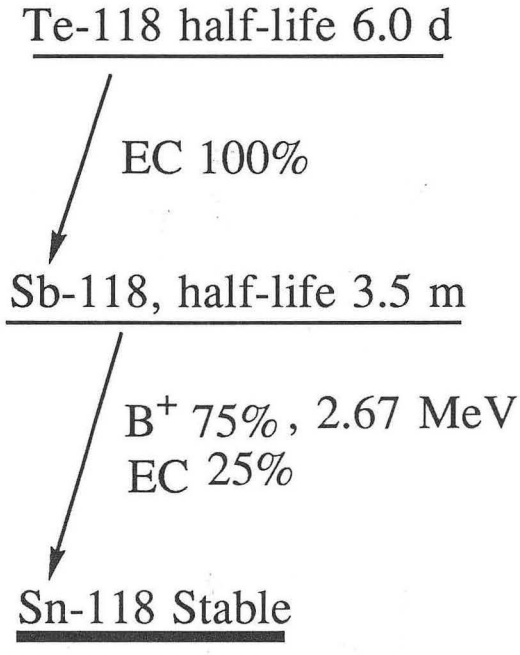


Fig. 1

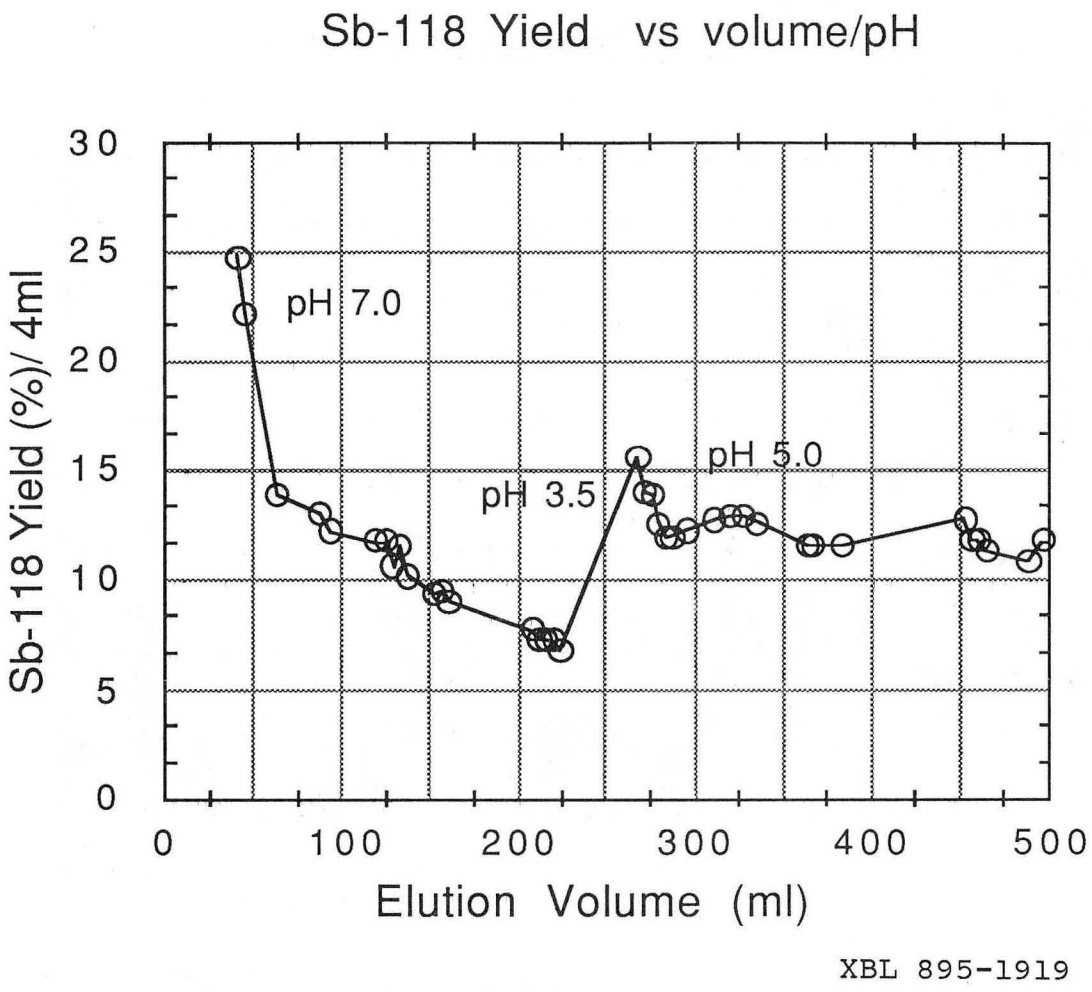

Sb-118 Yield vs volume/pH
Sb-118 Yield (%)/ 4ml
30
25
20
15
10
5
0
pH 7.0
pH 3.5
pH 5.0
0
100
200
300
400
500
Elution Volume (ml)
XBL 895-1919

Fig. 2

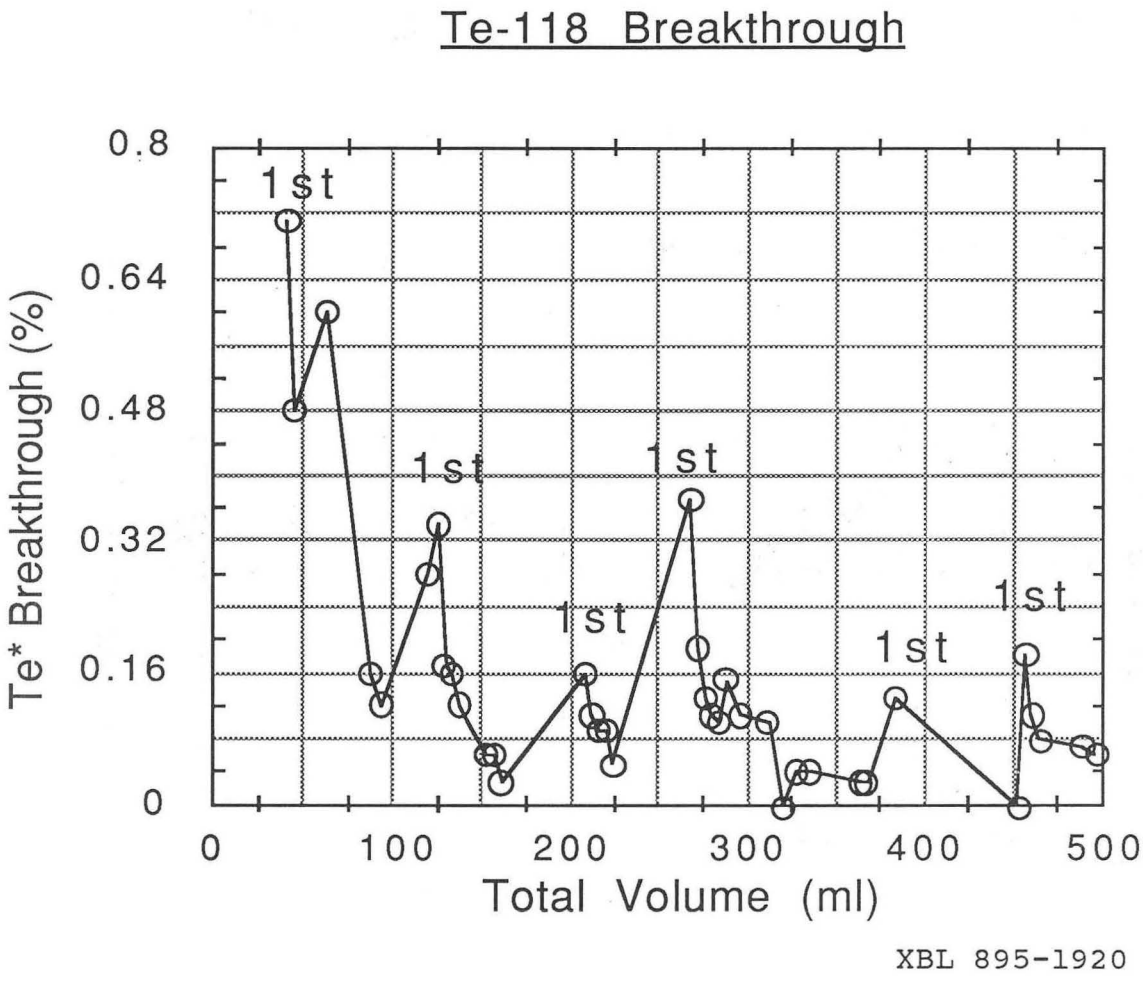

Te-118 Breakthrough
Te* Breakthrough (%)
0.8
0.64
0.48
0.32
0.16
0
1st
1st
1st
1st
1st
1st
0
100
200
300
400
500
Total Volume (ml)
XBL 895-1920

Fig. 3

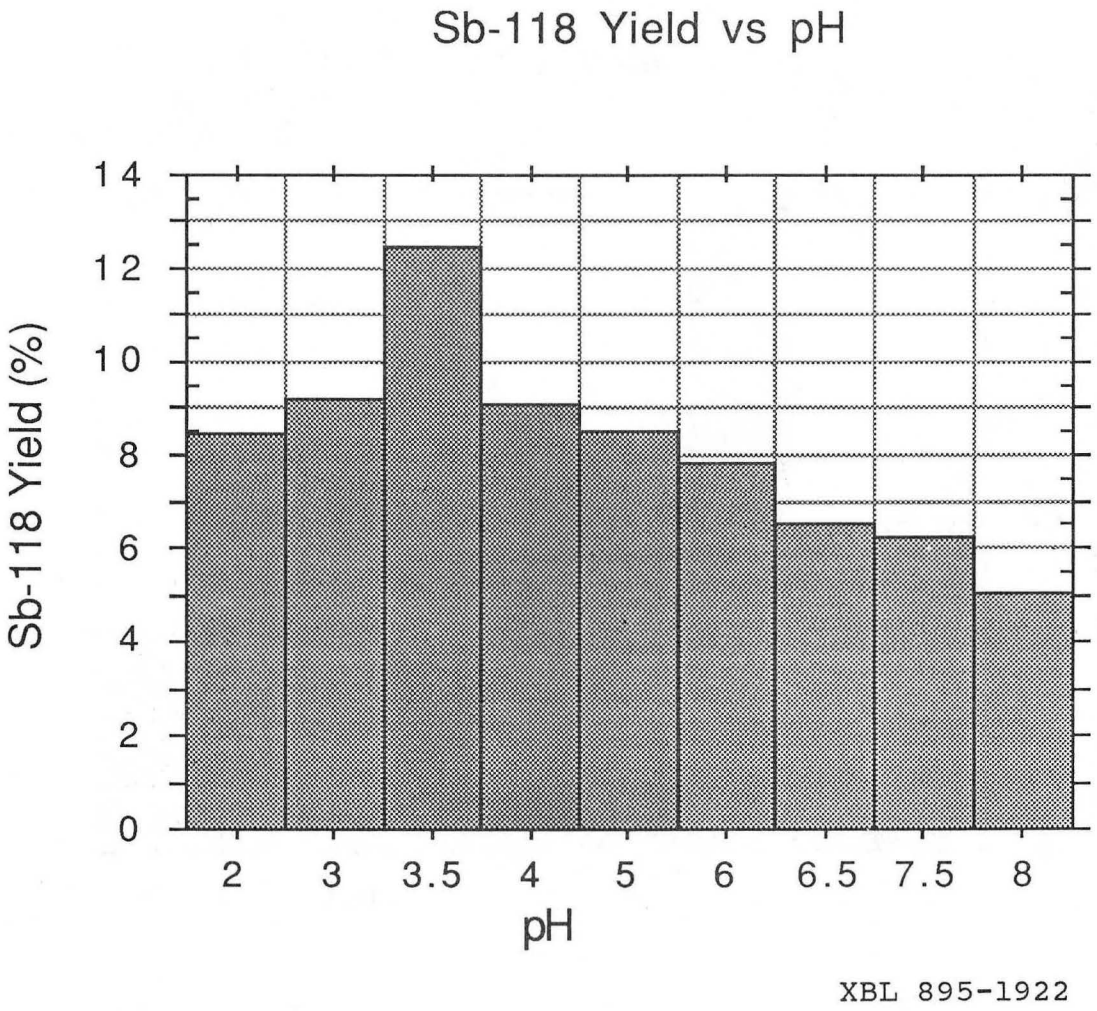

Sb-118 Yield vs pH
Sb-118 Yield (%)
0
2
4
6
8
10
12
14
2
3
3.5
4
5
6
6.5
7.5
8
pH
XBL 895-1922

Fig. 4

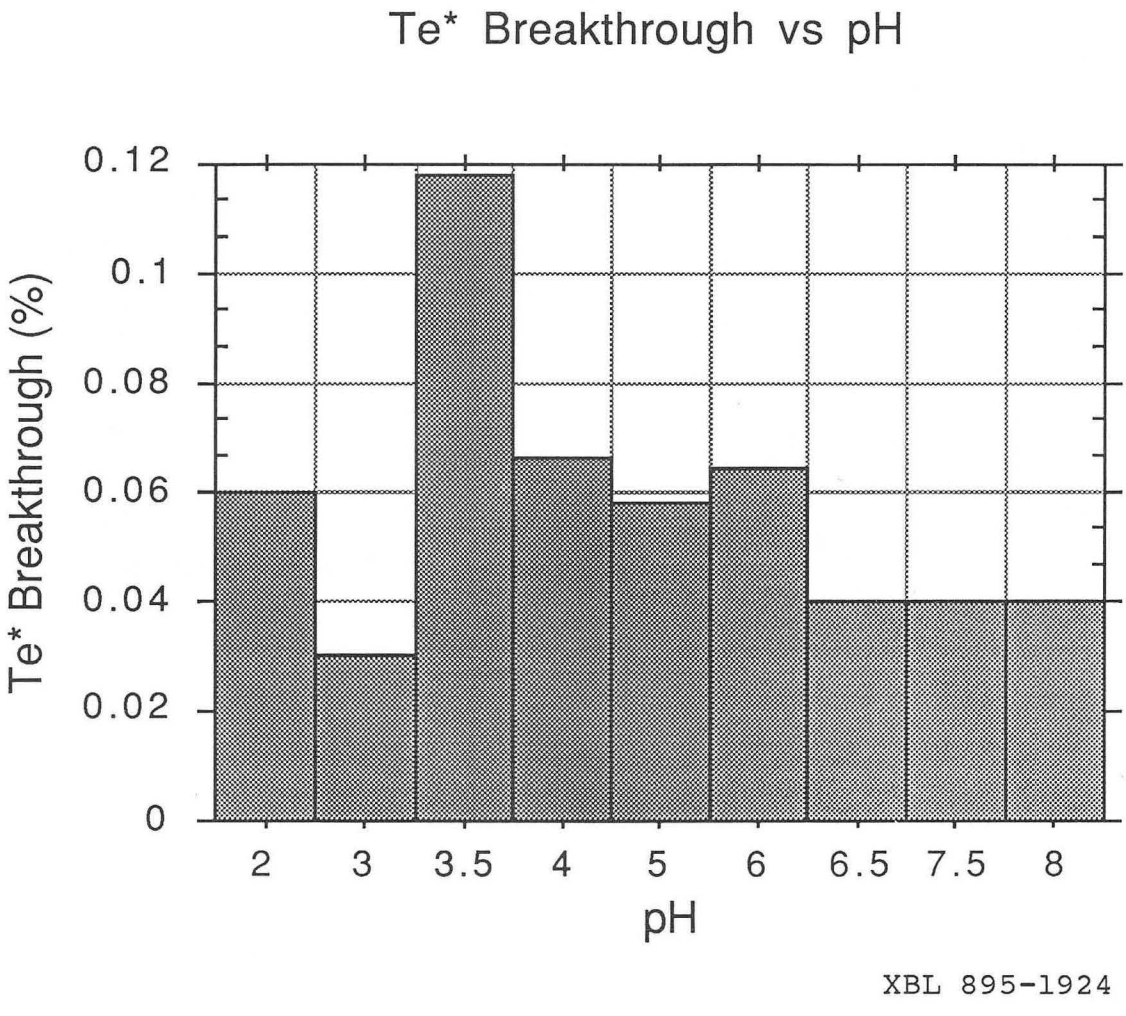

Te* Breakthrough vs pH
Te* Breakthrough (%)
0.12
0.1
0.08
0.06
0.04
0.02
0
2
3
3.5
4
5
6
6.5
7.5
8
pH
XBL 895-1924

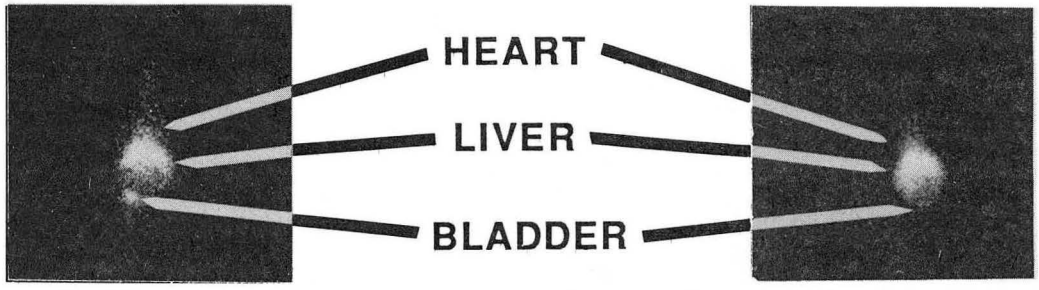
Fig. 5

COMPARISON STUDIES

^{118}Sb - Tartrate

^{118}Sb - Diethyldithiocarbamate

Positron Camera Images - rats



Five minute post-IV injection of ^{118}Sb- 6% Tartrate pH 7.0

Five minute post-IV injection of ^{118}Sb- Diethylthiocarbamate pH 7.0

XBB 891-168

Fig. 6

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