Comprehensive Radiation Management in a PET Radiopharmaceutical Production Facility

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PET & PET-CT W'shop
Armada Hotel, PJ, Malaysia
18 Sept 2005

Radiation management in a PET radiopharmacy facility

- Facility terms of reference, design. ... commissioning
- Environmental radiation management of Facility
- General management of the Facility; ISO9001; cGMP; KPIs
- FDG production; optimisation, QA & QC
- Product dispensing, transport & export
- Personnel radiation monitoring & protection
- Conclusions

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Radiopharmaceutical Production & Development (RAPID) Laboratories: terms of reference

2000: Funding; State & Fed. Govts

2000-2002: Concept & Design

Aug. 2003: Commissioning (FDG)

May 2005: Six tracers, 3000 doses/yr

- Provide ^{18}F radiotracers for West Austr., *plus* “stretch” capacity to Darwin & Adelaide
- Productive capacity for *all* PET tracer local demands **for ~25 years**
- Develop and supply *novel* radiopharmaceuticals, including solid targetry-based & non-^{18}F
- Centre for training; clinical, science & technology

Popular idea of a Cyclotron

Cyclotron selection criteria

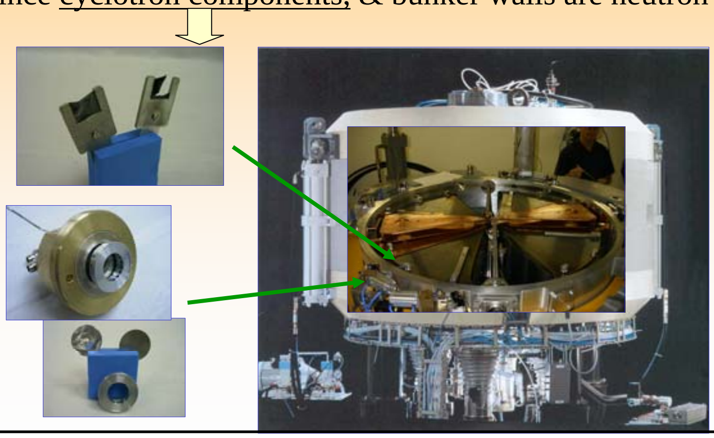
- Supply to 2.5M population & across Australia
- Potential supply of FDG to >5 PET cameras, within 50 km radius
- Development of novel products, including solid-targetry based radioisotopes (using external beam line)
- “Medium” energy particle acceleration, H^+ & D^+
- Offer science, technology & clinical training in PET & NM

Choice of cyclotron

Beam Energy	Protons Deuterons	18.0 MeV 9.0 MeV
Beam Current (on target)	Protons Deuterons	80 µA 35 µA
Beam Dimension (on target)	Gaussian profile	10 x 10 mm
Simultaneous Beam Extraction		Standard
External Beam Line		Customer developed
Targets		F-18 (two), F_2-18, C-11, N-13, O-15
Radiofrequency		42 MHz
Magnet		4 sector, 1.3 T

Assessment of bunker shielding requirements (I)

- The major task of shielding a cyclotron is to contain the **neutron** flux from the target region. This is relevant only when cyclotron operating
- Shielding against γ & **X-rays** is a secondary, longer-term task - since cyclotron components, & bunker walls are neutron-activated



Assessment of bunker shielding requirements (II)

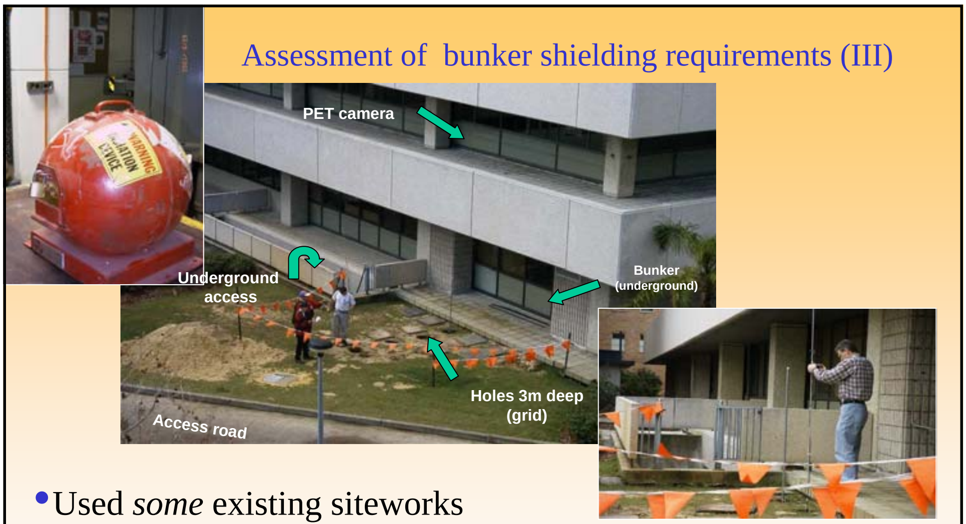
- Primary **H^+** beam is stopped in the target material. Activation of target, stripper foils, vacuum chamber, dees
- Proton rich nuclei decay by β^+ emission (511 keV γ)
- Reaction produces an intense forward directed **n^o** beam

Isotopes	Reaction	Neutron Dose at 1 m	Average n^o Energy
^{15}O	$^{14}N\ (d,n)^{15}O$	2.5 Sv/h	5 to 8 MeV
^{18}F	$^{18}O\ (p,n)^{18}F$	9.5 Sv/h*	4 to 5 MeV

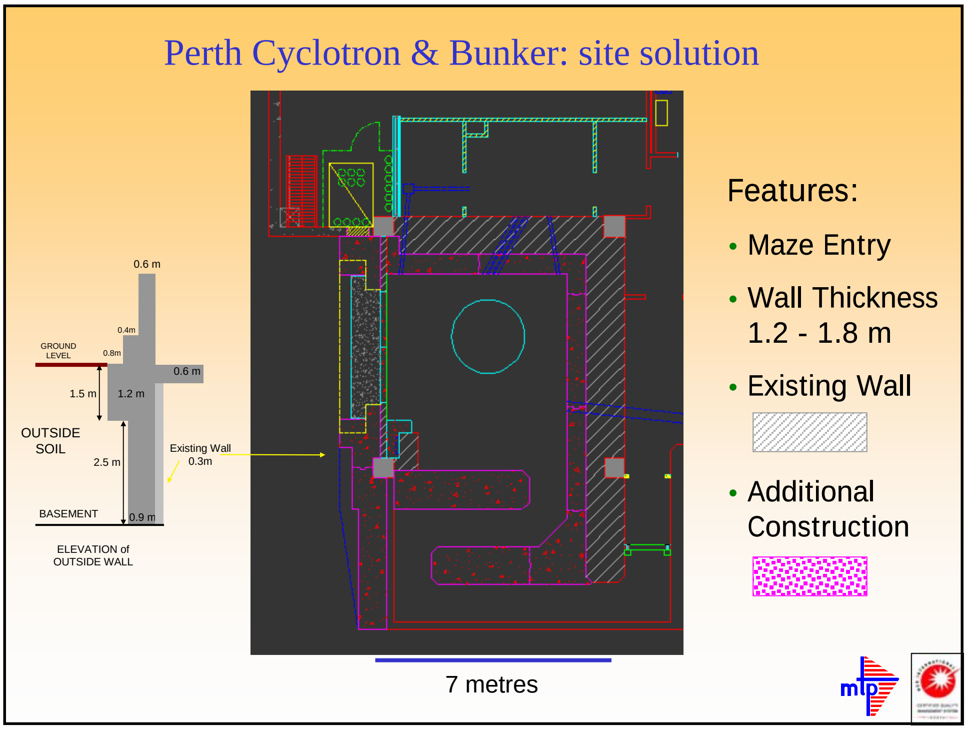
* $\phi_o = 6.0 \times 10^7\ n^0\ cm^{-2}\ s^{-1}$

- “Stray” neutron flux from medical cyclotron has been used productively (eg; neutron activation analysis; *Mukherjee B, 1996*

Assessment of bunker shielding requirements (III)



- Used *some* existing siteworks
- Exploited partly-shielded underground floor space at edge of building
- Performed neutron attenuation measurements as a part of shielding design “workup”, using sealed source

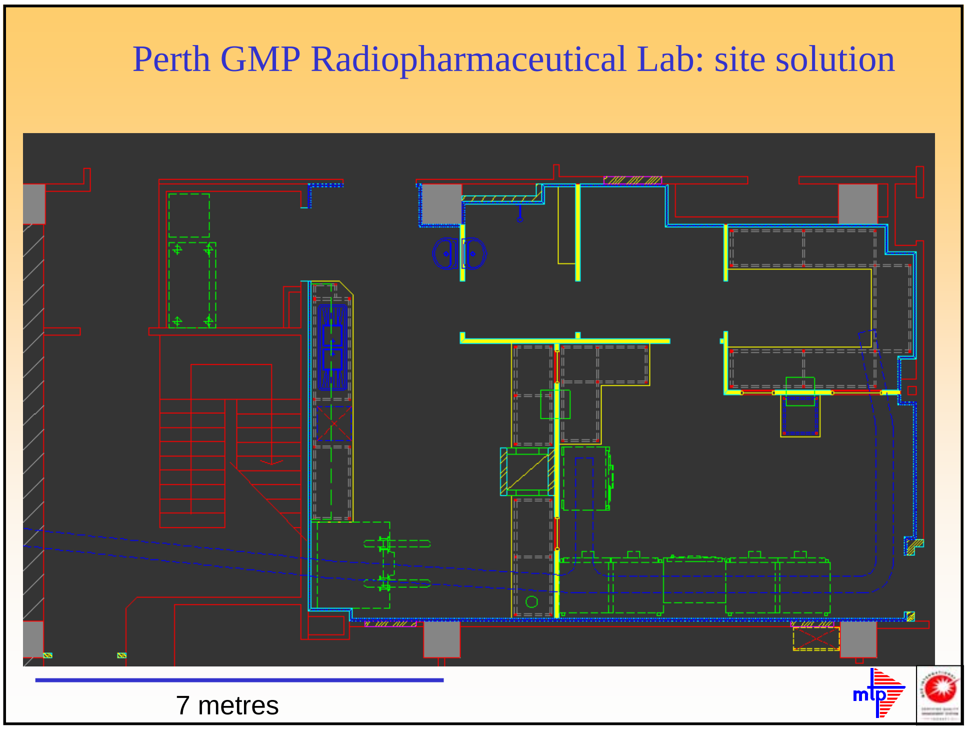


Perth Cyclotron & Bunker: site solution

Features:

- Maze Entry
- Wall Thickness 1.2 - 1.8 m
- Existing Wall
  ▨
- Additional Construction
  ▩

7 metres



Perth GMP Radiopharmaceutical Lab: site solution

7 metres

GMP laboratory

General view of GMP lab

"IBA" FDG box

Inside "Althea" automated dose dispensing hotcell

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“Environmental” issues in radiation management

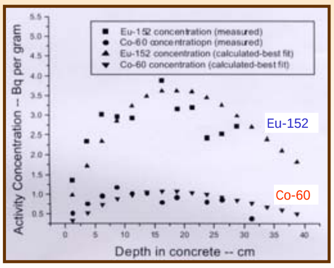
- Neutron activation of cyclotron, bunker & surroundings; long-term implications
- Neutron activation of air in bunker
- Gaseous or atomised liquid PET isotopes in air expelled from PET laboratories
- Radioactive waste disposal (none!)

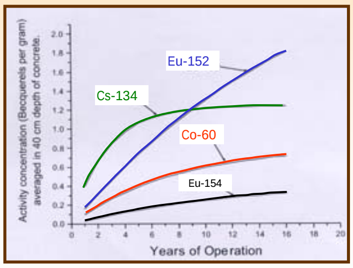
Neutron activation of bunker concrete

Relevant for concrete of 2.0 m thickness, nearest to the target

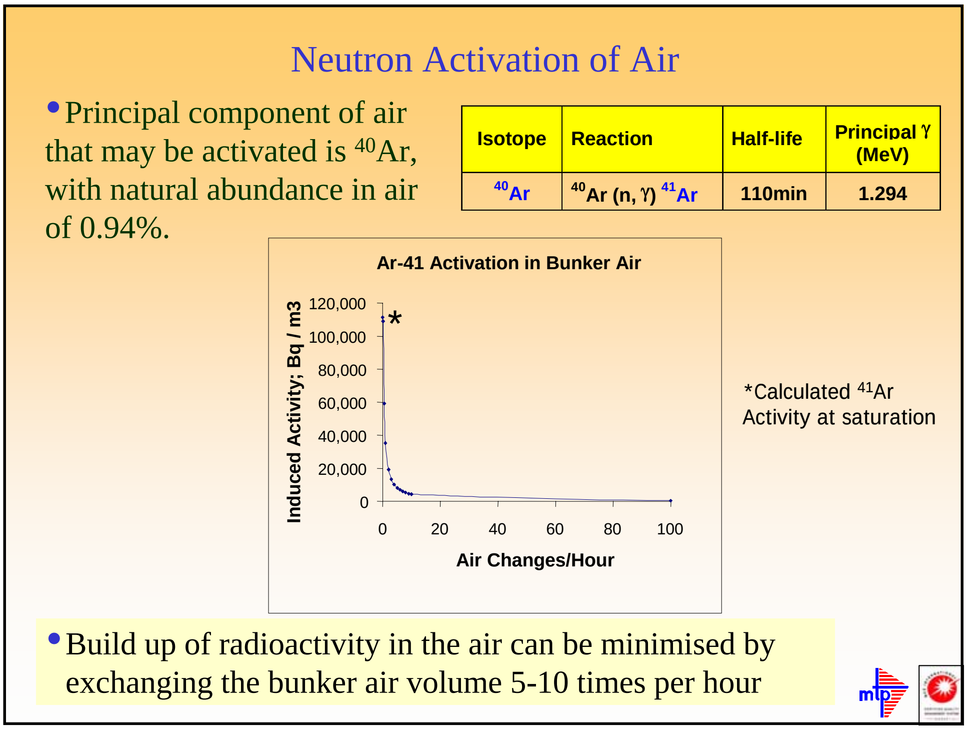
Isotope	Reaction	Half-life	Principal γ’s (MeV)	Activity Concentration*
^{152}Eu	$^{151}Eu(n, \gamma)^{152}Eu$	13.4	0.122, 0.344, 1.408, 0.960, 1.111, 1.087	89 Bq
^{154}Eu	$^{153}Eu(n, \gamma)^{154}Eu$	8.5	0.120, 1.278, 1.00	11 Bq
^{60}Co	$^{59}Co(n, \gamma)^{60}Co$	5.27	1.17, 1.33	110 Bq
^{134}Cs	$^{133}Cs(n, \gamma)^{134}Cs$	2.07	0.796, 0.605, 0.57	37 Bq

* per kg of concrete





JE Cehn & LR Caroll, **Proc of Health Physics**, San Jose, CA, 1997



Neutron Activation of Air

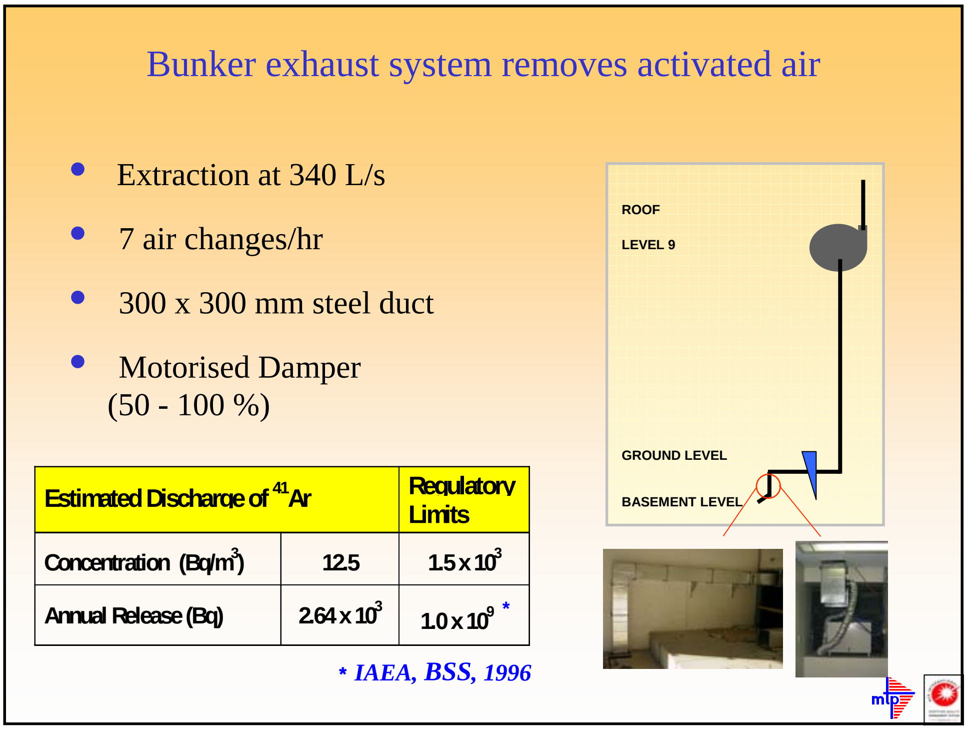
- Principal component of air that may be activated is ^{40}Ar, with natural abundance in air of 0.94%.

Isotope	Reaction	Half-life	Principal γ (MeV)
^{40}Ar	^{40}Ar (n, γ) ^{41}Ar	110min	1.294

Ar-41 Activation in Bunker Air

*Calculated ^{41}Ar Activity at saturation

- Build up of radioactivity in the air can be minimised by exchanging the bunker air volume 5-10 times per hour



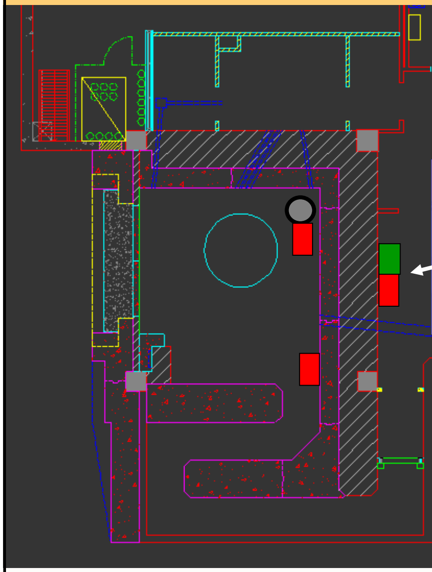
Bunker exhaust system removes activated air

- Extraction at 340 L/s
- 7 air changes/hr
- 300 x 300 mm steel duct
- Motorised Damper (50 - 100 %)

Estimated Discharge of ^{41}Ar		Regulatory Limits
Concentration (Bq/m^3)	12.5	1.5×10^3
Annual Release (Bq)	2.64×10^3	1.0×10^9 *

** IAEA, BSS, 1996*

Radiation monitoring of bunker

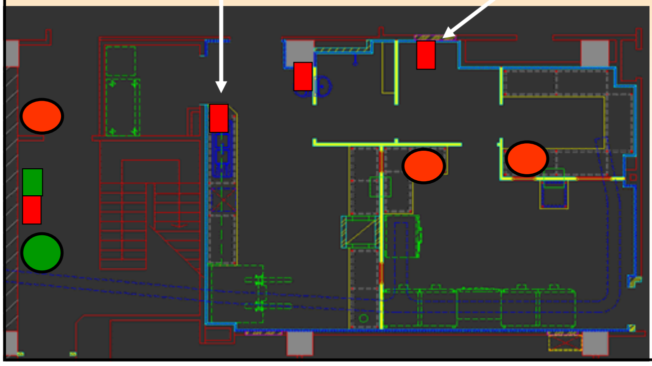


Features:

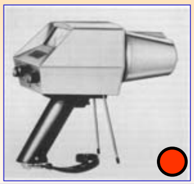
- 🟩 n° monitor
- 🟥 γ monitor
- ● Exhaust stack for ^{41}Ar (incl. γ "sniffer)

Neutron shielding door

Radiation monitoring of Lab



- 🟥 Fixed γ monitor
- 🟩 Fixed n° monitor
- 🔴 Portable γ monitor
- 🟢 Portable n° monitor



Summary; environmental radiation management

- Activated concrete a “problem” only if bunker were dismantled
- Build-up of radioactivity in concrete could be minimised by inserting a neutron absorbing material, ie. boronated polyethylene between the target and wall
- Ready availability of monitors encourages safe practice

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Maximising isotope production efficiency

- Maximisation of Cyclotron efficiency with a "Best Practice" QA Program reduces dose burdens
- **ISO9001:2000** provides a Quality Management / QA framework (and ethos) to measure and <u>improve</u> *performance*
- *Performance* achieved through
  - Standard Operating Procedures (eg; **cGMP**)
  - Careful staff selection & training
  - KPIs to optimise performance
  - <u>Total</u> commitment to safety
- *Otherwise*, accidents & doses can escalate

CERTIFIED QUALITY MANAGEMENT SYSTEM ISO9001

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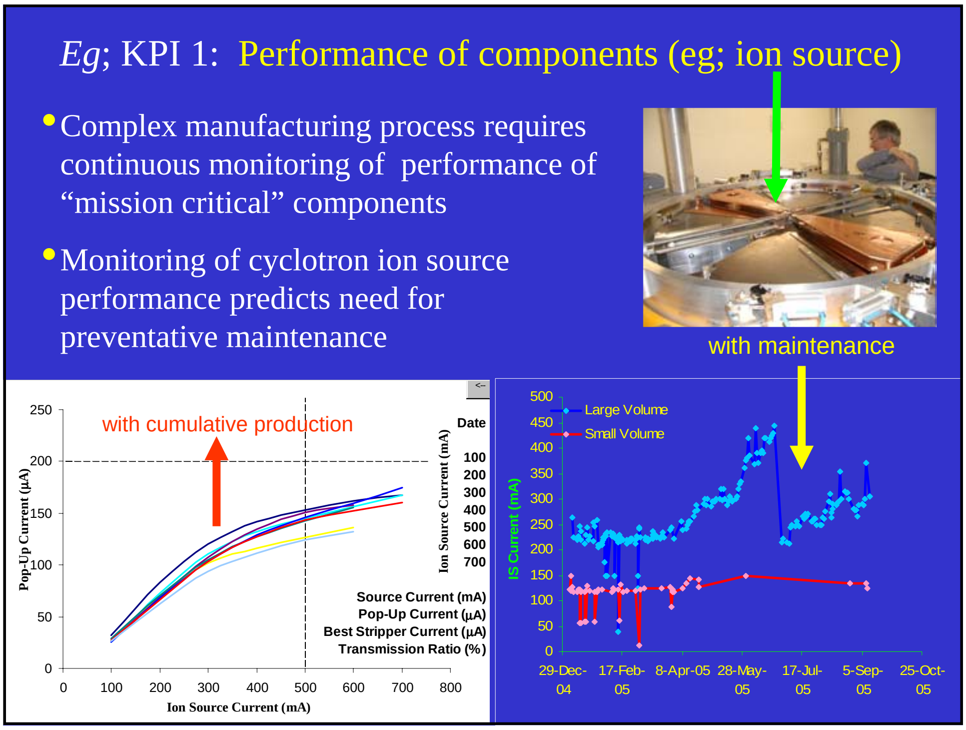
cGMP

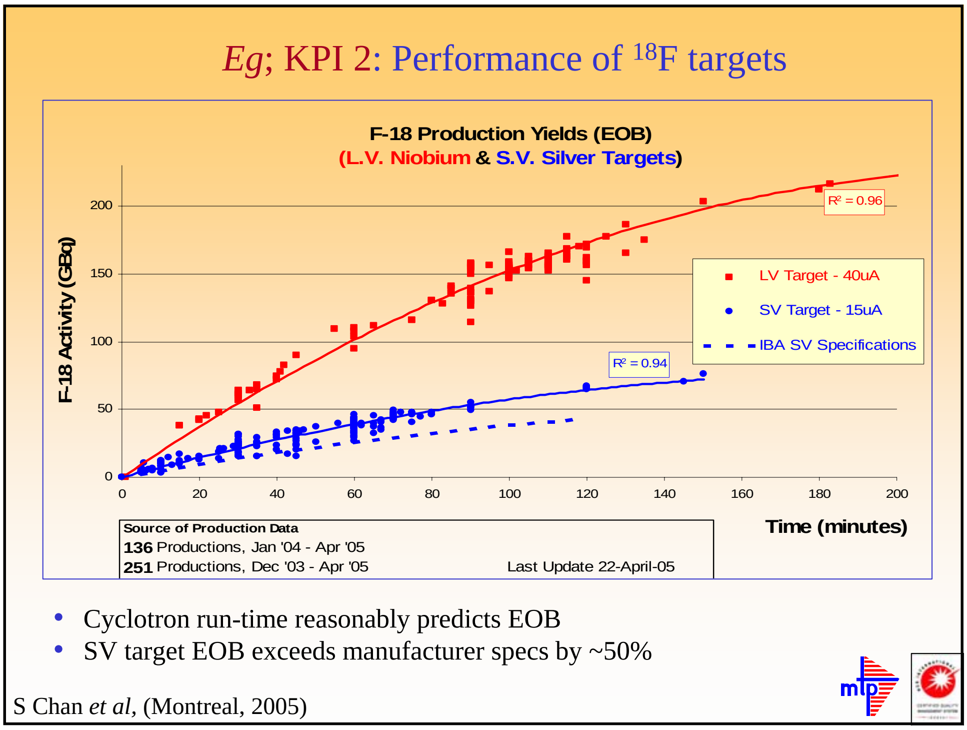
- "That part of QA which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorisation or product specifications"
- Basic requirements
  - All manufacturing clearly defined
  - Critical steps validated
  - Necessary facilities for GMP are provided
  - Clearly written instructions
  - Trained operators
  - Record keeping, traceable & accessible
  - No risk to the product on distribution
  - A system available to recall any batch of product from sale or supply
  - A system to deal with complaints, quality defects, to prevent re-occurrence

See Chris Jones presentation this meeting



Eg; KPI 1: Performance of components (eg; ion source)

- Complex manufacturing process requires continuous monitoring of performance of “mission critical” components
- Monitoring of cyclotron ion source performance predicts need for preventative maintenance



Eg; KPI 2: Performance of ^{18}F targets

Source of Production Data
136 Productions, Jan '04 - Apr '05
251 Productions, Dec '03 - Apr '05
Last Update 22-April-05

- Cyclotron run-time reasonably predicts EOB
- SV target EOB exceeds manufacturer specs by ~50%

S Chan *et al*, (Montreal, 2005)

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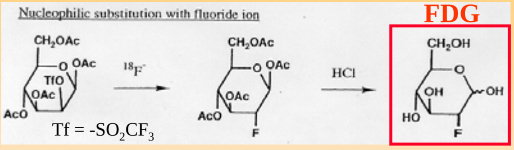
Semi-automated synthesis of FDG

^{18}F Labelling Chemistry

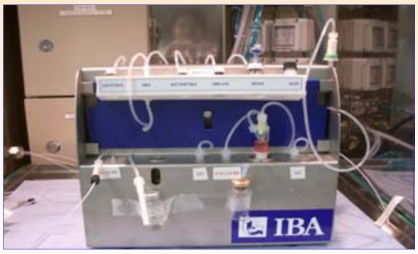


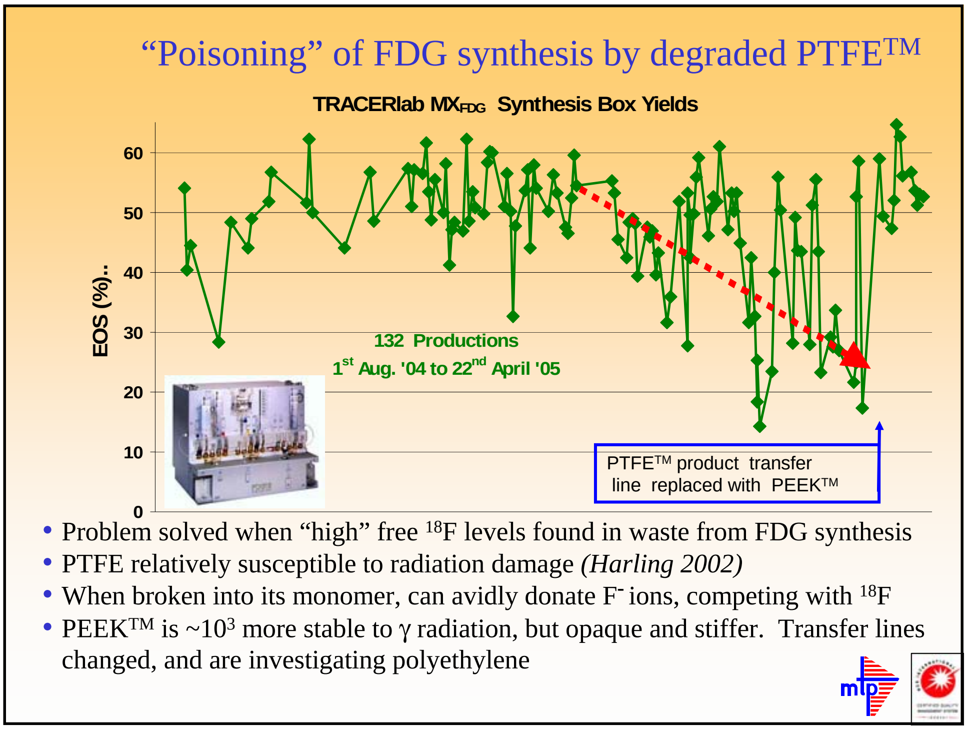
Tf = $-SO_2CF_3$

- multiple steps
- disposable kits
- episodic failures
- ?partial manual intervention

Eg; GE TRACERlab MX_{FDG}

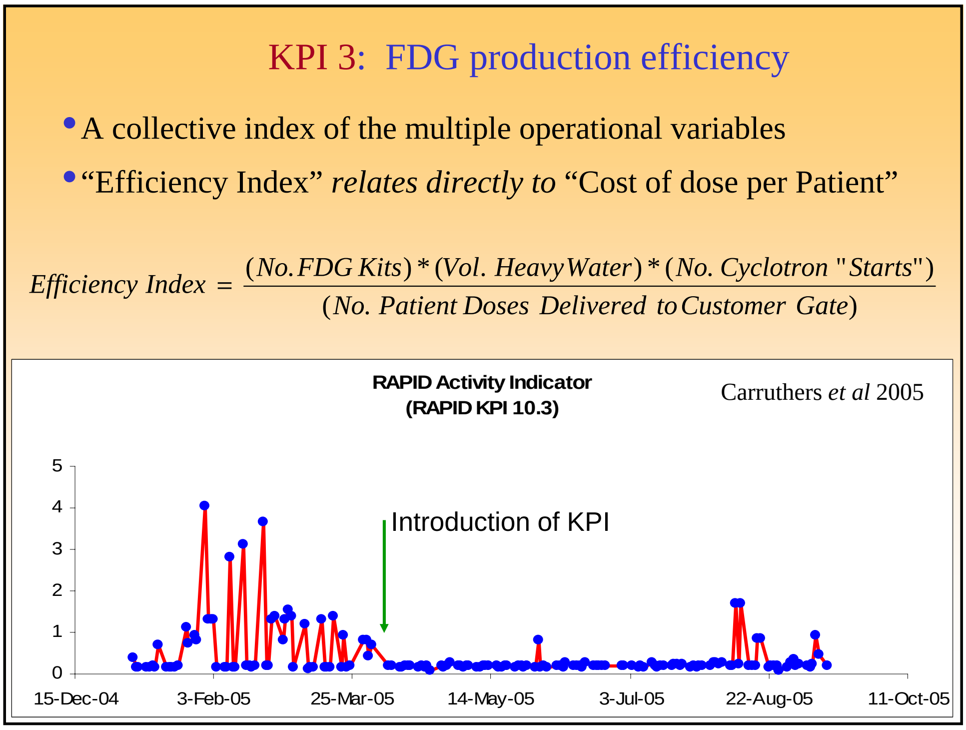
IBA





“Poisoning” of FDG synthesis by degraded PTFE™

- Problem solved when “high” free ^{18}F levels found in waste from FDG synthesis
- PTFE relatively susceptible to radiation damage *(Harling 2002)*
- When broken into its monomer, can avidly donate F^- ions, competing with ^{18}F
- PEEK™ is ~10^3 more stable to γ radiation, but opaque and stiffer. Transfer lines changed, and are investigating polyethylene



KPI 3: FDG production efficiency

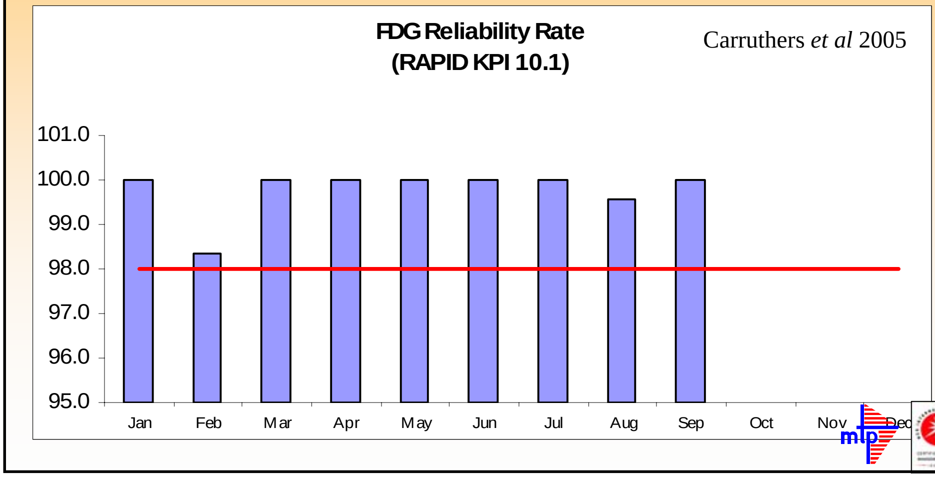
- A collective index of the multiple operational variables
- “Efficiency Index” *relates directly to* “Cost of dose per Patient”

$$\text{Efficiency Index} = \frac{(\text{No. FDG Kits}) * (\text{Vol. Heavy Water}) * (\text{No. Cyclotron "Starts"})}{(\text{No. Patient Doses Delivered to Customer Gate})}$$

Carruthers *et al* 2005

KPI 4: FDG delivery reliability rate

- Percentage of requested patient doses delivered “on time”
- 2005; >**99%**



FDG Reliability Rate
(RAPID KPI 10.1)

Carruthers *et al* 2005

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Product dispensing

automated

manual

- Robotic dispensing systems fail, leading to manual intervention & high personal doses
- Some robots cannot handle high activity boluses
- *However*, manual dispensing limits the number of individual doses dispensed

Product transport & export

- High activities (~10-75GBq) require shielded, robust containers
- Long distance transport requires container that satisfies international radiation containment standards (containment, strength, shielding)
- Transport Index (TI) for FDG is 1 < TI < 10; Yellow III

“In-house” transport

Interstate transport

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Management of personnel radiation safety:
Strategy for minimisation of radiation doses (I)

- A “managed” approach taken *(ISO9000; general compliance with ICRP 60 recommendations)*
  - Laboratory area “keycard-secured”
  - Staff wear passive radiation personal monitors (“luxels” & TLD rings)
  - Staff also wear active electronic monitors for instant feedback
  - Results of electronic monitoring rigorously tabled & discussed fortnightly
- ***Initially***, problems with FDG synthesis units, switching valves, xsfer lines *etc* led to manual-interventions; > than expected doses *(occ. >100μSv per run)*
- ***High lab staff commitment can lead to “high” radiation doses!***

Recommended Dose Limits (Occupational & Adult Public)

ICRP Recommended Dose Limits [a]

Application	Dose Limit	
	Public	*Occupational*
Effective Dose	1mSv/year [b]	20mSv/year
Annual Equivalent Dose in		
The lens of the eye	15 mSv	150 mSv
The skin	50 mSv	500 mSv
The hands and feet	---	500 mSv

Maximum total entrance surface dose (ESD) to abdomen during pregnancy = 2mGy

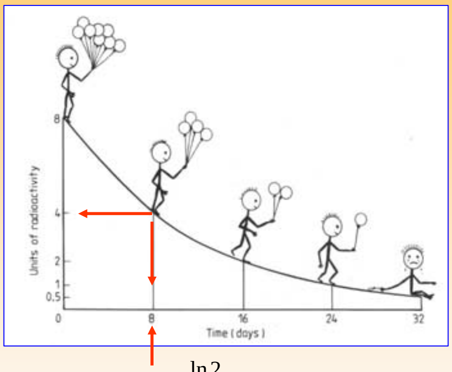
a. International Commission on Radiation Protection (ICRP60; 1990)
b. ICRP60; para 191

(Note that it is unlikely to exceed these dose limits in well-managed routine PET laboratory or clinical practice)

Management of personnel radiation safety:
Strategy for minimisation of radiation doses (II)

- ***Strict limits enforced by RAPID Management:***
  - *If* >30% of "monthly pro rata permitted dose" is exceeded, *then* cease radiation work that month (0.5mSv)
  - >1.67mSv in a month; investigate as above *and* report to State Regulator
- Leads to group analysis of work practices
- ISO9000 Service Improvement Form raised
- Inevitably, protection is provided by **"Time", "Distance" & "Shielding", plus attention to ALARA**

Radioactive half lives of PET isotopes is short!



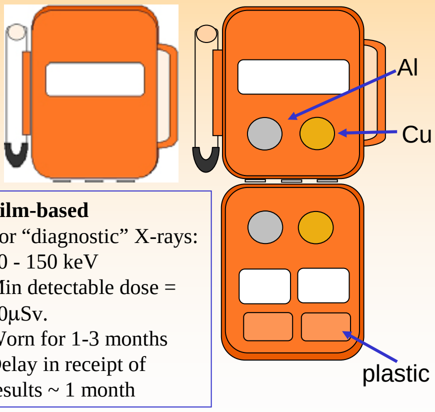
$$T_{1/2} = \frac{\ln 2}{\lambda}$$

- PET isotopes have half lives ranging from 2 minutes to two hours.
- This means that overnight all the activity is lost and the isotope is converted to a harmless compound, either in the body or in the lab

- Interventions such as entry into the bunker & cyclotron maintenance should be delayed as long as feasible (a few hours makes a large difference!)

Personal Radiation Monitoring: the Technology (I)

- **Passive personal recorders.** Film badges, “luxels” or “TLDs” that are pinned to the Technologist for 1-3 months. They measure cumulative dose. Then, they are sent to a certified laboratory for analysis



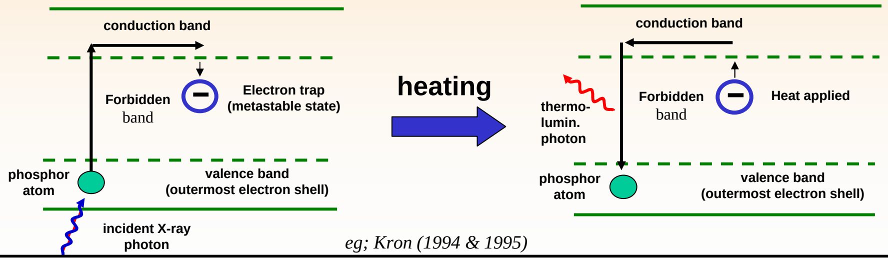
- **Film-based**
- For “diagnostic” X-rays: 30 - 150 keV
- Min detectable dose = 20μSv.
- Worn for 1-3 months
- Delay in receipt of results ~ 1 month

- **Electron entrapment -based,**
- For X-rays: 5keV - 10MeV
- Dose range = 10μSv - 10Sv
- Worn for 1 month
- Delay in receipt of results ~ 3weeks; sent to US for readout by laser scanning

eg; Martin & Harbison (1996); Rennhack (2005)

Personal Radiation Monitoring: the Technology (II)

- **Thermoluminescence dosimeters (TLDs)** exploit *phosphoresence* of a material such as Lithium Fluoride (LiF), activated with Mg or Ti, creating "electron traps" by inducing crystal "defects". γ photons promote electrons to these "traps"
- **TLDs** range from badges to small, needle-like detectors
- **TLDs** measure cumulative dose from 1 to many months
- **TLDs** require expert facilities for reading neutron tracks

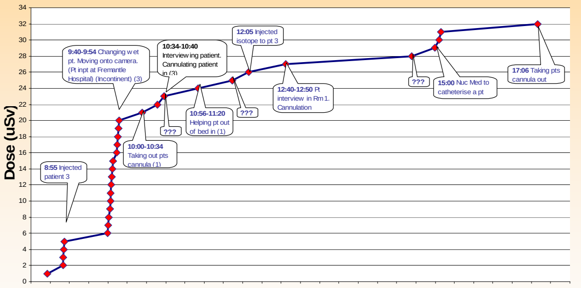


eg; Kron (1994 & 1995)

Personal radiation monitoring: real-time logging

- **Active electronic personal dose loggers.** Attached to technologist; provides instant readout and time-log.
- Deployed when a work practice needed to be more deeply and dynamically analysed, than is possible with a film badge

Time dependent record of accumulated dose



- Usually relevant for tracking unexplained doses
- Example shown is for PET imaging technologist

Adapted from Andrew Trang (2004)

Radiation dosimetry: RAPID individual staff 2004

category of worker	Total Year Dose (mSv)
Maintenance	1.15
Production	0.79
Production & Maintenance	3.42
Maintenance	2.24
Maintenance	1.71
Production & Maintenance	1.44
Prod. Chief Radiochemist	1.49
Research	2.74
Production & Maintenance	1.69
Production	1.84
Principal Medical Physicist	0.18
Head of Department	0.10

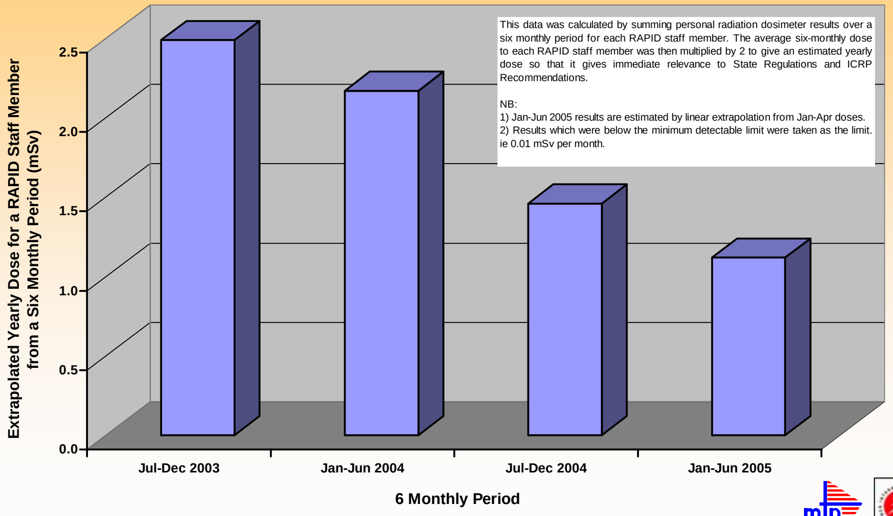
Beware of radiation work practice multi-skilling! 🟥 (Production & Maintenance 3.42)

Management leads! 🟦 (Principal Medical Physicist 0.18)

- <5 mSv/yr whole-body eff. dose is theoretical "acceptable" max in Perth Centre
- <20 mSv/yr is Perth regulatory limit (ICRP 60)

Mean PET laboratory doses decline after "startup" of service

Estimated Yearly Dose for a RAPID Staff Member



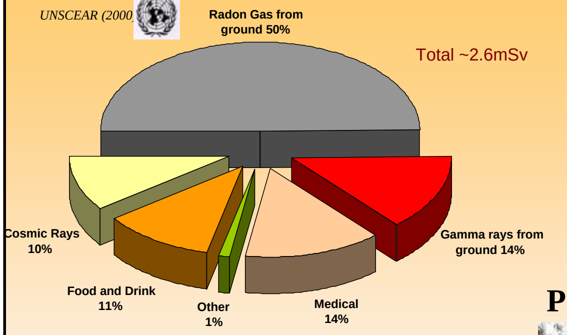
This data was calculated by summing personal radiation dosimeter results over a six monthly period for each RAPID staff member. The average six-monthly dose to each RAPID staff member was then multiplied by 2 to give an estimated yearly dose so that it gives immediate relevance to State Regulations and ICRP Recommendations.

NB:
1) Jan-Jun 2005 results are estimated by linear extrapolation from Jan-Apr doses.
2) Results which were below the minimum detectable limit were taken as the limit. ie 0.01 mSv per month.

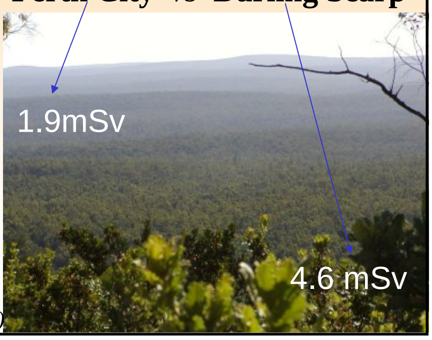
Andrew Trang

Annual Effective Dose in Australia: Location matters!

UNSCEAR (2000



Yearly “background” dose:
Perth City *vs* **Darling Scarp**



- Perth yearly regional difference (**2.7**mSv) is about the *extra yearly dose* received by a PET worker in Perth

Toussaint (2004)

Conclusions

- Comprehensive radiation management requires attention to both environmental and personal monitoring
- Radioactive waste is not a problem, but personal exposure can be
- ISO9001, cGMP, training, ICRP60 are all important QA management tools
- QC depends on “Best Practice” SOPs, monitoring of KPIs, and close cooperation within radiopharmacy production team
- “Best Practice” doses are low (~natural background), particularly after first operational year
- **Quality of original design of facility determines difficulty of subsequent radiation management**

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Terima Kasih

RAPID TEAM.

Murray Bottomley
Ben Carruthers
Hwee Carter
Sun Chan
David Cryer
Tom Deans
John De Roach,
Janelle D'Souza
Christopher Jones
Nat Lenzo
Laurence Morandeau
Roger Price
Andrew Trang
Thomas Tuchyna

Aug 2003. Some of the RAPID staff
(most have non-PET duties as well); with
Yves Jongen, Cyclotron Designer (IBA), at centre