PET TOPICS

Producing the Radionuclides

Overview of Production Process for FDG

Production — Pharmacy

Cyclotron F-18 → Chemistry → FDG Vial → Unit Doses

FDG Vial → QC

Production of PET radionuclides

- Starts with an accelerator
  - Usually between 10 and 20 MeV proton cyclotron
  - Most “proton” cyclotrons now accelerate negative ions
    - Proton with two electrons attached
    - Lower activation
  - Can also be produced using deuterons

Target Reactions

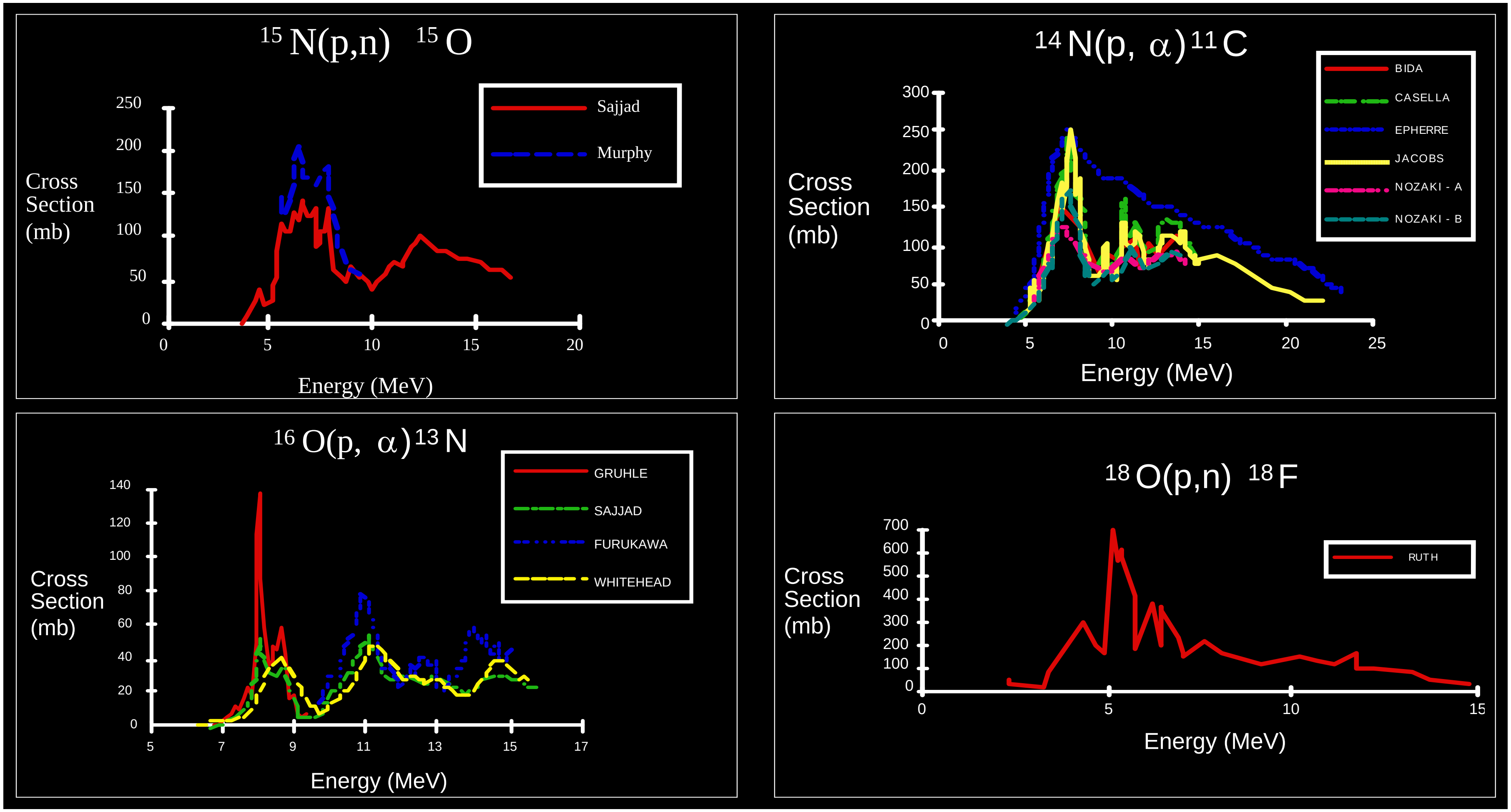
- (proton, neutron) reactions
  - $^{18}O(p,n)^{18}F$ (liquid or gas targets)
  - $^{15}N(p,n)^{15}O$ (gas target)

- (proton, alpha) reactions
  - $^{16}O(p,alpha)^{13}N$ (liquid target)
  - $^{14}N(p, alpha)^{11}C$ (gas target)

Typical Activity Yields

O-18 (p,n) F-18	60 min	1000 mCi
O-16 (p,a) N-13	10 min	100 mCi
N-14 (p,a) C-11	50 min	1500 mCi
N-15 (p,n) O-15	10 min	2000 mCi
O-18 (p,n) F-18[F2]	60 min	500 mCi

Nuclear Reaction Cross Sections for Protons



Isotope Production

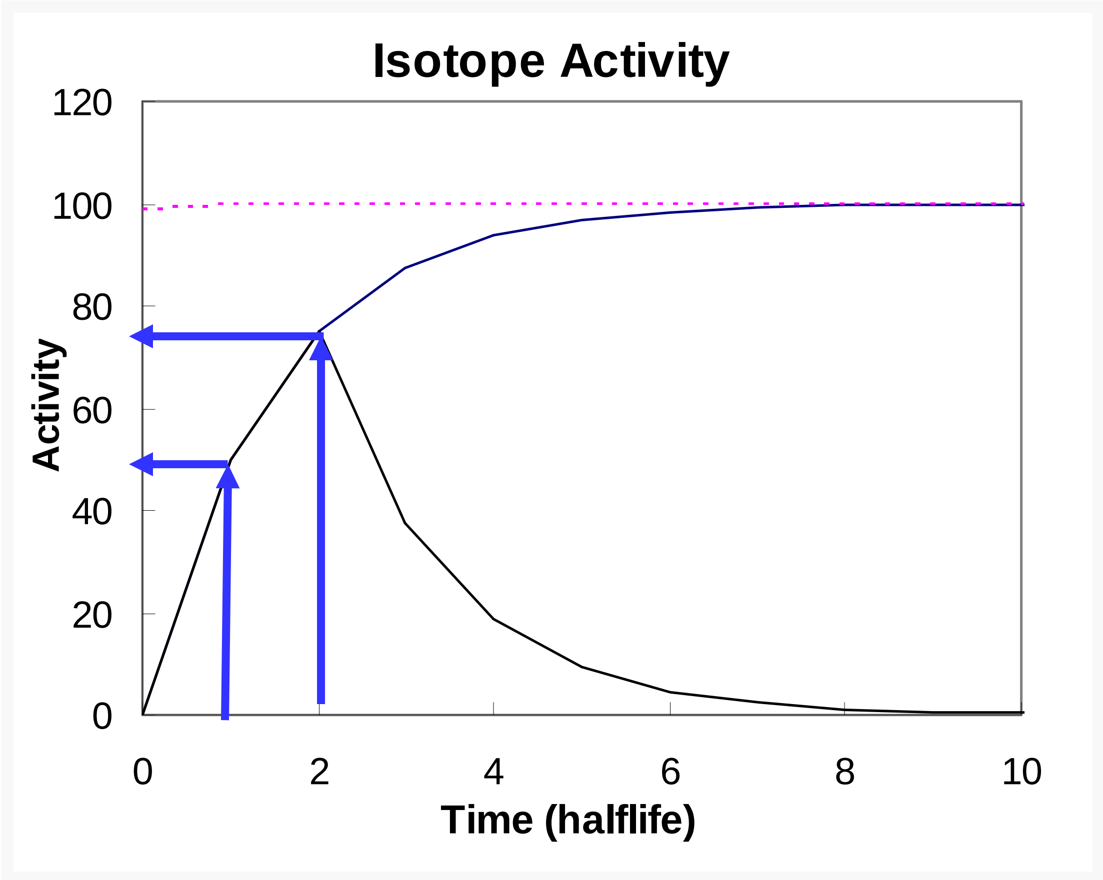
Because the most commonly used PET isotopes decay quickly, they need to be produced on demand using a cyclotron.

Production of the isotope is related to the half life, with decay starting at the moment of creation, limiting the amount that can be produced

$$A = N\sigma\phi\left[(1-e^{-\lambda t_{irrad}})(e^{-\lambda t_{decay}})\right]$$

A: Isotope activity at time (t) (Bq)
λ: Isotope decay constant (sec^{-1}) = ln(2)/half life
N: Number of target atoms present
Φ: particle flux
σ: cross section for the reaction of interest

Isotope Buildup

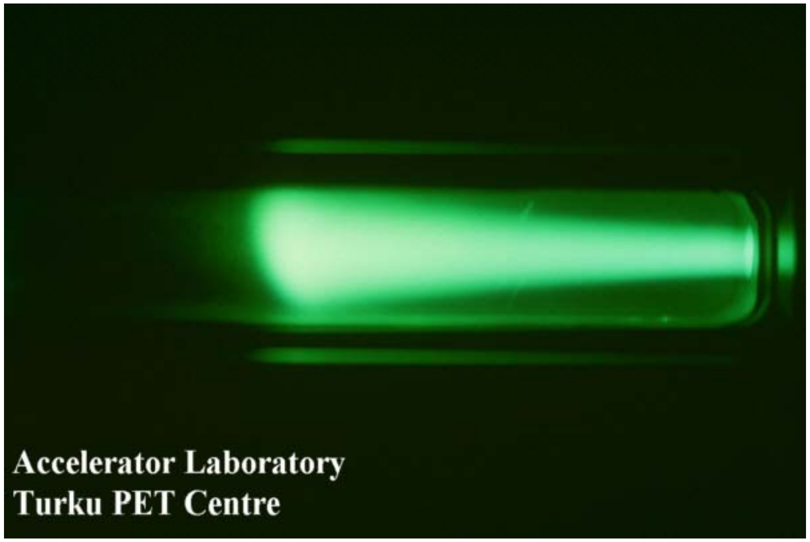


The activity at any given time, A_t, is a function of the number of atoms produced, P, and the decay rate, which is related to the half life. Production of the isotope falls off with the half life, as the newly produces atoms begin to decay. Once the cyclotron is turned off, production stops and decay follows exponential decay.

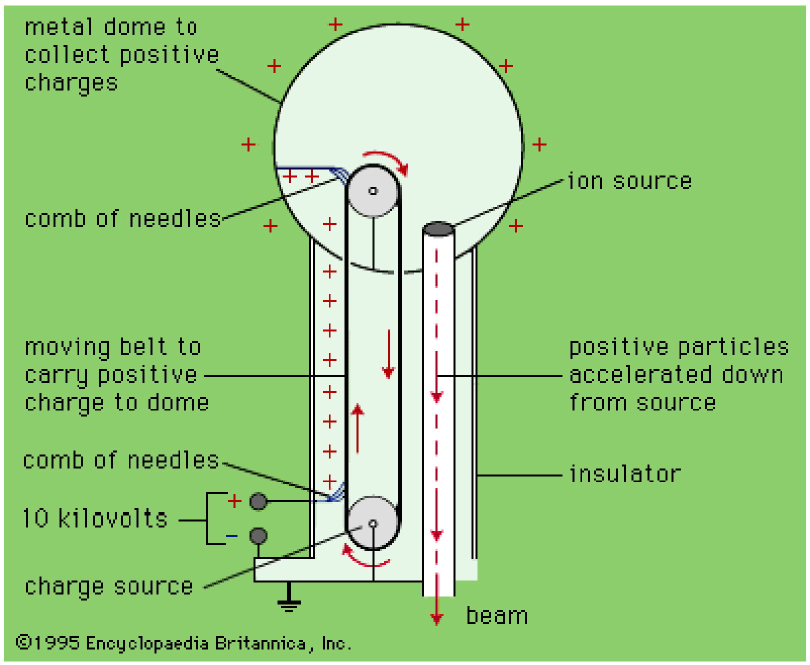
Basic charged particle acceleration

Basic charged particle acceleration

- Among the many uses of energetic streams of charged particles (beams) are physics research, materials modification, lithography, material properties characterization, radiation therapy, secondary radiation production for imaging, and radioisotope production - including PET tracer production.

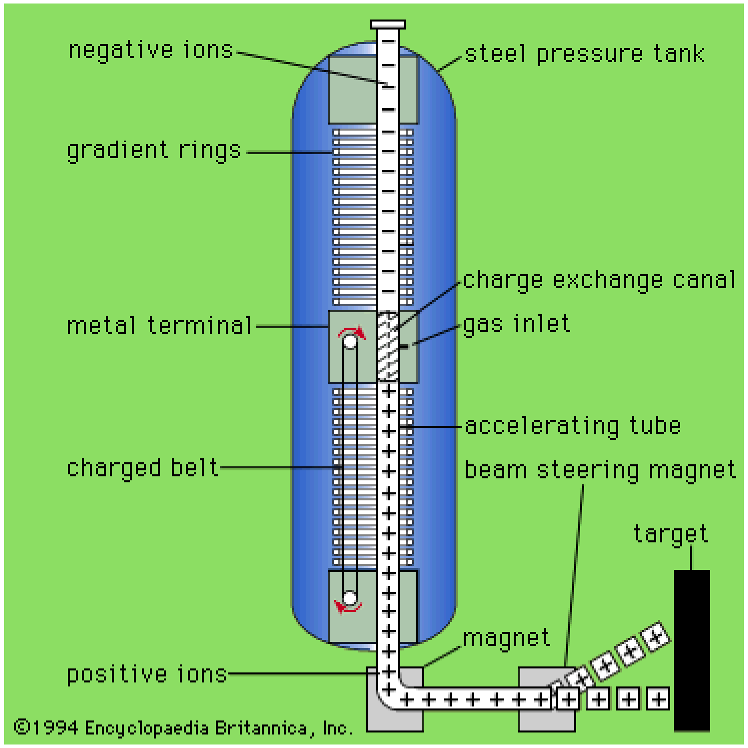


Basic charged particle acceleration



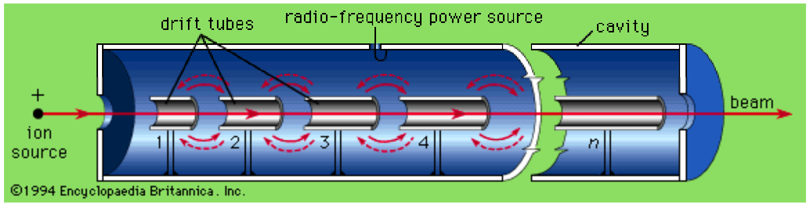
- **In an electrostatic accelerator, a DC electrostatic potential accelerates the ion. Although one of the simplest accelerators, they require quite large structures to attain high enough voltages for uses such as PET tracer production.**

Basic charged particle acceleration



- **A tandem electrostatic accelerator has the advantage of using the terminal potential for two stages of acceleration with little addition of complexity. Still, a machine for PET tracer production energies would be ~ 10 meters long X 3 meters diameter. Although these machines have existed for research, it is not profitable to convert them for PET tracer production.**

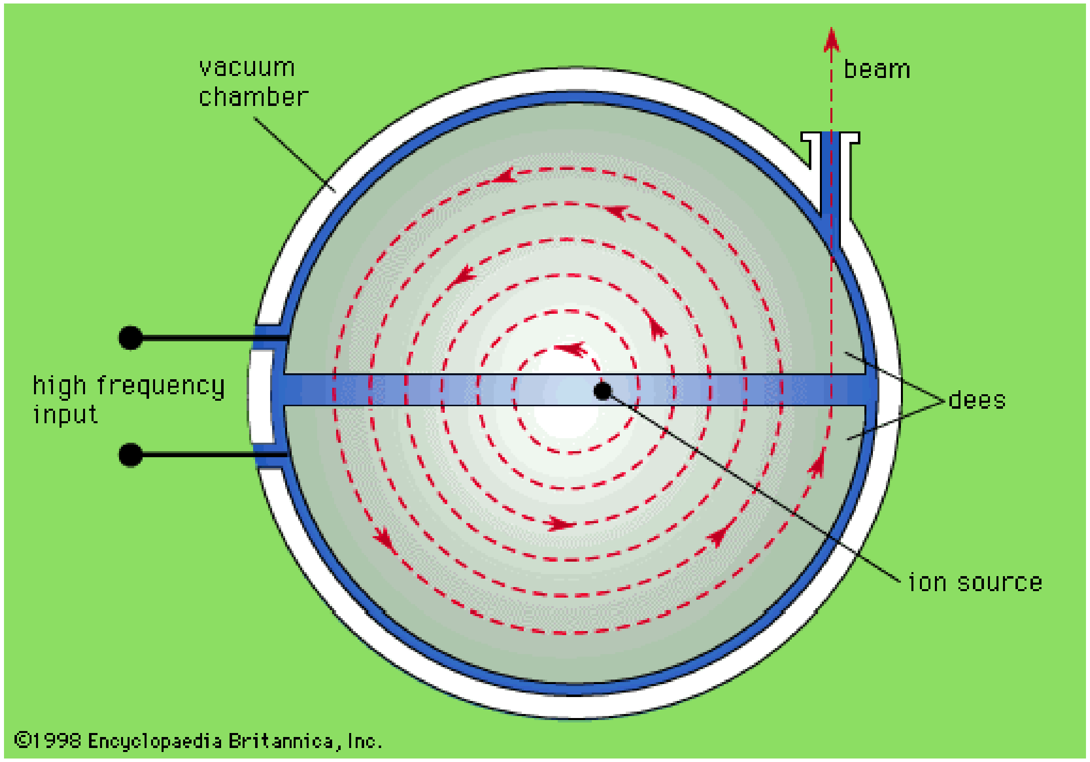
Basic charged particle acceleration



- In a linear accelerator (linac), the ions are accelerated by alternating potentials on resonators that increase in length to permit the ions to arrive at the proper time in the RF phase for acceleration at each stage. This requires a rather long structure for achieving PET tracer production energies. They also are quite complex to maintain. Although superconducting technology has greatly increased acceleration densities, it has added even more complexity and delicately balanced systems.

Basic charged particle acceleration

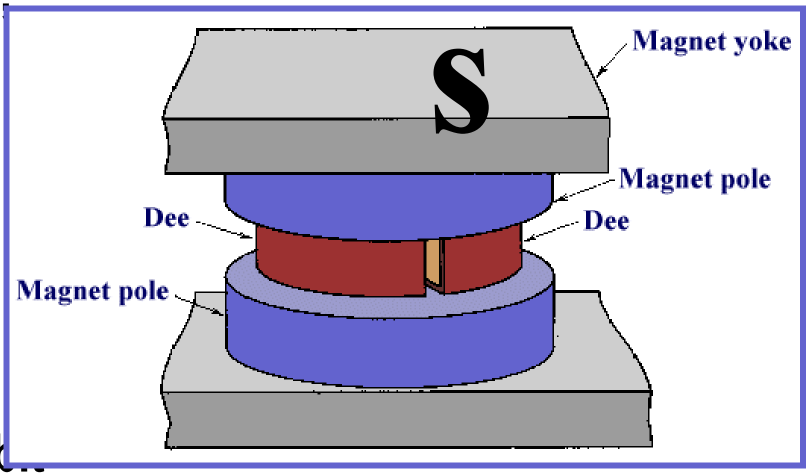
- Invented by Lawrence in 1929, the cyclotron makes use of a modest RF voltage to accelerate an ion to high energies in a small machine. The use of a magnetic field to confine the ion to a (nominally) circular orbit has the added benefits of an increased resonator path length as the ions spiral outward at higher velocities, and a single vacuum chamber that has modest vacuum requirements.



Basic charged particle acceleration

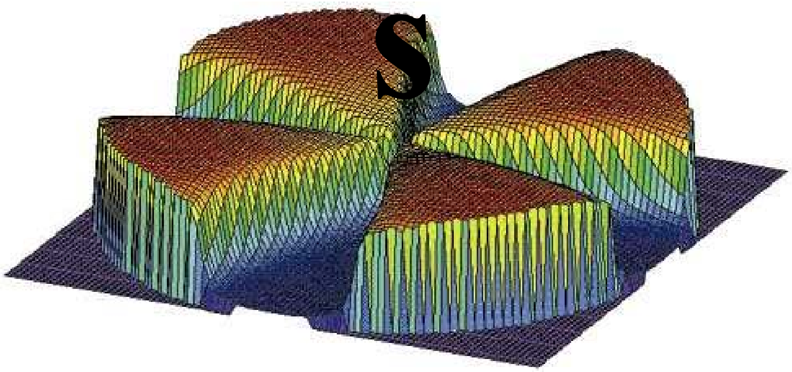
Cyclotron

- In its simplest form, the cyclotron has the same requirements as all accelerators: A vacuum to prevent collisions with gas molecules, a source of charged particles, and a system to maintain optics of the beam . In addition, the cyclotron has:
- A magnet to contain the ions to orbits.
- Dees to place the acceleration potentials at the correct position for acceleration.
- A system to extract the beam from its orbit for use.



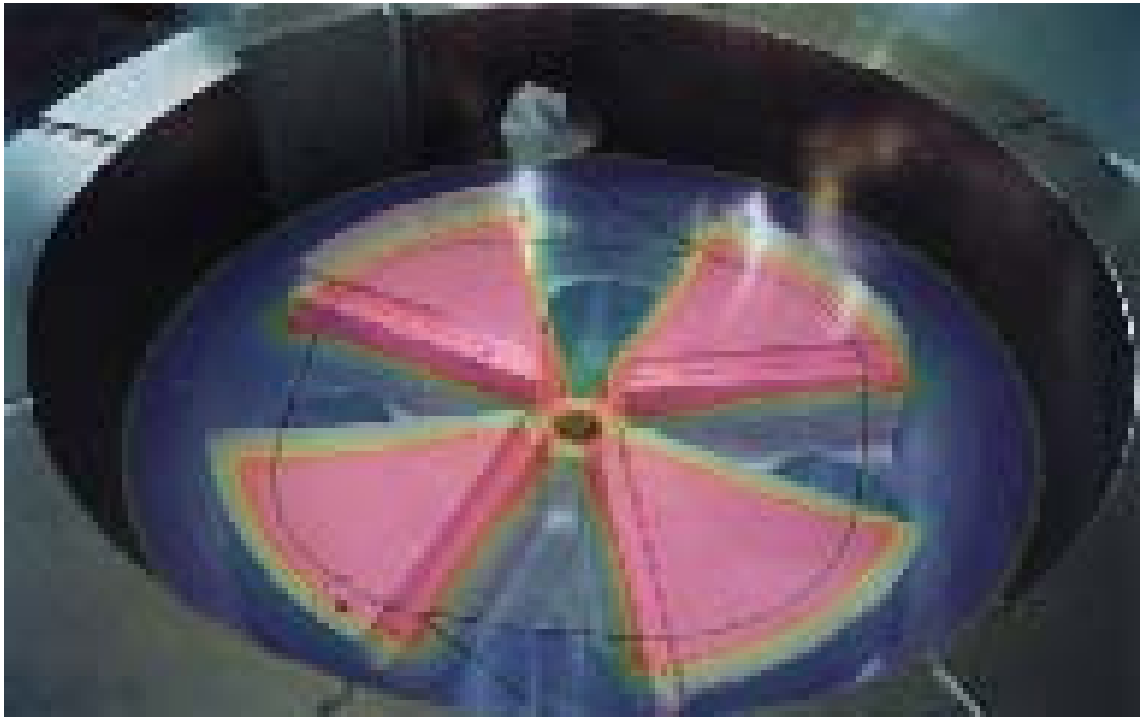
Basic charged particle acceleration

Cyclotrons



- Shaping of the magnetic field in a cyclotron is used to control the beam path.
- Shaping of the field strength from the inside out keeps ions in sync with the RF frequency as they gain higher velocities. This condition is called "isocronous".
- Azimuthaly varying fields provide repeated refocusing of the beam as it circulates. This prevents beam loss due to straying from the median plane of the machine.

Basic charged particle acceleration



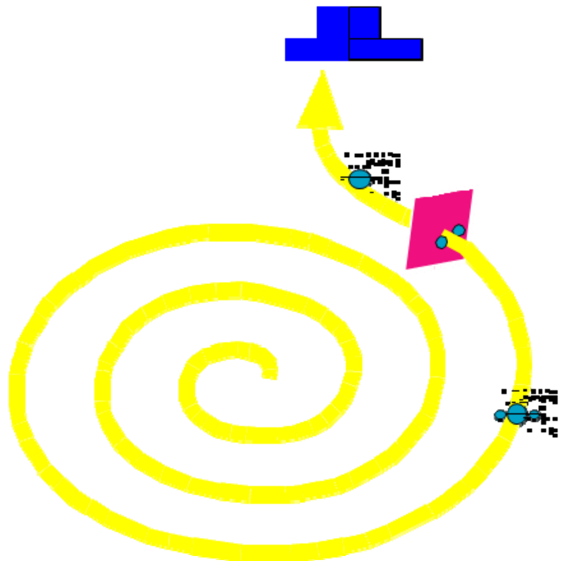
Due to the large hill/valley difference in fields, the beam takes on a four-corner orbit shape in the RDS 111 design. Most of the bending is done over the hills, while the beam travels a fairly straight path through the dees, which are in the valleys.

11 MeV Energy Cyclotron

- All (p,n) and (p,a) reactions have maxima at or below 11 MeV, allowing Curie level yields of PET radioisotopes
- Higher energies often allow unwanted competing reactions to take place and can add radionuclidic impurities: $^{14}N(p,pn)^{13}N$
- Self-shielded
- Low internal activation
- Target design and beam optics are the most important issues with respect to yield

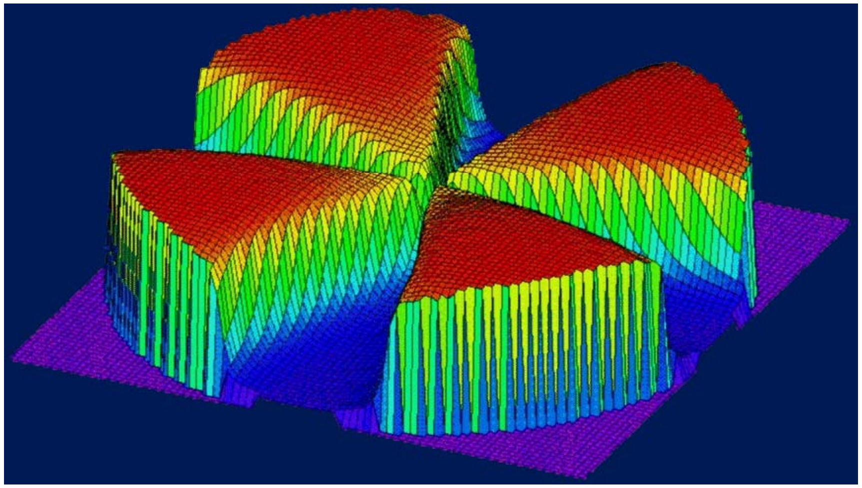
Negative Ion Acceleration

- Improved beam uniformity
- No electrostatic deflector to become activated
- High extraction efficiency
- Dual bombardment capability
- Reduced complexity
- CTI designed first commercial negative ion cyclotron



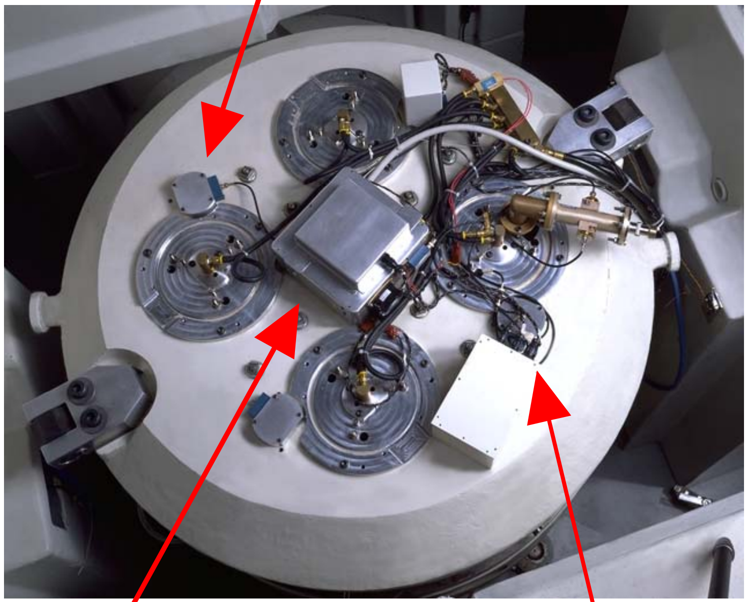
What is the Deep Valley Concept?

- Steel sectors form the hills and provide large valley-to-hill gap ratio
- Steep gradients in the magnetic field provide improved axial beam focusing
- Sectors act as powerful lenses to confine particles to the midplane



Vertically Mounted Components

- Improved access for simplified service
- Ensures consistent alignment even if accelerator needs to be opened
- Reduced pump-down time

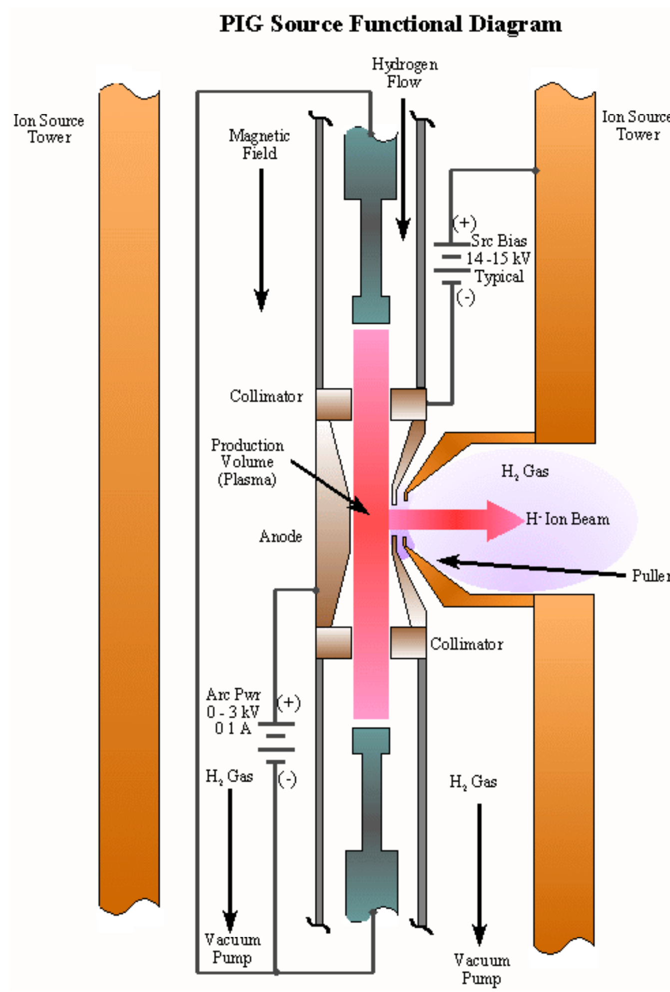


Vertically Mounted Ion Source

- Allows faster service
- Dedicated vacuum pump
- Better vacuum
- Allows differential pumping

Essential Siemens Eclipse Penning Source Elements

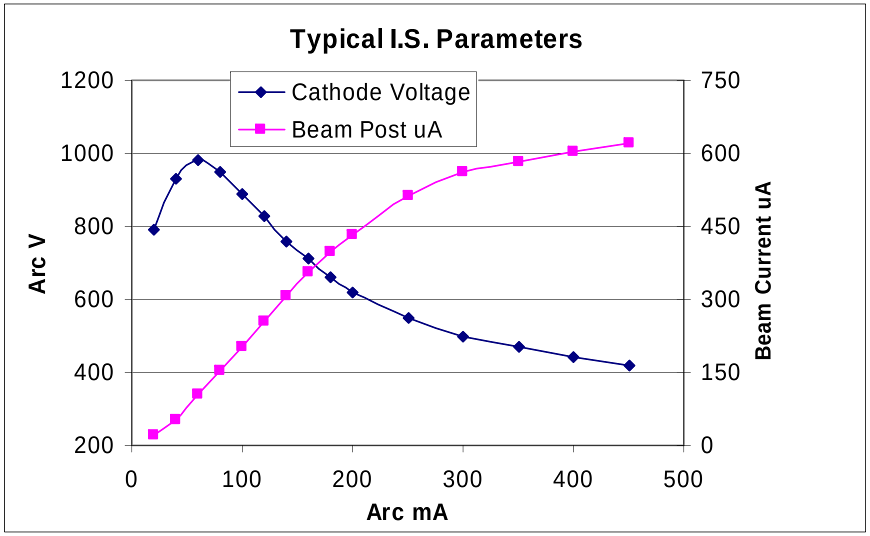
- High-purity Ta cathodes (electron emitters)
- Anode/collimators defining the cylindrical discharge volume
- Cyclotron axial magnetic field providing radial plasma confinement
- Low-pressure H_2 gas fed into discharge region (~5 sccm)
- ~15 kV source bias for radial extraction thru anode/puller slits
- Tower providing differential pumping, decoupling source & cyclotron vac. vessel volumes



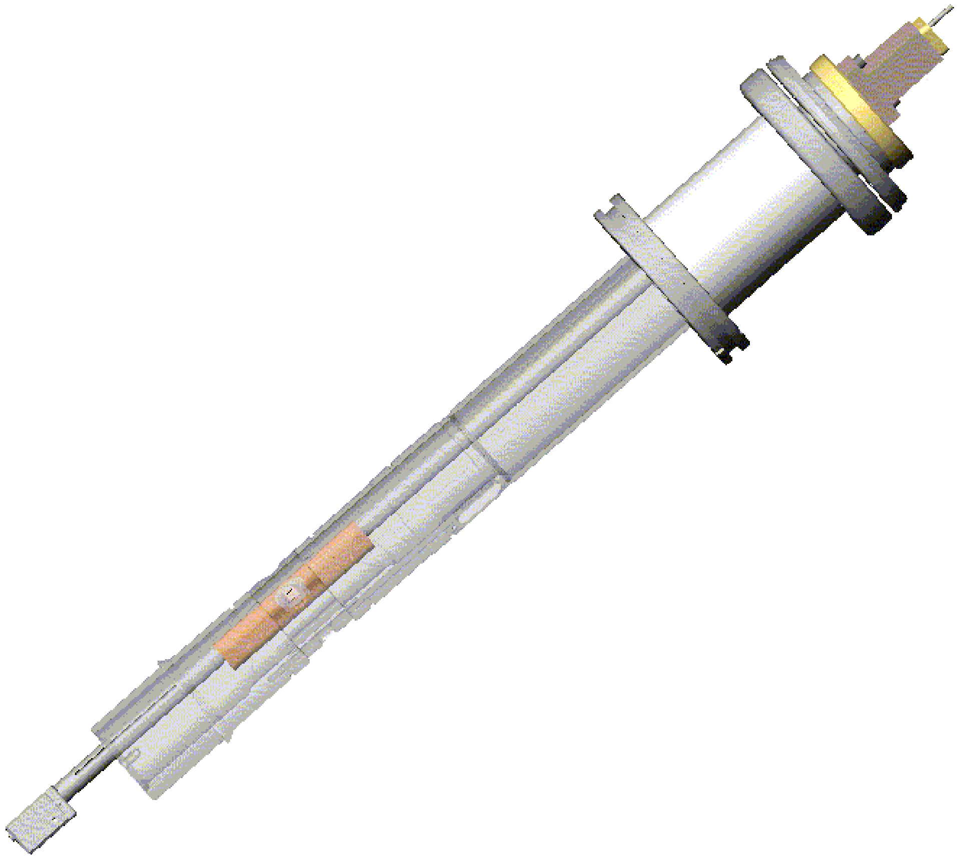
Theory of Operation

- Initiate discharge by field ionization
- electrons oscillate thru anode, repelled from cathodes
- back-bombardment of positive ions heats cathodes
- Thermionic emission maintains discharge above ~80 mA
- Two-step production of H^-

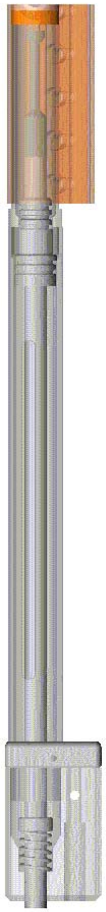
1. $H_2 + e^- \Rightarrow {}^*H_2^+ + 2\,e^- \Rightarrow {}^*H_2 + e^-$
2. ${}^*H_2 + e^- \Rightarrow {}^*H_2^- \Rightarrow {}^*H + H^-$



PIG Source mounted in Tower

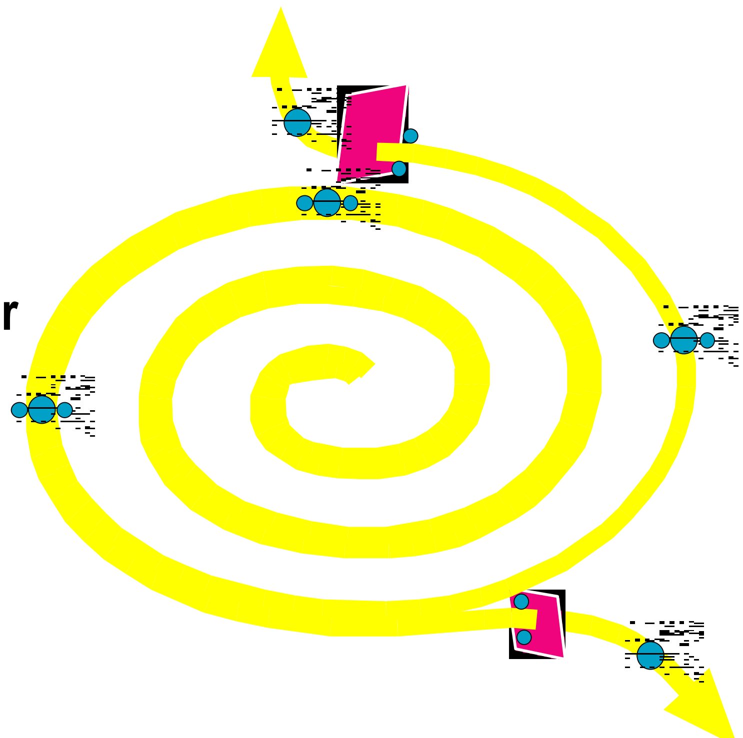


PIG Source Features



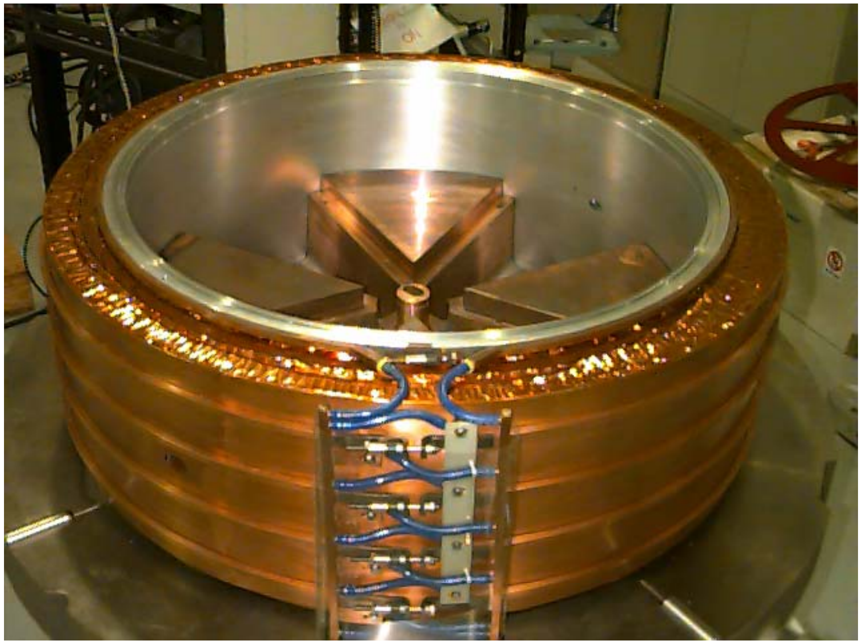
Dual Bombardment Capability

- Can irradiate two targets at once
- Allows simultaneous production of longer-lived isotopes while making short-lived isotopes
- Provides very high production levels for distribution centers
- Affords flexibility for clinical and research applications



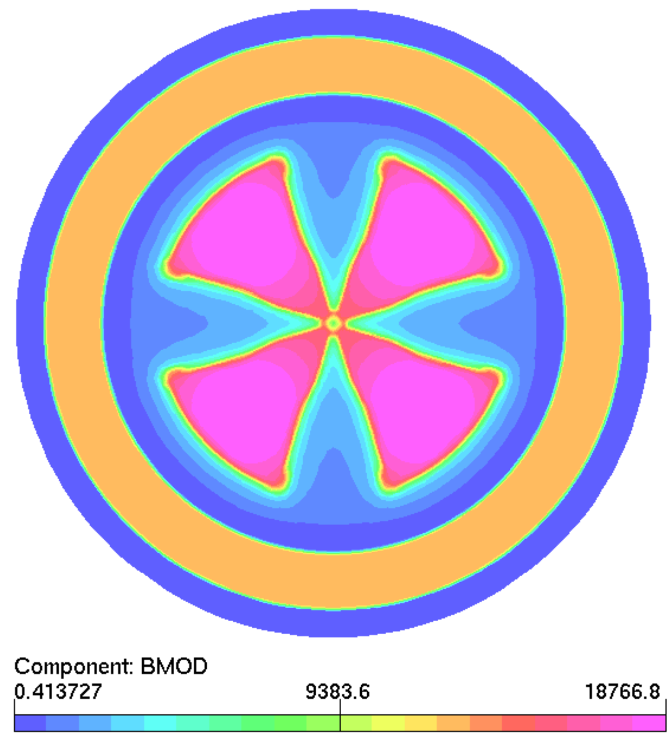
Single-Coil Magnet Design

- Magnet Coil comprised of single strip of copper sheet
  - more than 10x reduction in power consumption
  - reduced cost
  - lower operating expenses
  - enhanced reliability

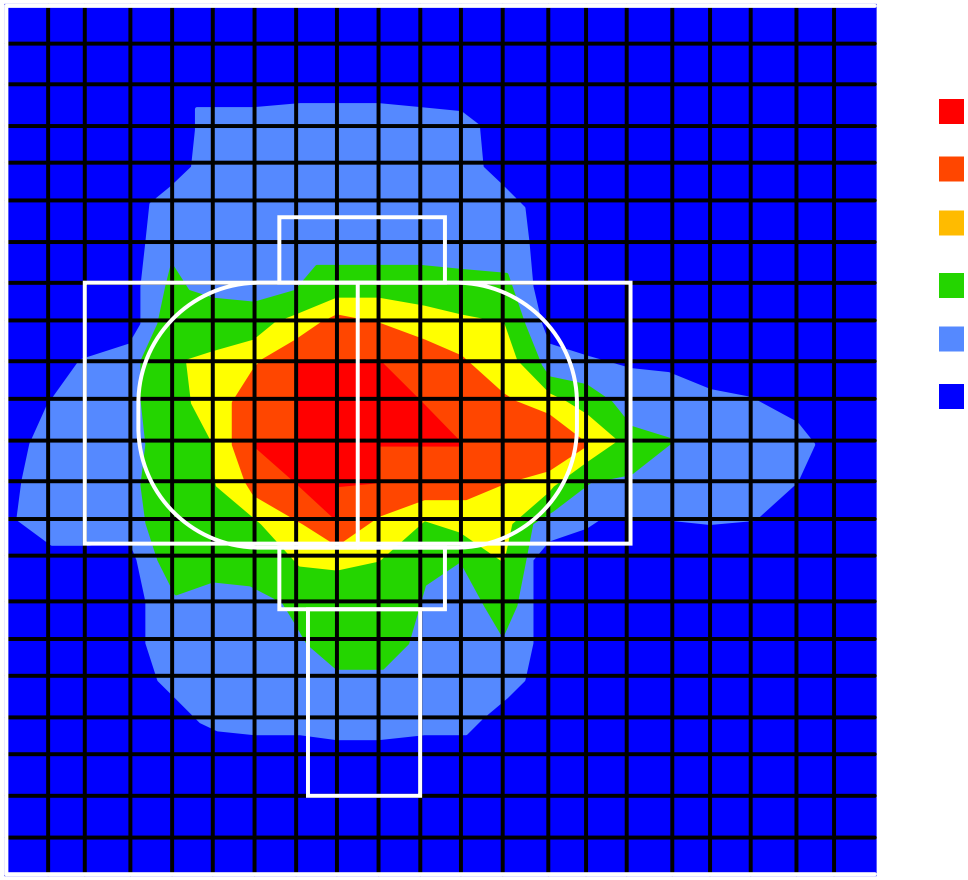


Completely Surrounding Return Yoke

- Reduced magnet field outside the cyclotron
  - enhanced siting options
- Stronger magnetic field for a given current
  - higher efficiency
- Complete symmetry
- Self-shielding provided internally by return yoke



Reduced Magnetic Fields Outside Cyclotron



Accelerator Design Utilizing Four Dees

- Four dees provide more periods of acceleration per orbit
  - particles spend less time in accelerator
  - reduced internal activation
- Top-mounted components
  - easier service
  - improved alignment

Cyclotron Shielding

- Bunker
  - Cyclotron placed into concrete bunker
  - Usually three to five feet (0.9 – 1.5m) thick
  - Can include high density concrete as well as various types of neutron shielding to decrease footprint
  - Interlocks on entrance door
  - Scram buttons inside
  - Refer to manufacturer's site planning guide

GE Mini-Trace

IBA Cyclone 10

Cyclotron Shielding

- Self-shielded
  - Constructed with concrete/borated poly/lead mix
  - Cyclotron room may require additional shielding in the walls for compliance with public dose limits
  - Interlocks on movable shields
  - Scram buttons
  - Refer to manufacturer's site planning guide

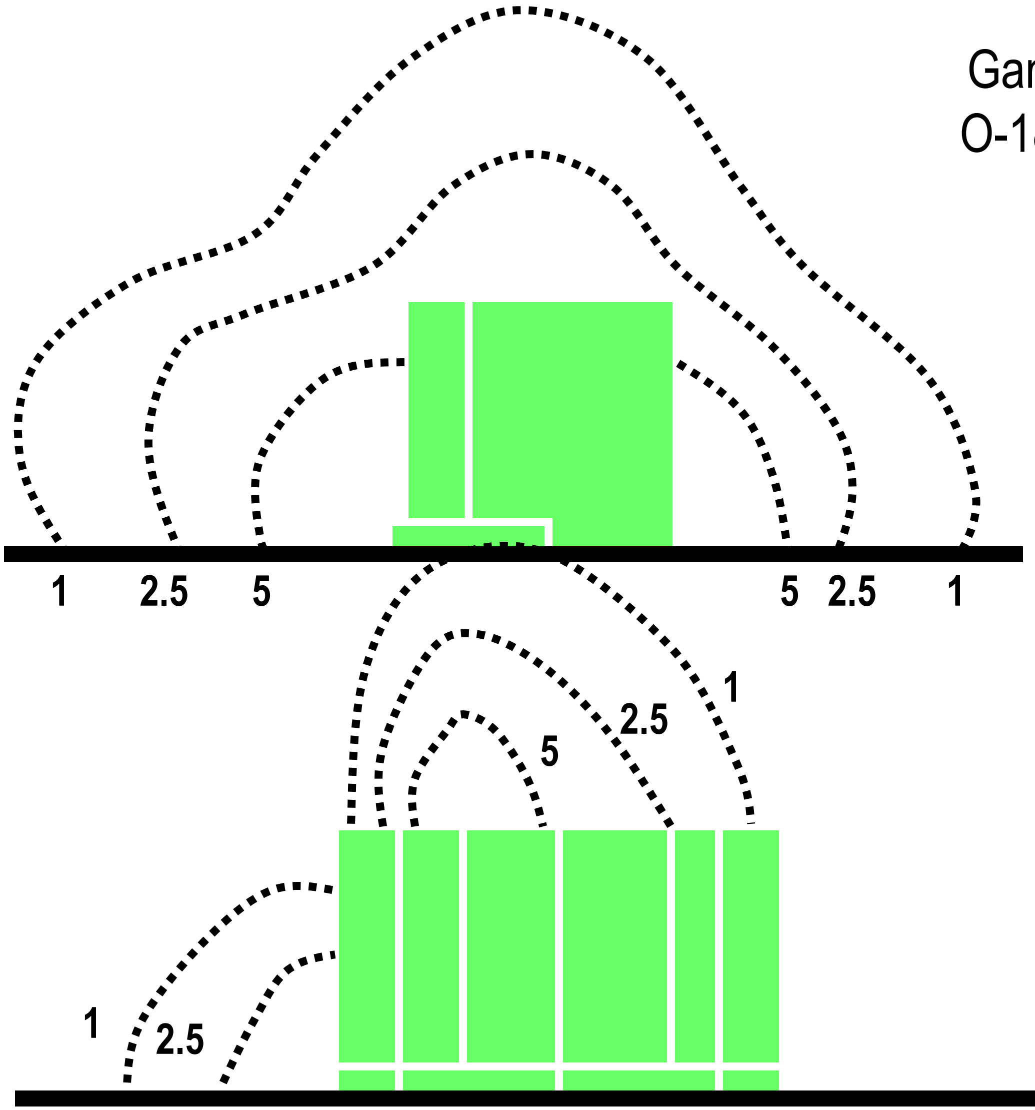
Siemens RDS Eclipse HP

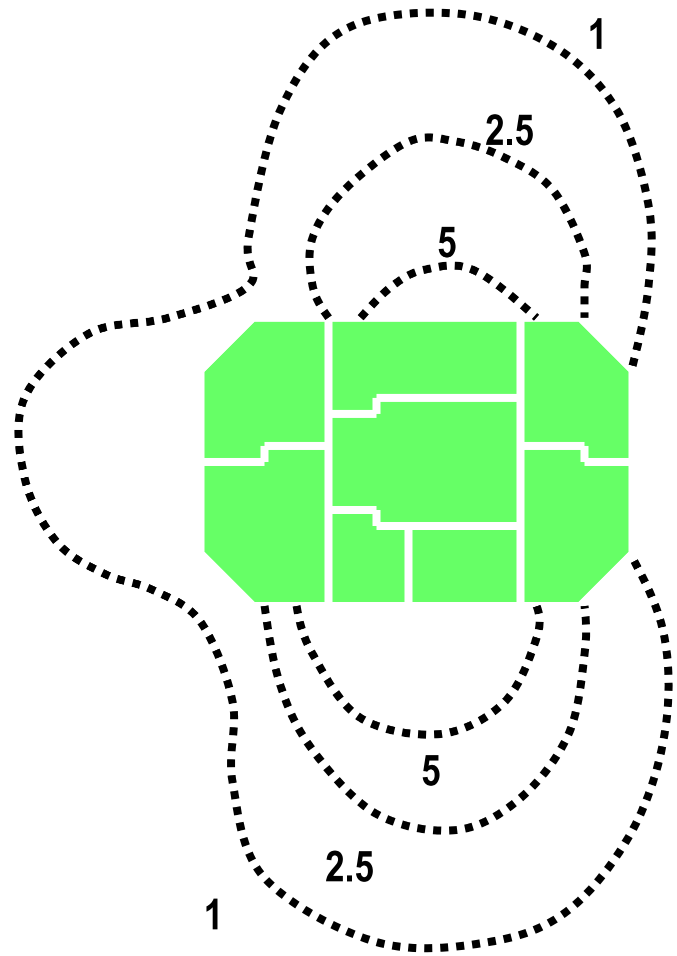
Cyclotron Radiation Fields

- Prompt Radiation Fields (outside shielding)
  - Primarily photon with some neutron component
  - Dependent on reaction taking place – highest for (p,n) process
  - Do not rely on surveys taken while operating onto beam stops or using O-16 water

GE PETTrace Gamma Isodose Curves

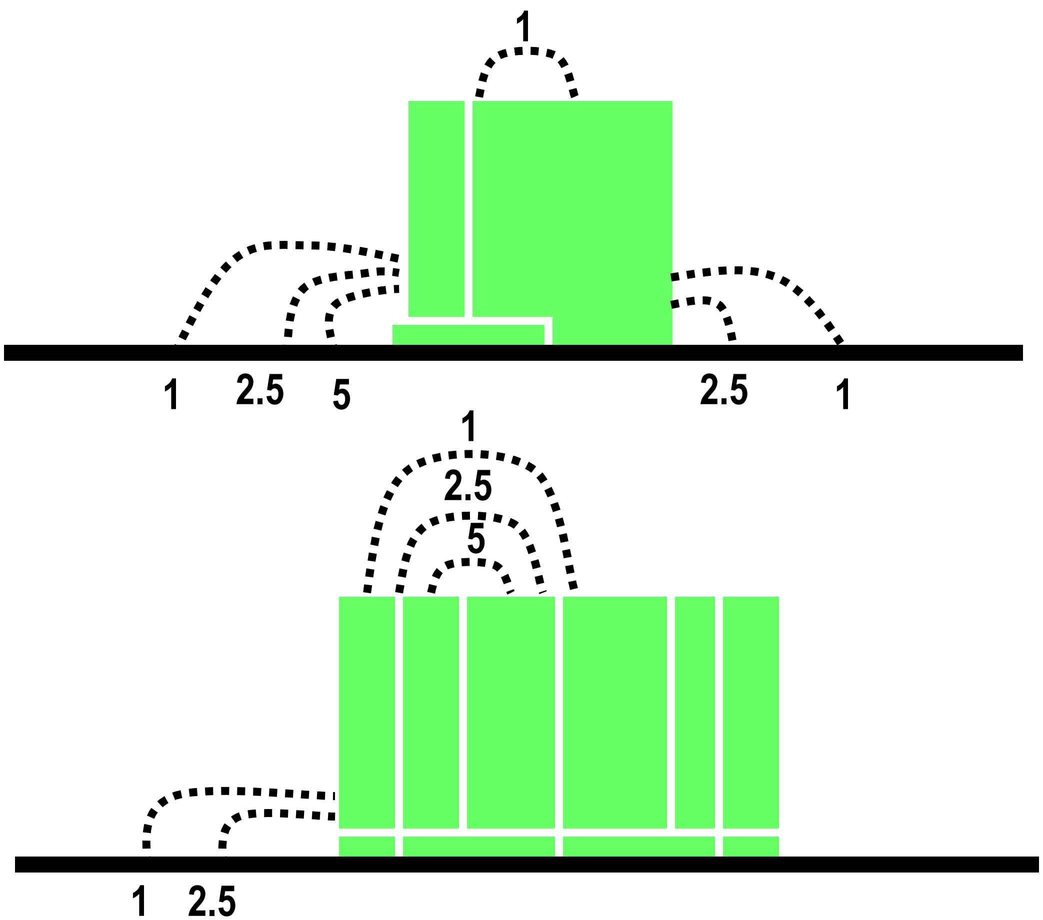
Gamma dose rates in mrem/hr
O-18 target, dual 40 mA beams

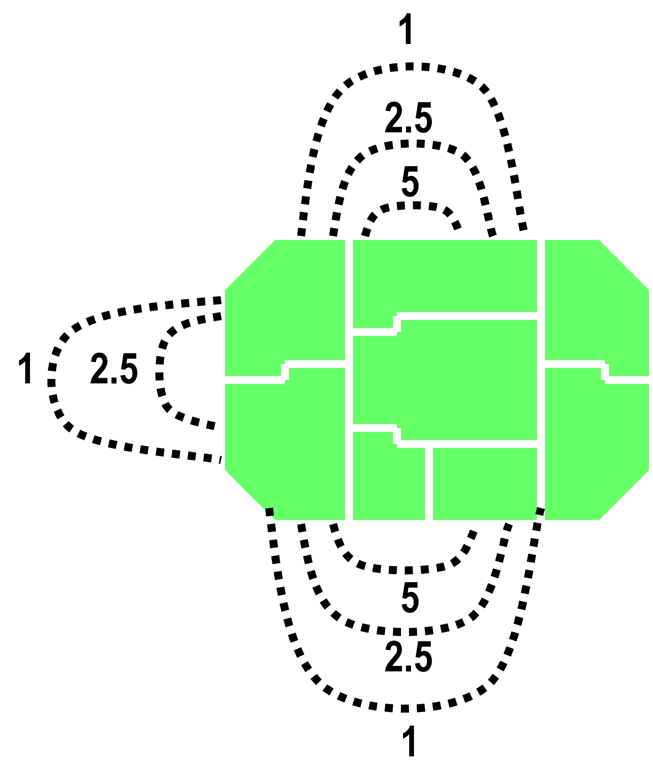




GE PETTrace Neutron Isodose Curves

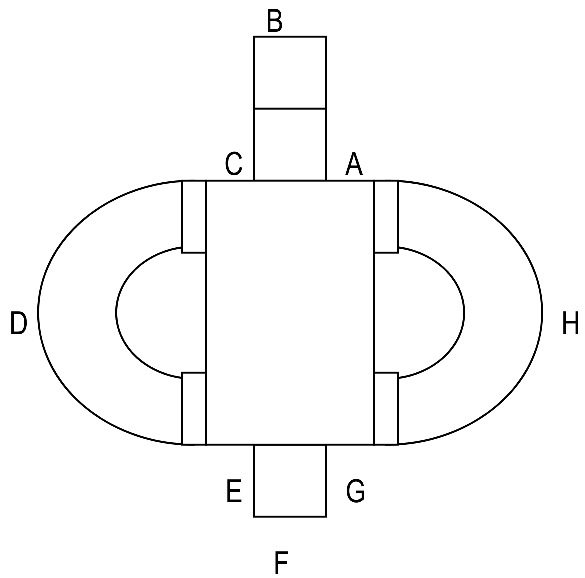
Neutron dose rates in mrem/hr
O-18 target, dual 40 mA beams





Siemens RDS Eclipse HP
60 μA – dual beam onto $H_2{}^{18}O$ targets
Contact with cyclotron surface and 1 m height

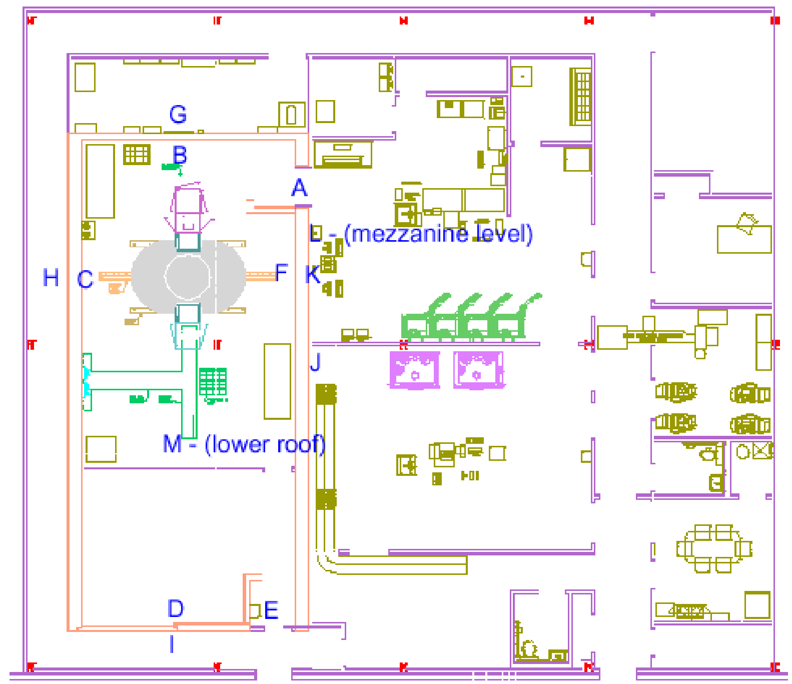
	Gamma (mrem/h)	Neutron (mrem/h)	total (mrem/h)
A	20	10	30
B	1.2	1.0	2.2
C	22	65	87
D	8.0	0.8	8.8
E	20	8.0	28
F	2.0	1.2	3.2
G	20	14	34
H	8.0	7.7	15



Siemens RDS Eclipse HP
60 μA – dual beam onto $H_2{}^{18}O$ targets
Room boundary and 1 m height

	gamma (mrem/h)	n (mrem/h)	total (mrem/h)	occupancy factor	annual dose (mrem) (with adjustments)
A	0.4	0.3	0.7	1	1065
B	0.8	0	0.8	1	1202
C	2.5	0.9	3.4	1	5130
D	0.2	0.2	0.4	1	629
E	0.1	0	0.1	1	150
F	1.9	0.4	2.3	1	3441
G	0.2	0.2	0.4	1/16	35
H	0.06	0.2	0.26	1/16	22
I	0.1	0.1	0.2	1/16	22
J	0.05	0	0.05	1	75
K	0.1	0	0.1	1	150
L	0.2	0.1	0.3	1/16	27
M	0.5	0.1	0.6	1/16	59

PETNET - Hackensack NJ
Cyclotron Survey 16 Dec 2004



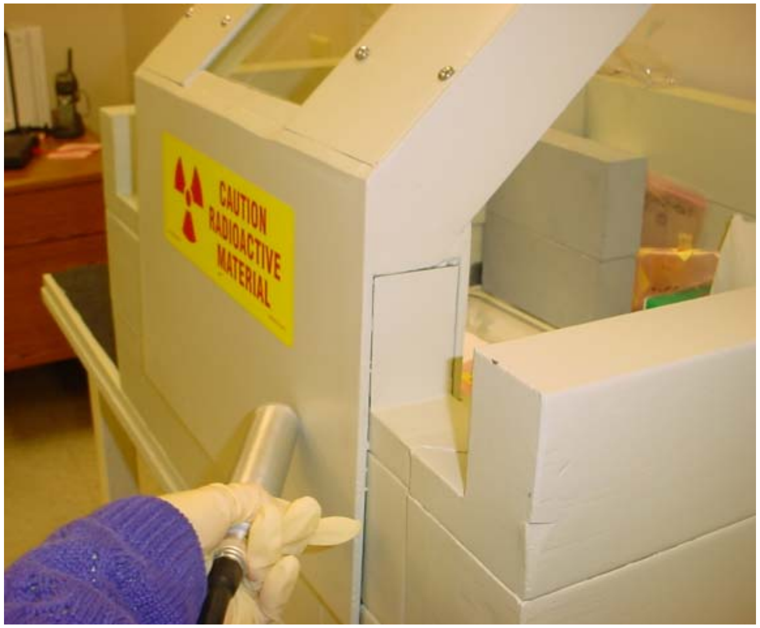
Residual Radiation Fields

- Proton activation confined to beam path and target
  - graphite extraction foils
  - Havar or Titanium foil on target entrance window
  - Target body (aluminum, silver and tantalum most common)

Activation Products in Target Windows

(p,n) Reaction Product	Half-life	Gamma Energy (keV)
HAVAR Windows .001 inch thick		
Mn-52m	21m	2456
Mn-52	5.7d	4134
Co-56	78d	2302
Co-57	272d	122
Cu-60	23.2m	3106
Cu-61	9.7m	-------
TITANIUM Windows .001 inch thick		
V-47	31m	2816
V-48	16d	3317

Gamma Exposure Rates
Target Window



Unshielded	Shielded
2.7 R/hr	25 mR/hr
After 15 days in storage	Same target window

Gamma Exposure Rates
RDS Eclipse Target

58 uA, 3 hr Bombardment

40 minutes after end of bombardment:

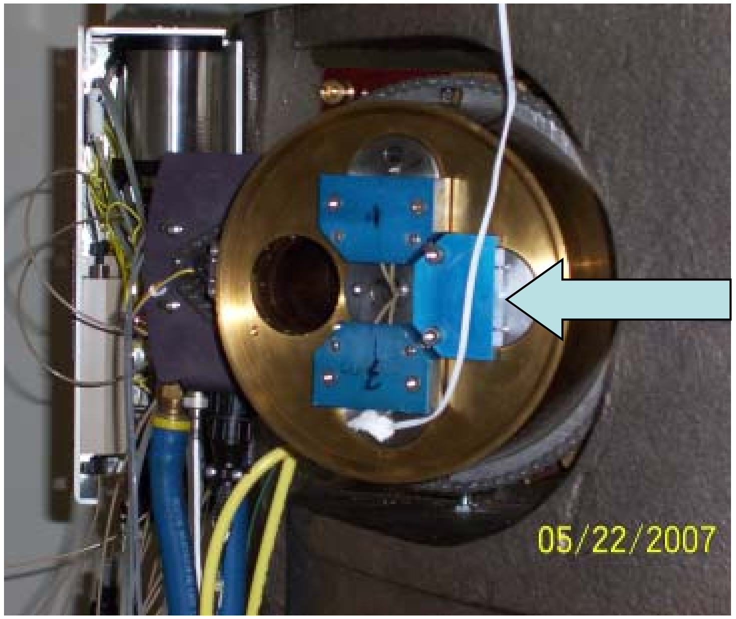
At contact 11 R/hr

6 inches 2 R/hr

150 minutes after end of bombardment:

At contact 5 R/hr

6 inches 1 R/hr



Other Cyclotron Radiation Safety Issues

- Interlock Testing
  - Maze entrances (bunker) and movable shield blocks (self-shielded)
  - Failure in interlock combined with software bug created potential for potentially life-threatening whole-body irradiation
- Emergency Shutdown testing
  - Reluctance to test due to potential for equipment damage
  - Work with factory personnel to develop a test method

Other Cyclotron Radiation Safety Issues

- Target Rebuilding
  - Radiation fields can be very high – up to 3 R/h
  - Additional targets to allow for decay prior to rebuilding
  - Technique
    - Remove entrance windows and place in shielded storage
    - Awareness of radiation fields
    - Keep work area clean
- Storage of components
  - Often parts are reused
  - Frequent surveys of storage areas and work benches

Other Cyclotron Radiation Safety Issues

- Ruptured targets & delivery/fill lines
  - Ruptured targets can result in a loss of vacuum depending on cyclotron type and options
  - Identified by sudden loss of pressure in target, and loss of vacuum in cyclotron
  - Most of the activity will go into the vacuum system
  - If early in the run, then little activity will have been created
  - Later in the run, can result in significant (> 2 Ci) activity released into vacuum system, and some will make its way out through the ventilation system
  - ^{18}F will be reactive and plate out
  - ^{13}N and ^{11}C will go out through exhaust system

Other Cyclotron Radiation Safety Issues

- **Ruptured targets & delivery/fill lines**
  - Fill and delivery line failures will result in a spray of target contents onto nearby surfaces
  - Identified by loss of target pressure w/o loss of cyclotron vacuum, or if during delivery, no activity received
  - Very high contamination levels if later in run
  - Some activity will go out exhaust system similar to target failure
  - Additional PPE should be worn (double gloves, sleeve covers, bunny suit) to prevent skin contamination
  - Identifying contamination levels will be difficult given the ambient field
- **Delivery and fill lines are normally replaced on a set schedule and well before radiation damage could weaken lines**
- **Failure to properly tighten connection seems to be most common cause of failure**

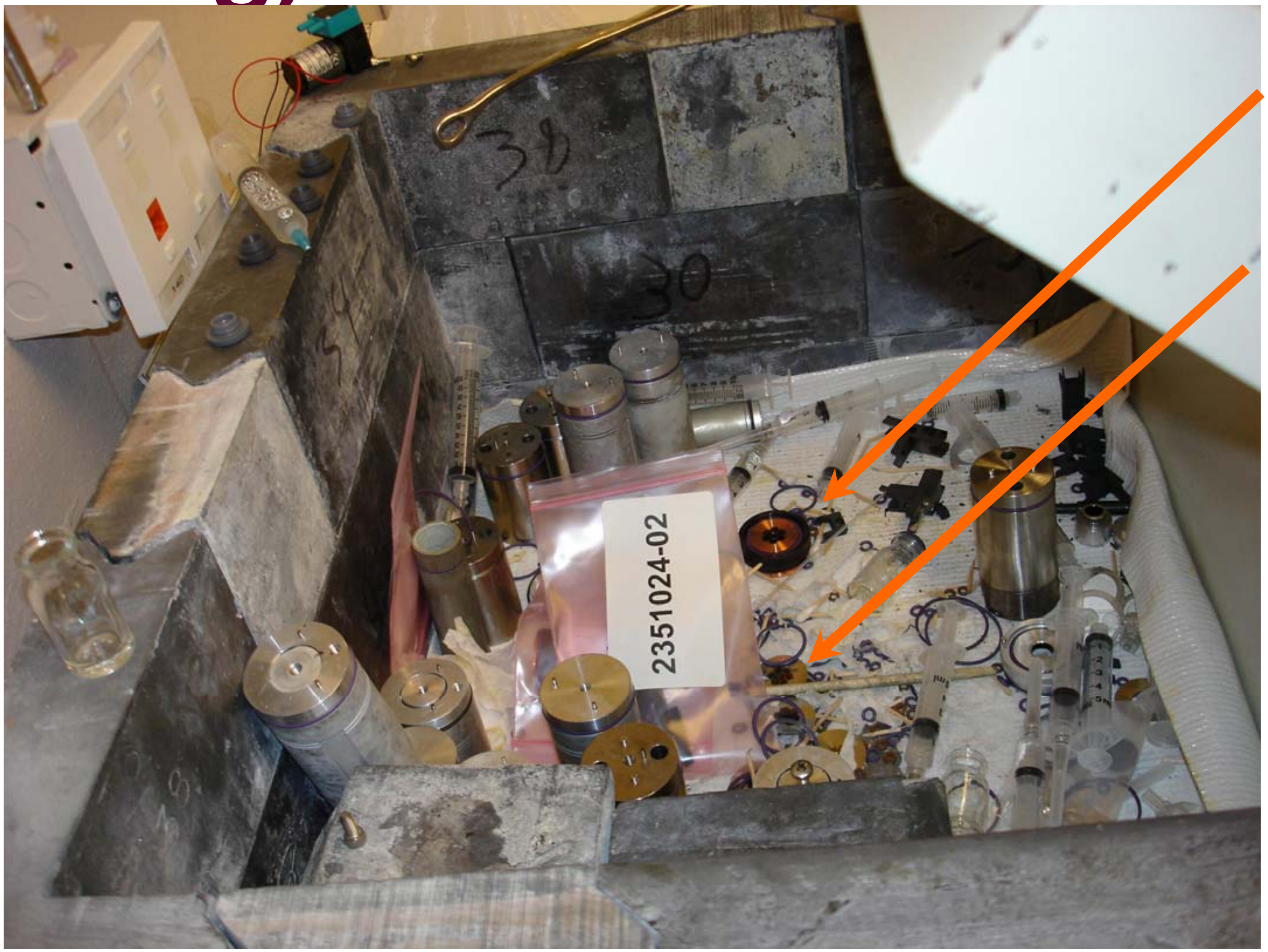
Cyclotron Maintenance
Before, During, and After

- Pre-Planning Dry Runs
  - Learning Process
  - Cold Parts
  - Removal/Installation
  - Techniques/Exposure & Contamination Controls
- Maintenance Set-up
  - Cart
  - Tools/Supplies
  - Survey Meter
  - Storage Area Prep
- Post Maintenance
  - Tools/Left over supplies
  - Surveys
- Documentation/Logbook
- Communication

RDS-111 Target Window Handling

Window @ plastic bag = 4 R/hr
Hand = 0.2 R/hr

Target Rebuild Area (after some cleaning)



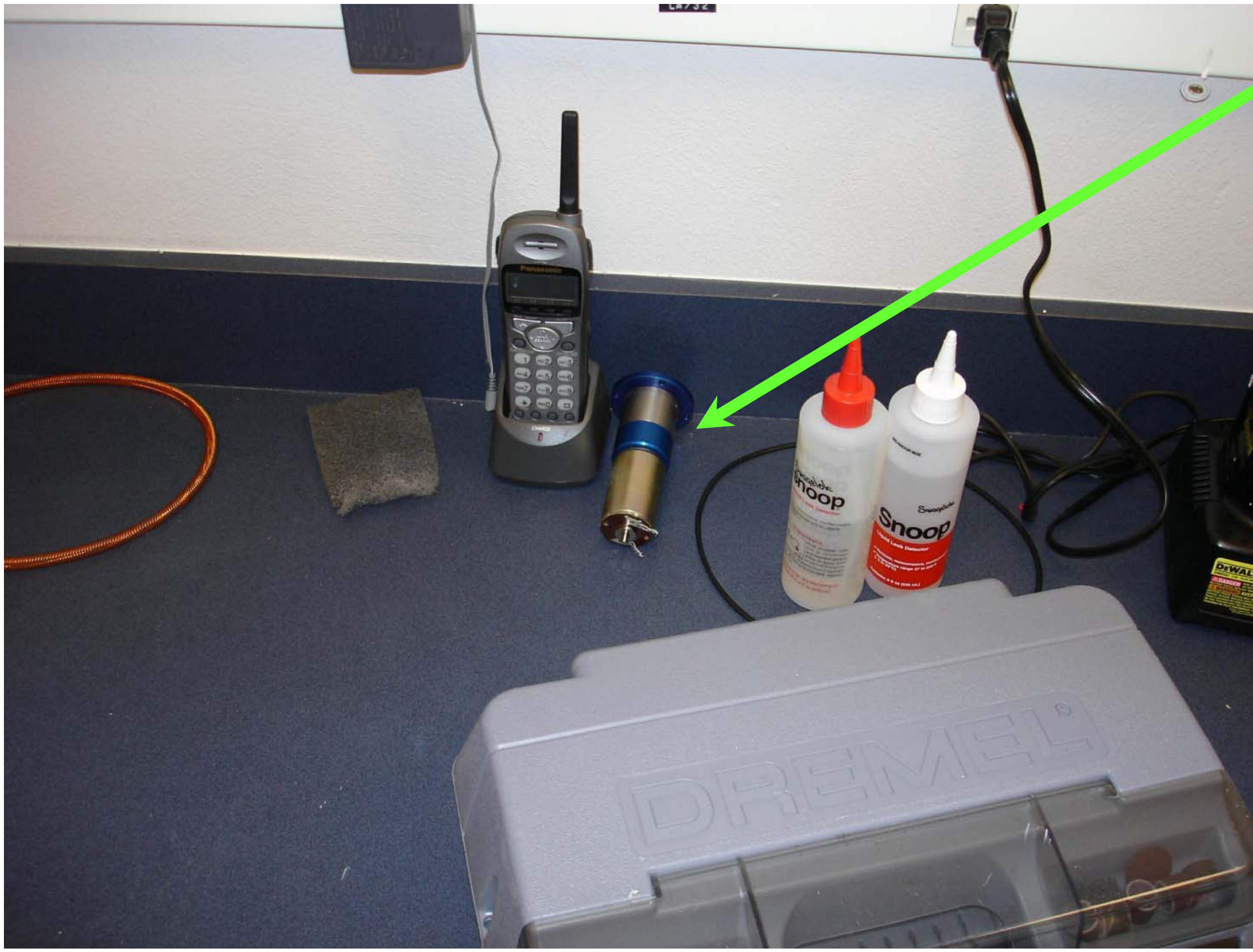
hex grid 2 R/h

Window 1.5 R/h

Target Re-build Station

w/ mounted Survey Meter

Unlabeled cyclotron components



motor 50 mR/h

“Clean” Rebuild Area

Waste bagged

Residual Radiation Fields

- Neutron Activation
  - Widespread throughout cyclotron and shielding
  - Much lower levels than from proton activation

Neutron Activation Reactions

Element	Component	Reaction	Product	Half-life	Gamma Energy MeV
Copper	Magnet Coils	^{63}Cu(n,alpha)	Cobalt 60	5.27 y	1.15/1.33
Iron	Magnet Yoke	^{56}Fe(n,p)	Manganese 54	312 d	0.835
Iron	Magnet Yoke	^{56}Fe(n,alpha)	Manganese 56	2.58 h	0.847
Zinc	various	^{64}Zn(n,g)	Zinc 65	244 d	1.115
Aluminum	Vacuum Tank / concrete	^{27}Al(n,alpha)	Sodium 24	15 h	2.75
Aluminum	Vacuum Tank / concrete	^{27}Al(n,p)	Magnesium 27	9.5m	0.844

Neutron Activation Reactions

Element	Component	Reaction	Product	Half-life	Gamma Energy MeV
Silicon	Concrete	$^{28}Si(n,p)$	Aluminum 28	2.25m	1.78
Sodium	Concrete	$^{23}Na(n,g)$	Sodium 24	15h	2.75
Antimony	Lead	$^{121}Sb(n,g)$	Antimony 122	2.7d	0.56
Antimony	Lead	$^{123}Sb(n,g)$	Antimony 124	60d	0.6/0.7/1.7

Cyclotron Activation Issues

- Licensing & Decommissioning
  - Determination of activities for licensing
    - Some States and the NRC will allow a 3-83 approach for all activation products
    - Tendency to over-estimate for possession purposes but…
    - Could increase financial assurance funding requirements

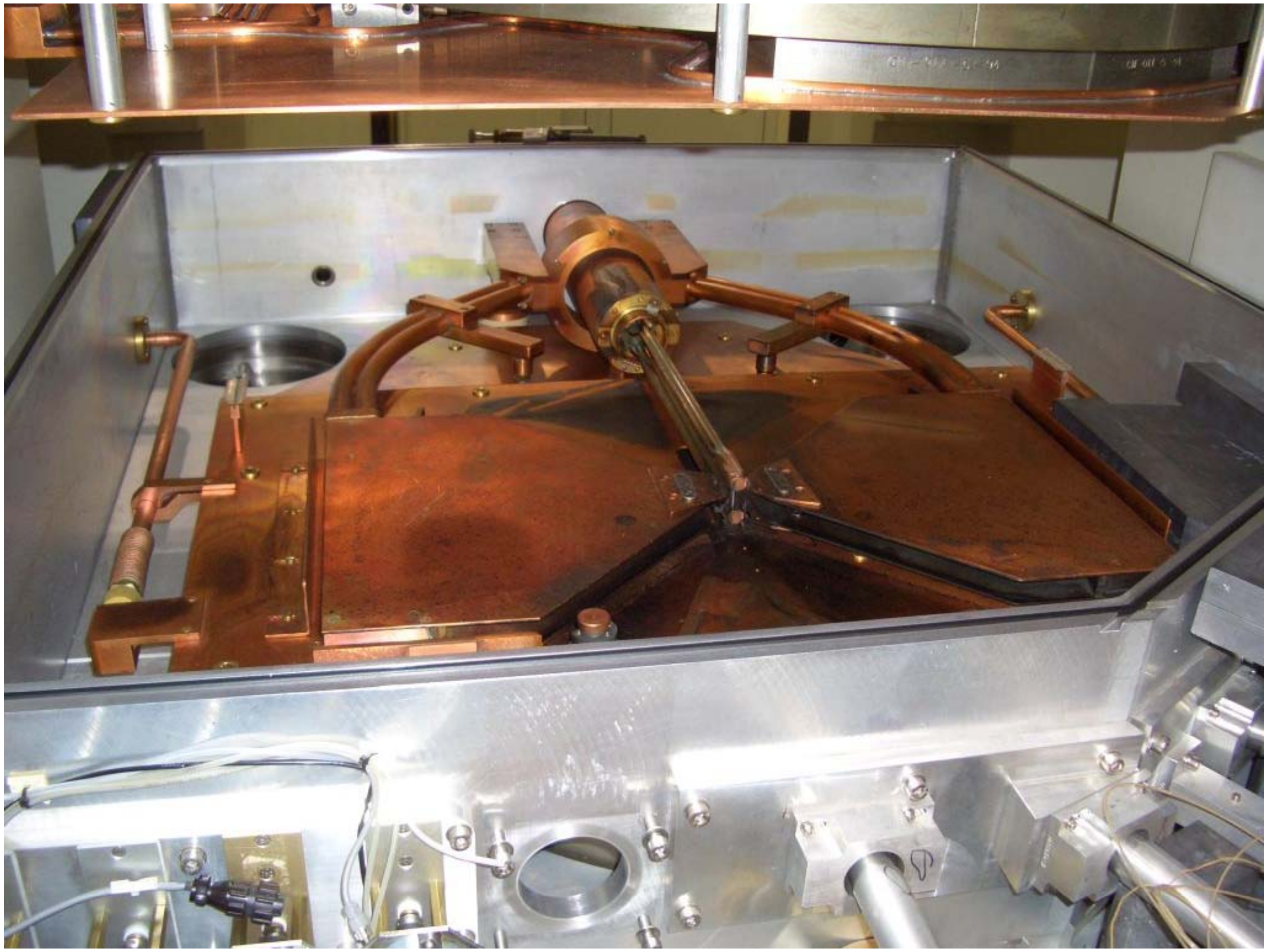
Cyclotron Activation Issues

- GE Cyclotrons
  - Refer to documentation
    - Generated using Monte Carlo techniques
- IBA
  - Refer to manufacturer

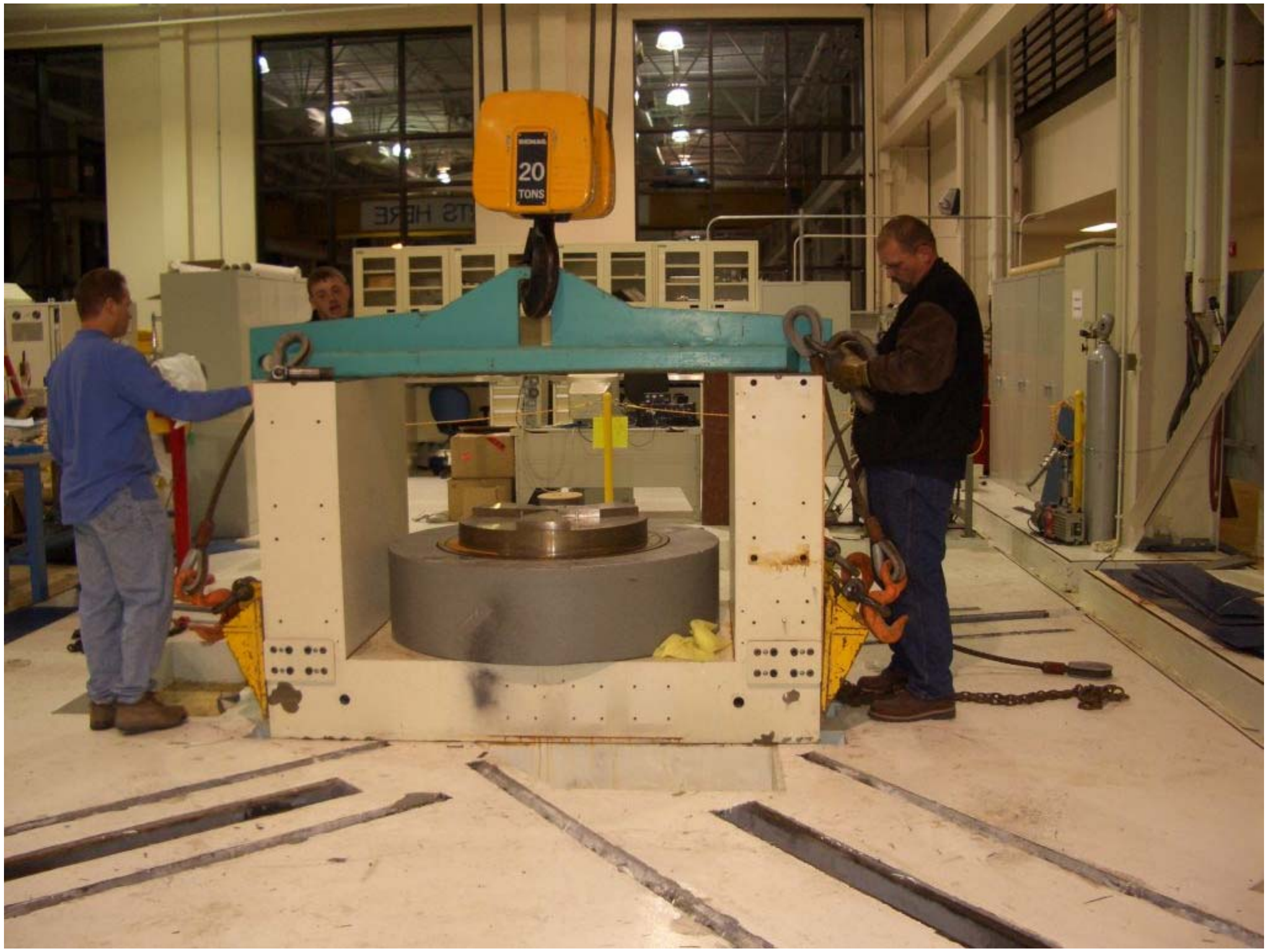
Cyclotron Activation Issues

- Siemens (CTI) Cyclotrons
  - Completed gamma spectroscopy of a decommissioned RDS-112
  - Used ISOCS system
  - Combined with gamma spectroscopy conducted on replacement components to arrive at a basis for possession quantities for licensing and decommissioning purposes

Cyclotron Decommission



Cyclotron Decommission



Cyclotron Decommission

Cyclotron Decommission

Cyclotron Decommission

Cyclotron Decommission

Cyclotron Activation Issues

- Developed two categories of activation products
  - Fixed components
    - Cyclotron structure and shielding
  - Removable components
    - Target carousels, bodies and windows
    - Ion source parts (typically very low activation)
    - Extraction carousels and foils
    - Other miscellaneous consumable parts
    - Chemistry modules components (ion exchange columns)

Cyclotron Activation Issues

- Fixed components such as cyclotron structure, shielding, and floor structure
  - Will remain in place throughout life of facility and will be the focus of decommissioning efforts
  - Concrete activation products, < 100 µCi each
    - ^{134}Cs, ^{152}Eu
  - Rebar, < 1 mCi
    - ^{60}Co
  - Cyclotron Structure
    - Table on following page for radionuclides with $t_{1/2}$ > 120 days
    - Does not include radionuclides with $t_{1/2}$ < 120 days so request a total 3-83 with a limit of 400 mCi; or
    - NUREG 1556 Vol 21 suggests listing any radionuclide > 50 mCi separately so list ^{65}Zn at 300 mCi and the remainder at 100 mCi

Fixed component radionuclides

Element and Mass Number	Maximum amount, mCi, per cyclotron
Sodium-22	0.05
Manganese-54	10
Cobalt-57	10
Cobalt-60	1
Zinc-65	285
Cadmium-109	0.05
Silver-110m	0.05
Cesium-134	0.005
Europium-152	0.025
Tungsten-181	20
Total Activity	**326.2**

Replaceable Component Radionuclides

- Partial Listing
  - Target foils (windows)
  - Target bodies (Ag and Ta)
  - Hex grids
  - Target carousels
  - Ion source parts (typically very low activation)
  - Extraction carousels and foils
  - Other miscellaneous consumable parts
  - Chemistry modules components (ion exchange columns and ^{18}O water filters)
- For a single cyclotron site a 50 mCi 3-83 limit covering replaceable components would be sufficient
- These make up the waste requiring periodic off-site disposal and the annual volume generated will usually fit in a five gallon pail

Replaceable Component Radionuclides

- Target Foils
  - As mentioned earlier, these range up to 5 R/h when first removed
  - Extensive shielding required due to presence of ^{56}Co and ^{52}Mn
  - Hold for two years to allow for ^{56}Co to decay
  - Volume is less than the size of a soda can (minus the shielding!) for a year's worth of foils
- Hex grids can be up to several R/h also and are bulkier

Replaceable Component Radionuclides

Nuclide	Activity (mCi)
V-48	1.5
Mn-54	0.002
Co-56	20
Co-57	1
Fe-59	0.5
Co-60	0.05
Zn-65	25
Cd-109	0.5
Ag-110m	0.005
W-181	0.05
Ta-182	0.02
Total	**48.6**

Tritium

- Where the heck did that come from???
  - $^{18}O(p,t)^{16}O$ threshold energy around 4 MeV
  - Differential cross-section at 18 MeV has been determined, but not for lower energies
  - ^{18}O water is expensive up to $25/g
  - Very little ^{18}O is used up, so recycling makes sense
  - Analytical results average 3.4 µCi/g of ^{3}H
  - For a very busy commercial PET radiopharmacy, total inventory of ^{18}O will equate to < 5 mCi of ^{3}H
  - Threshold for requiring bioassays is handling > 100 mCi/month
  - ALI is 80 mCi, monitoring threshold of 10% = 8 mCi

Decommissioning Experience

- Full Decommissioning of a Siemens RDS 112 and associated PET radiopharmacy
  - Concrete activation in floor and in shield blocks similar to Lewis Carroll's paper, "Predicting Long-Lived, Neutron-Induced Activation of Concrete in a Cyclotron Vault (http://www.carroll-ramsey.com/)
  - Decommissioning survey completed following MARSSIM protocols
  - License terminated and site released for unrestricted use
- San Raffaele-Milano, Italy HPS Journal June 2006, Volume 90 Number 6
  - Siemens RDS 112 replaced with newer Siemens Eclipse
  - RDS 112 Cyclotron stored on-site
  - Monte Carlo techniques used