Nanoparticle Radiolabelling

Neil Gibson

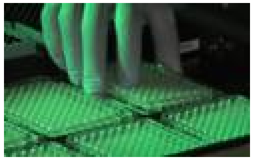
Joint Research Centre, Ispra

Institute for Health and Consumer Protection

CERN-JRC workshop
CERN, 27 January 2014

European Commission

Institute for Health and Consumer Protection
JRC – Ispra site

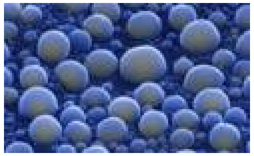


- **Alternatives to Animal Testing**

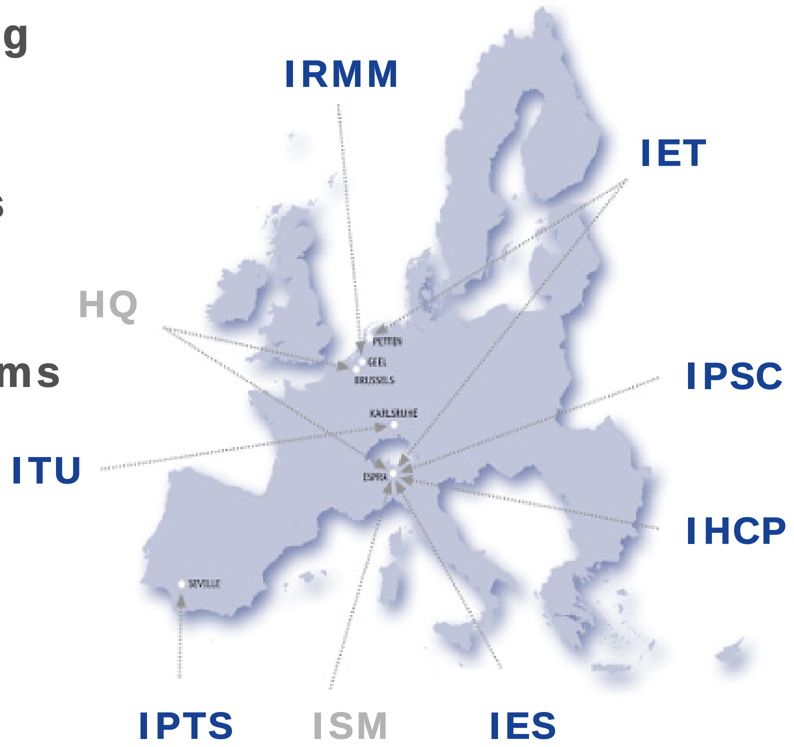
- **Food and Consumer Products**

- **Genetically Modified Organisms**

- **Public Health**



- **Nanotechnology**



Joint Research Centre

Development of the IHCP work on NP radiolabelling
(the most sensitive and quantitative method for NP tracing)

Several years ago, worldwide concern was increasing about nanoparticle use, exposure and potential negative health or environmental effects.

The work of the **Nanobiosciences Unit** became **more and more focused on NP detection/tracing, characterisation, nanotoxicology, etc**.

--- plus **support to policy makers** in the area of development of regulation (for human and environmental protection)

The **NBS cyclotron group** (which previously had focused on radioisotope production for Nuclear Medicine) began work on **nanoparticle activation by ion-beam irradiation** in order to support *in vitro* nanotoxicology work.

Applications of radiolabelled nanoparticles

- Medical diagnosis and therapy, and tracing of other medical NPs
- *In vitro* studies (e.g. cell uptake studies related to nanotoxicology, barrier crossing studies, etc.,)
- *In-vivo* studies (e.g. biodistribution experiments related to nanotoxicology studies, NP dosimetry, etc.)
- Several other areas (e.g. radiotracer studies related to the use of nanoparticles in industry/consumer products/etc., NP release studies, environmental transport, plant uptake, …..)

Several European collaborative research projects require/d radioactive nanoparticles:

DIPNA, CellNanoTox, ENPRA, NanoReTox, INBARCA, NeuroNano, QNano …..

TO BE RELEVANT FOR MANY STUDIES, IT IS NECESSARY TO RADIOLABEL INDUSTRIALLY FABRICATED NANOPARTICLES

Nanotoxicology - which nanoparticles ?

List of representative nanomaterials

Fullerenes (C60)
SWCNTs
MWCNTs
Silver nanoparticles
Iron nanoparticles
Carbon black
TiO_2
Al_2O_3
ZnO
SiO_2
Polystyrene
Dendrimers
Nanoclays

Physical-Chemical Properties and Material characterization

Agglomeration/aggregation
Water solubility
Crystalline phase
Crystallite size
Dustiness
Representative TEM pictures
Particle size distribution
Specific surface area
Zeta-potential

Surface chemistry
Photocatalytic activity
Pore density
Porosity
Octanol-water partition coefficient
Redox potential
Radical formation potential
Other relevant information

OECD Working Party on Manufactured Nanomaterials Steering Group 3

Others of interest:
CeO_2
Pigments
Etc.

Institutional/Collaborative Research work – Summary

- Ion-beam activation of TiO_2, ZnO, CeO_2, Fe_3O_4, carbon-based NPs, …..

- Studies on the thermal conditions of NPs under irradiation

- Neutron activation of NPs (Au, Ho, …)

- Development of a recoil method for NP radiolabelling (SiO_2, nanodiamonds, other carbon-based NPs, Al_2O_3, ….

- Radiochemical synthesis of labelled NPs – SiO_2, Ag, Au, ….

- Electrode tip activation for spark-ignition production of NPs (Ag, Au, TiO_2, ...)

(other methods like diffusion, laser ablation, physical vapour techniques, surface linking, etc. can be used for radiolabelling NPs)

European Commission

"Direct" radiolabelling of industrial nanoparticles

Irradiation with neutrons

Suitable activation reaction available with a high activation cross se… tion ?

Radiation damage ?

Thermal damag…

'No' rec… …r radiotracer

R… …cer is usually of the same ch… …ical species as NPs

Activation of NPs in liquid dispersions

Only really useful for Au and a few other NPs

Irradiation with ion-beams

Suitable activation reaction available?

Radiation damage ?

Thermal damag…

Recoil tra… …otracer (re-impla…

Ra… …er is often of a different che… …cal species as NPs

Not practical to activate liquid suspensions

Wider range of activation possibilities

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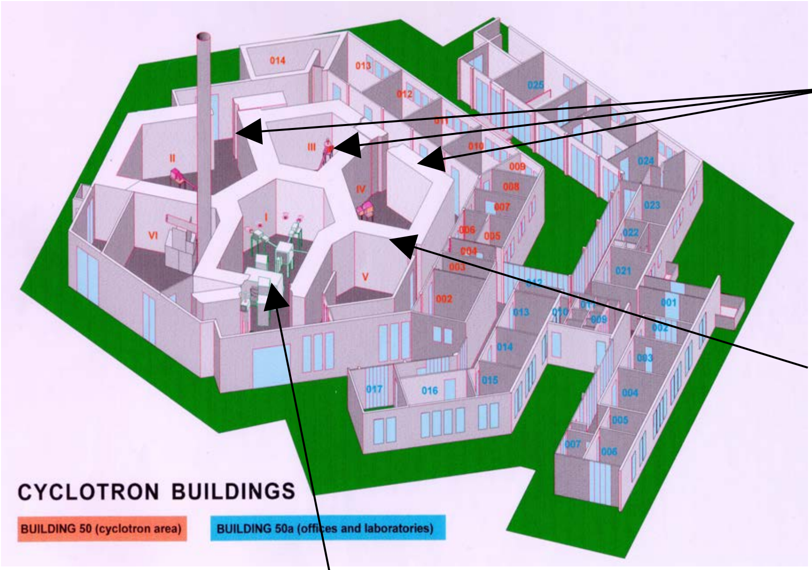
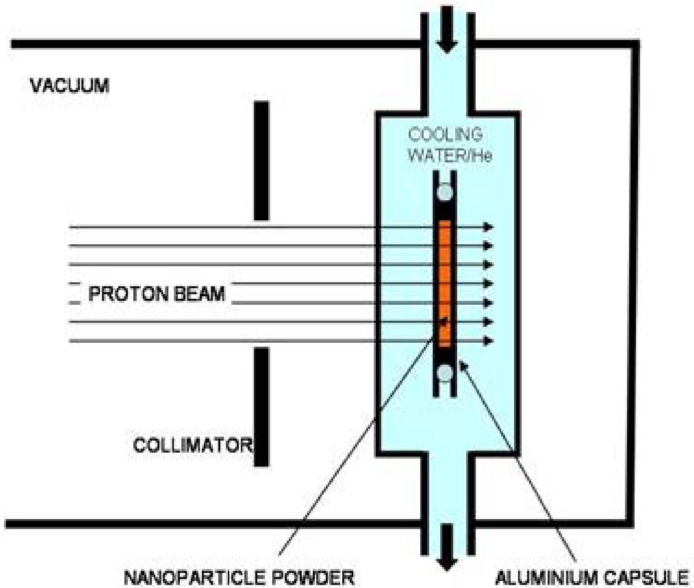


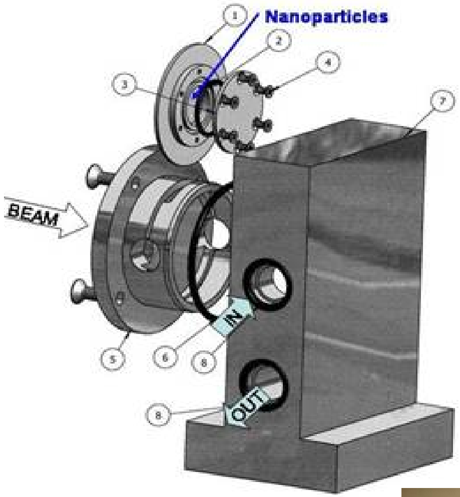
3 irradiation halls
7 beam lines

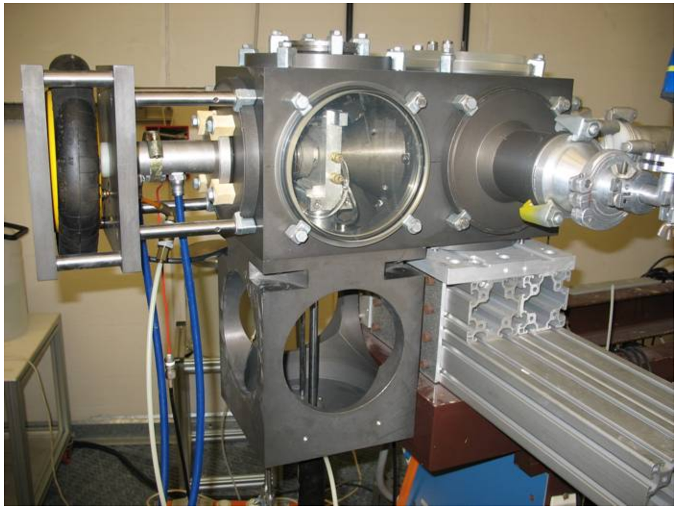
2 meter thick concrete walls (radiation shielding)

Particles	Minimum Energy (MeV)	Maximum Energy (MeV)	Maximum Extracted Current (µA)
p	8	40	60
α	8	40	30
$^3He^{2+}$	8	53	30
d	4	20	60

Target Design (for dry NP-powders)





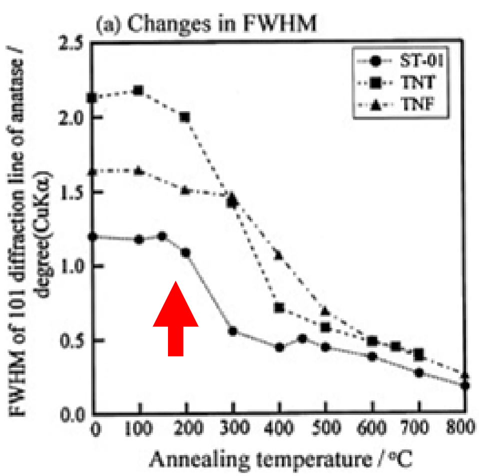


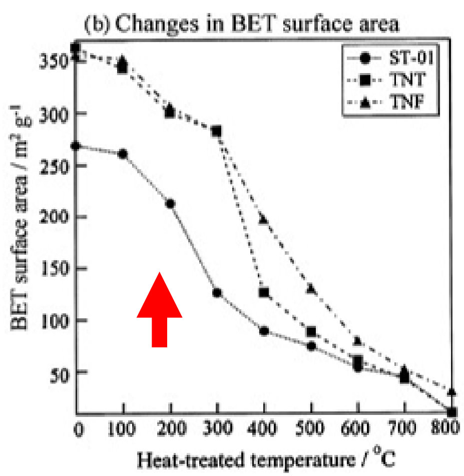
- 300µm entrance window
- 400 µm "target thickness"
- typical payload 20 mg
- front and rear side cooling
- water cooling
  or refrigerated He

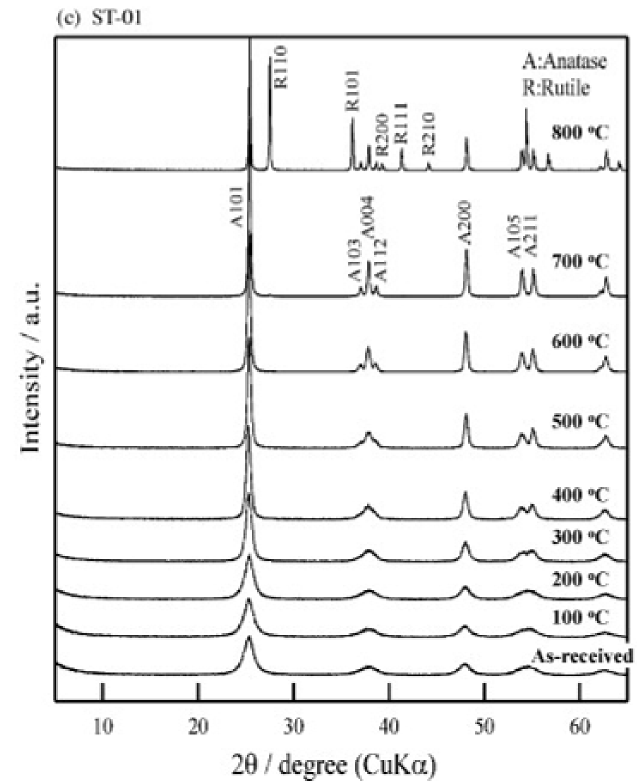
Thermal Effects - Sensitivity of NPs compared with more conventional powders

NPs are much more sensitive to temperature than micron-size powders and tend to aggregate, grow, and/or change phase at lower temperatures than larger mesh powders

TiO_2 melting point 1843℃, changes at ≈200 ℃

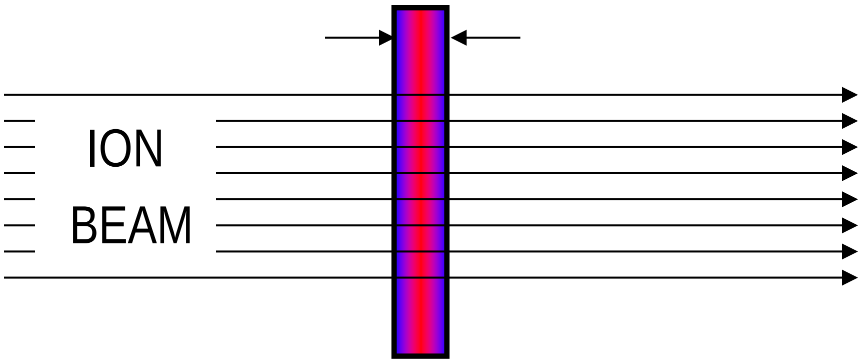




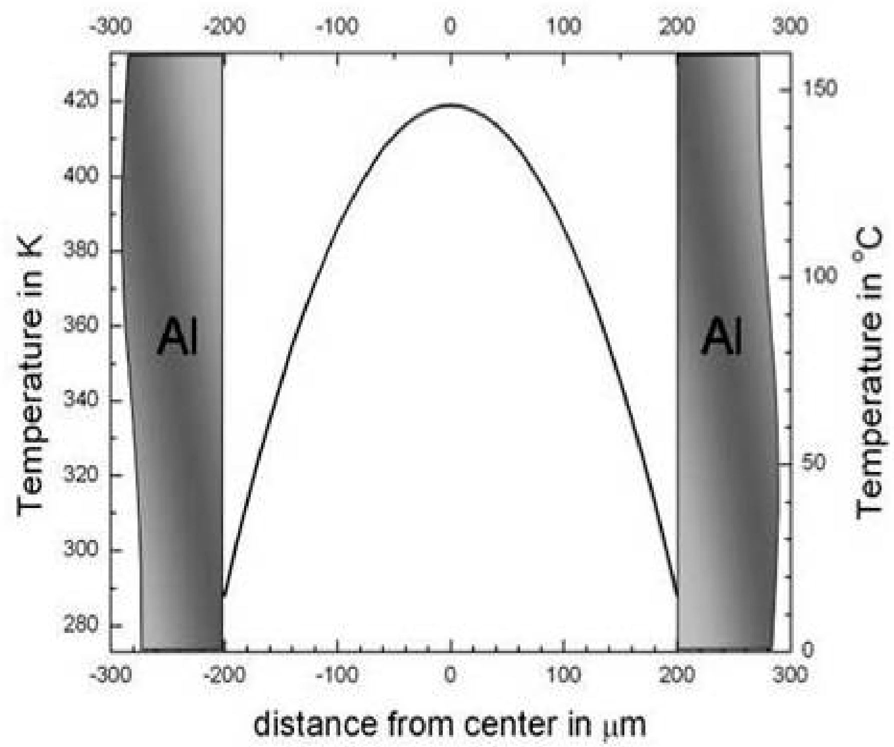


Ref: Inagaki et al.
J. Hazardous Materials 2009

Critically Important: Efficient Target Cooling



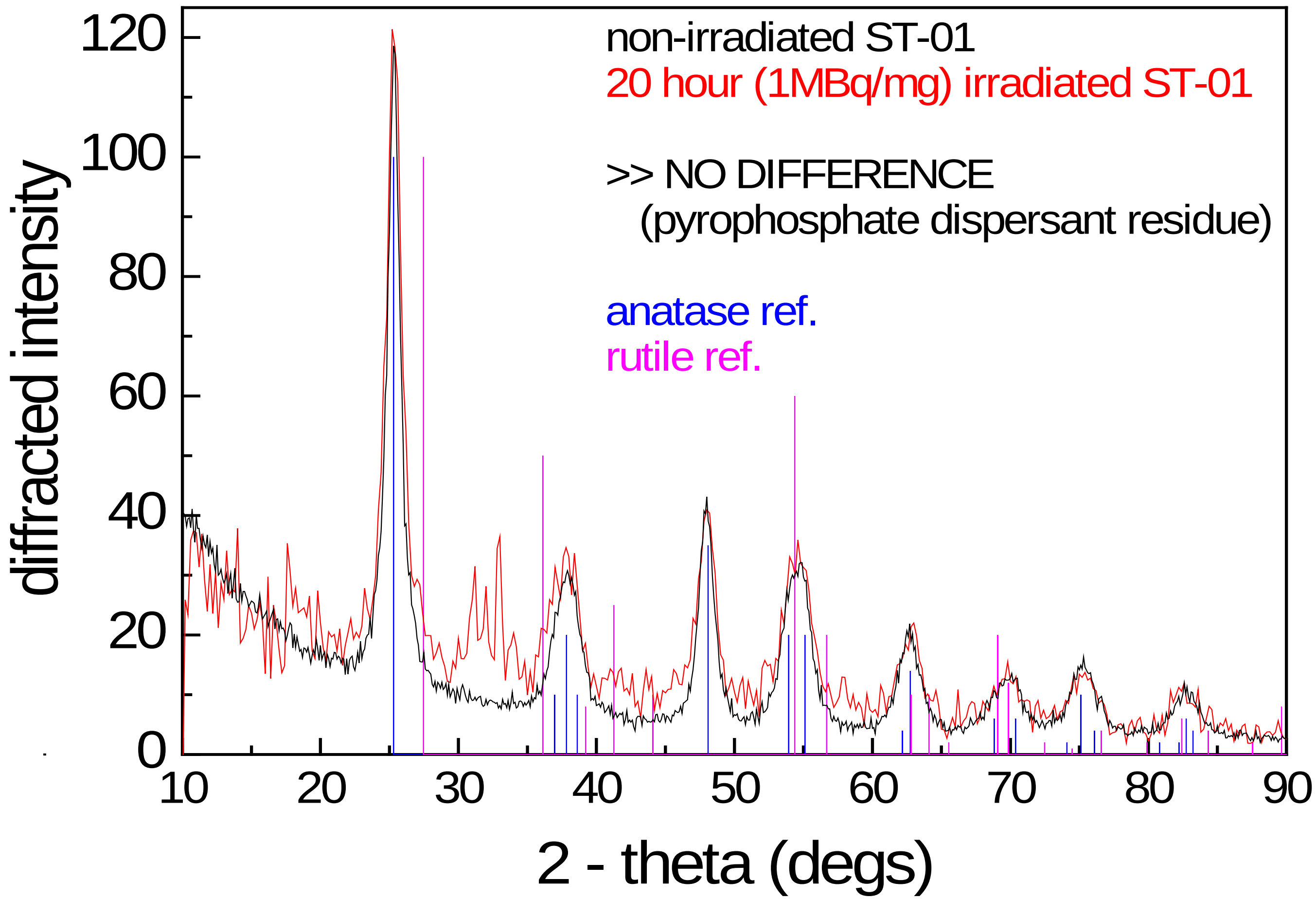
Problem: low density,
low thermal conductivity



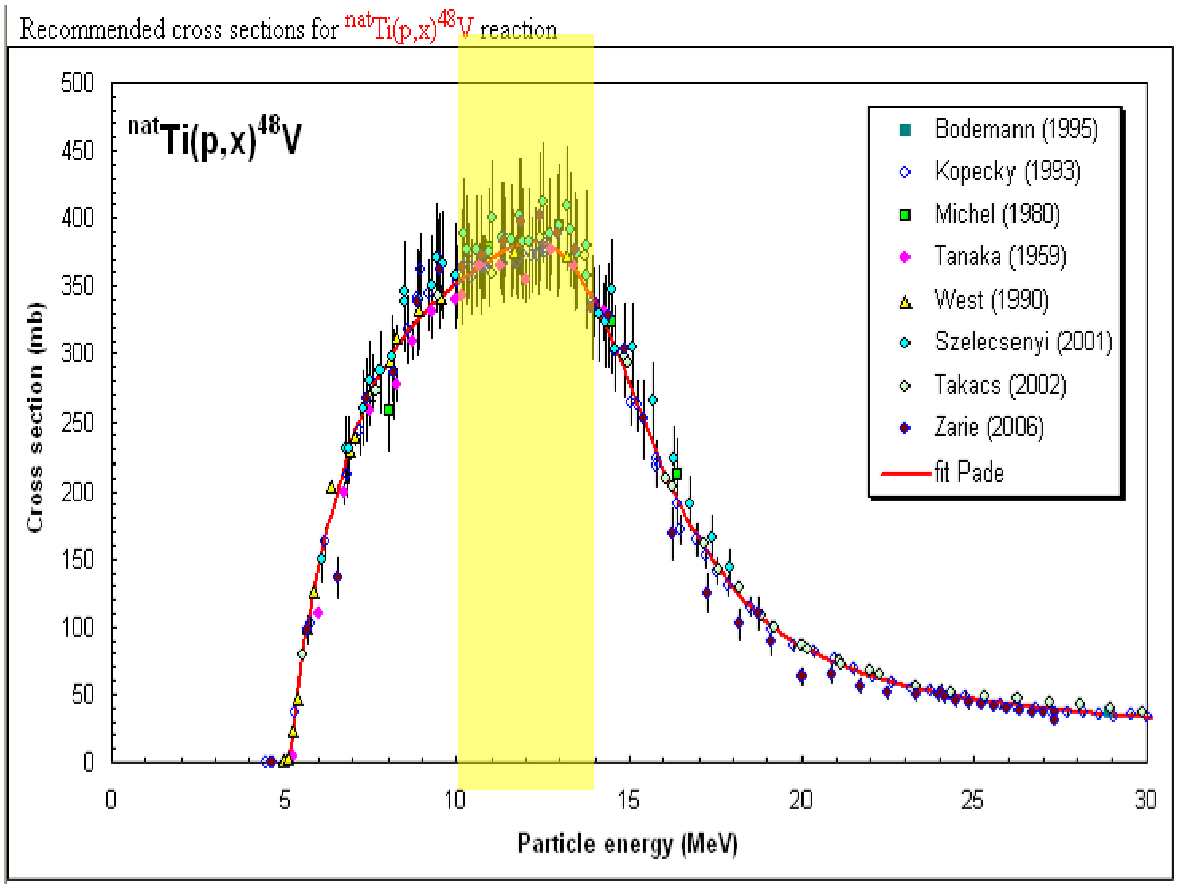
⇒ thin target capsule (l = 0.4 mm)

E_p^{in} = 14.5 MeV; E_p^{out} = 13.7 MeV, ΔE = 0.8 MeV, current = 5μA

XRD – Primary Beam Thermal Effects under Control



Thin target advantage – maximised yield per milligram



Data from IAEA NDS

highest yield

10 MeV $\leq E_p \leq$ 14 MeV

Q = - 4.795 MeV

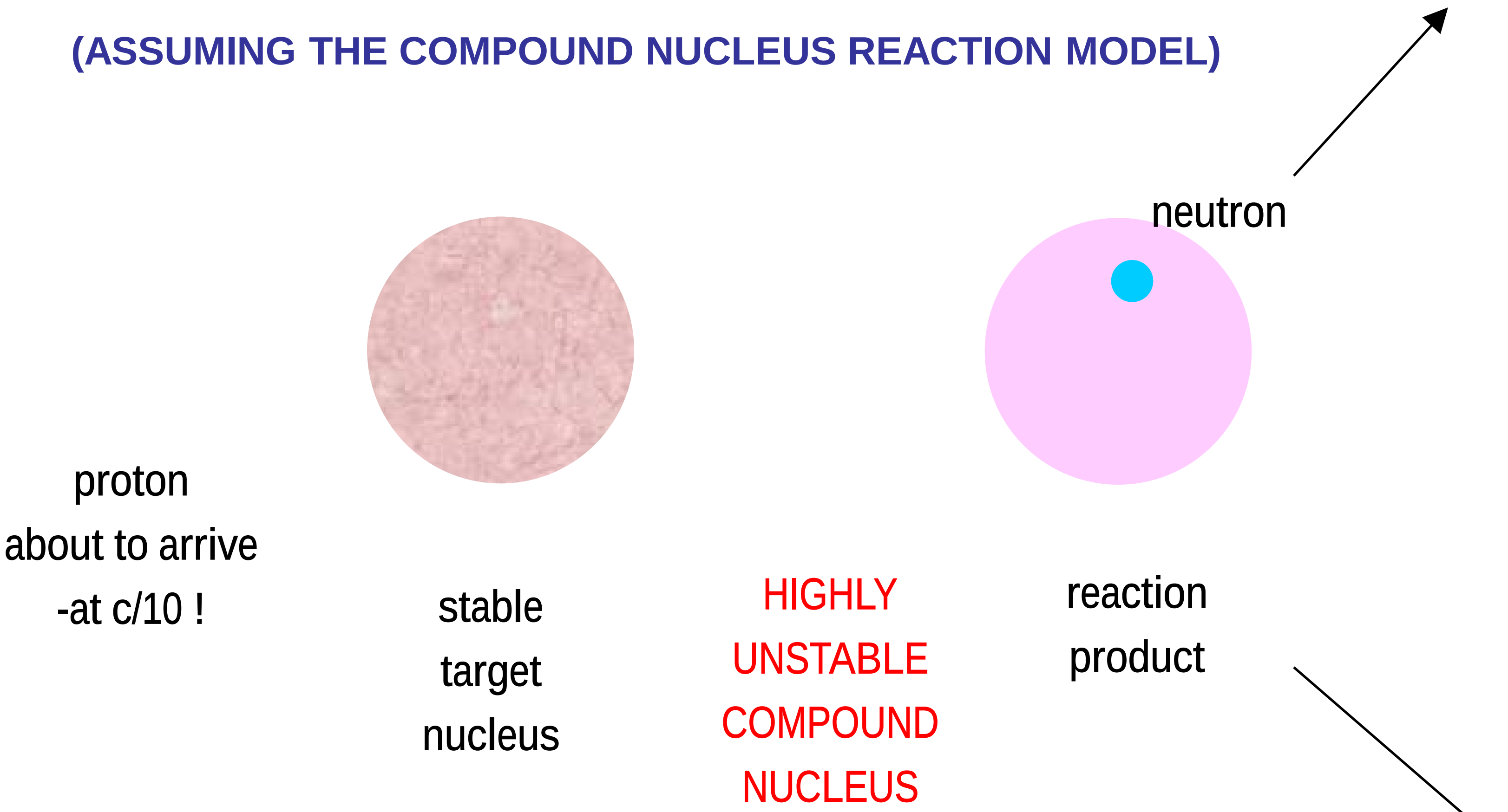
E_{thr} = 4.895 MeV

Interaction of projectiles with matter:

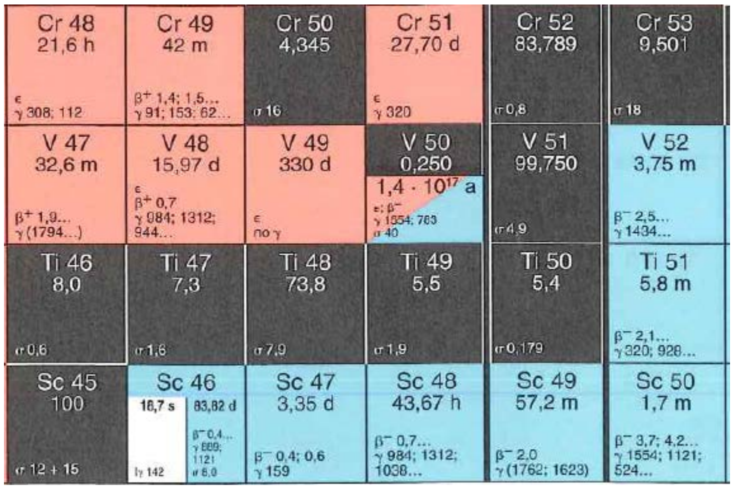
decreasing E_p with increasing penetration

Reaction kinetics – recoiling radiolabels: (p,n) reaction

(ASSUMING THE COMPOUND NUCLEUS REACTION MODEL)



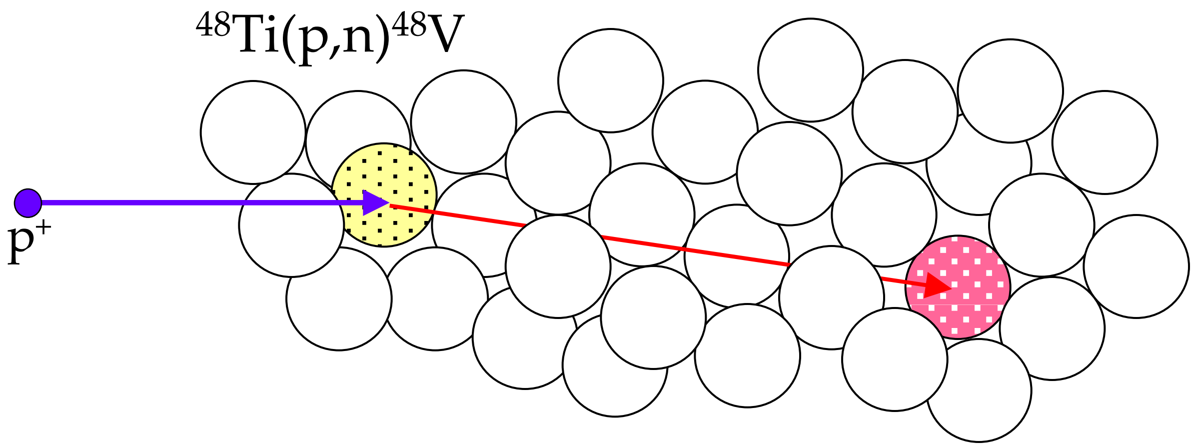
Reaction kinetics – recoiling radiolabels



Average range 150 nm for ^{48}V in TiO_2

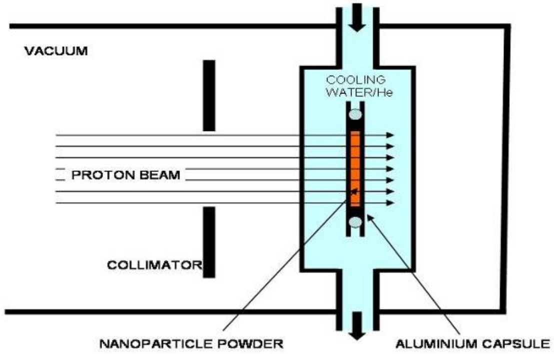
(1 μm in NP powder !)

<u>ONLY DRY POWDERS CAN BE ACTIVATED</u>



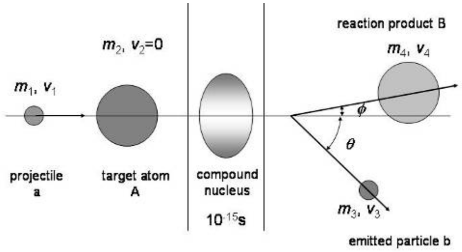
Radiation damage – by primary ion beam

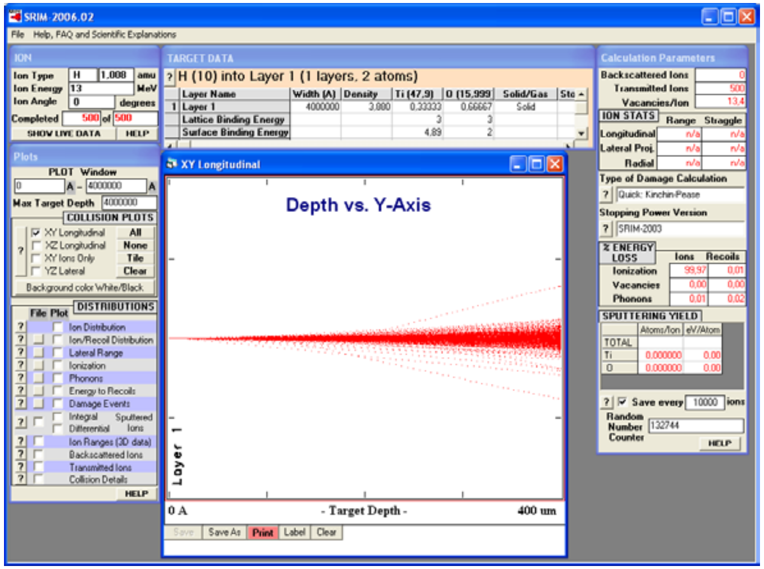
Most primary particles pass straight through the target slowing down by ionisation processes.



Some displace nuclei

(either colliding or reacting with) which in turn go on to displace others quite efficiently.





SRIM/TRIM calculations of this process are considered to be reliable

Radiation damage – by recoiled radiotracers

Is the labelled NP damaged by "end of track events"?

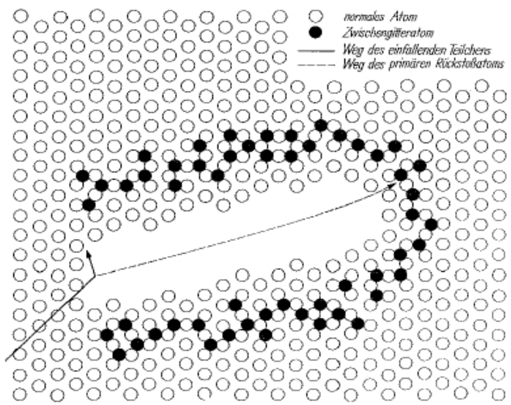
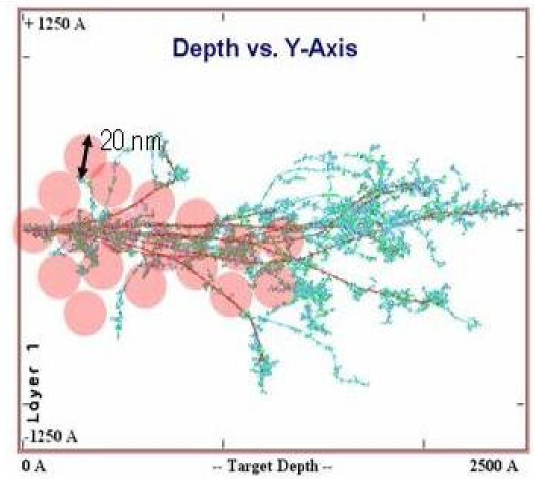
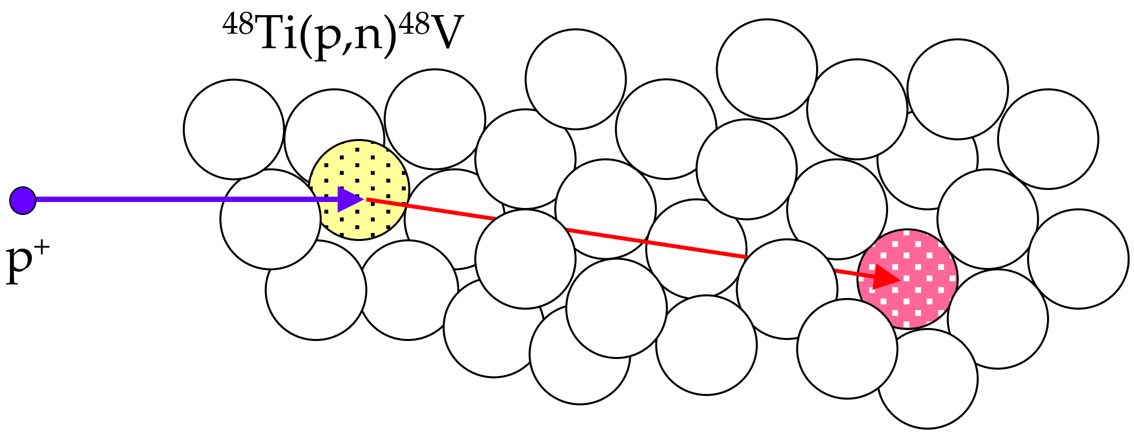


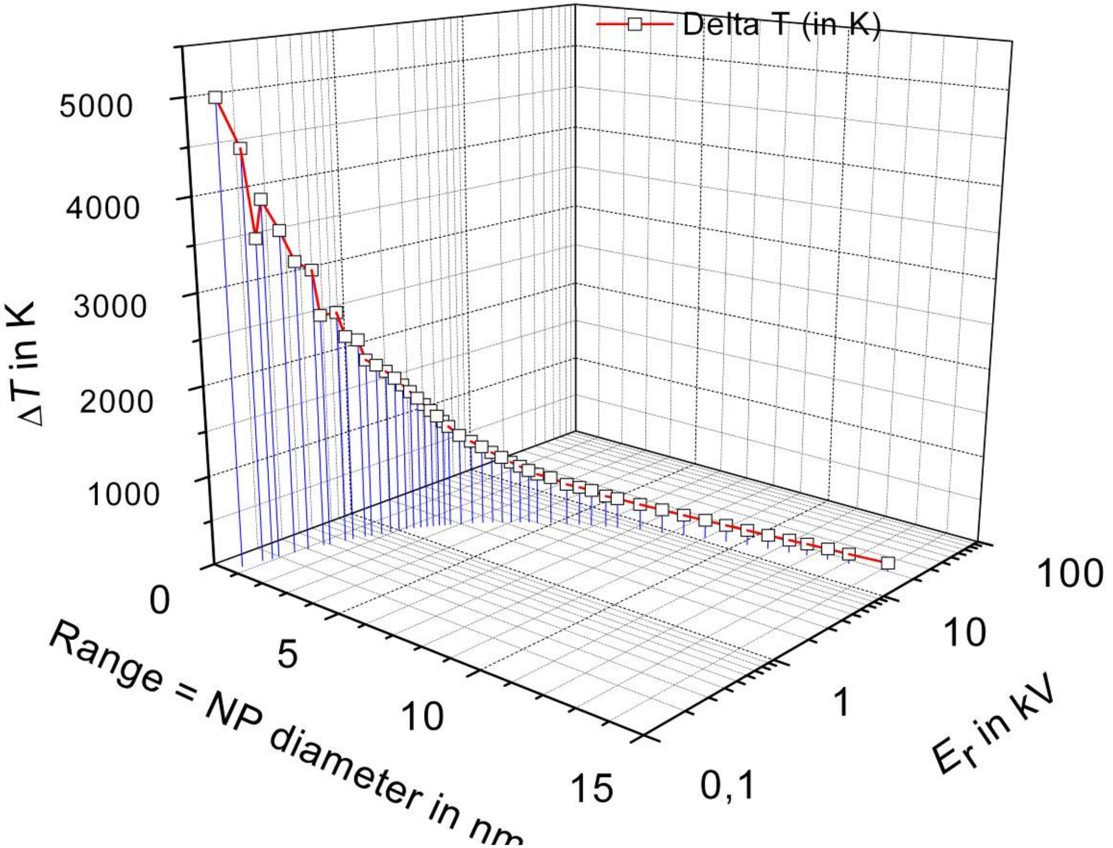
Fig. 20. Entstehung einer Brinkmanschen Verlagerungszone (displacement spike). Nach [91]





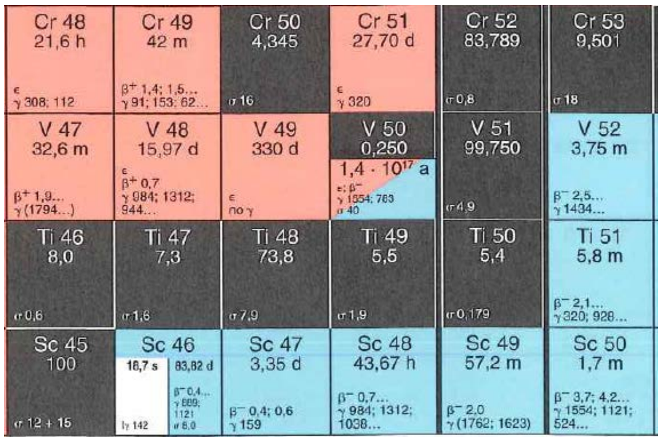
Calculations indicate that such collision damage will be very limited at useful levels of activation

Nanoparticle "nano-heating" by recoiled radiotracers: calculation of temperature rise by low energy recoils

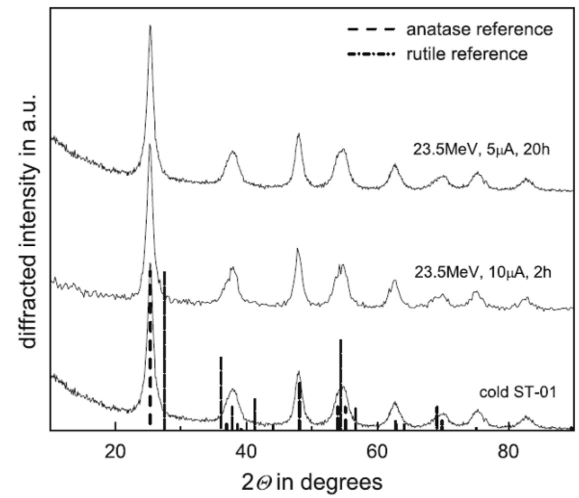


EXAMPLES

Direct proton activation of TiO_2 nanoparticles



ST-01 titania NPs
100% anatase
Size ~ 7 nm



Irradiation followed by size selection using dispersant, sonication and filtration

Sample 1
A = 500 kBq (^{48}V)
m = 0.4 mg TiO_2
V = 1.4 mL
Z-average = 107 nm, PDI = 0.18

Sample 2
A = 300 kBq (^{48}V)
m = 0.2 mg TiO_2
V = 1.8 mL
Z-average = 103 nm, PDI = 0.22

[^{48}V]TiO_2-NP
activity of
3 MBq/mg possible

J Nanopart Res (2010) 12:2435–2443
DOI 10.1007/s11051-009-9806-8

RESEARCH PAPER

Radiolabelling of TiO_2 nanoparticles for radiotracer studies

Kamel Abbas · Izabela Cydzik · Riccardo Del Torchio · Massimo Farina · Efrat Forti · Neil Gibson · Uwe Holzwarth · Federica Simonelli · Wolfgang Kreyling

J Nanopart Res (2012) 14:880
DOI 10.1007/s11051-012-0880-y

RESEARCH PAPER

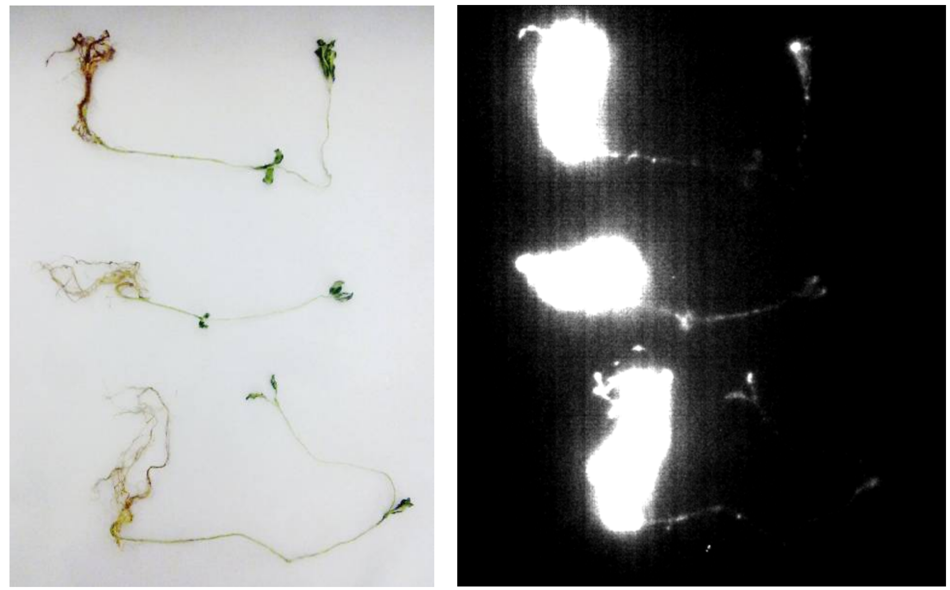
Radiolabelling of nanoparticles by proton irradiation: temperature control in nanoparticulate powder targets

Uwe Holzwarth · Antonio Bulgheroni · Neil Gibson · Jan Kozempel · Giulio Cotogno · Kamel Abbas · Federica Simonelli · Izabela Cydzik

Joint Research Centre

European Commission

[^{48}V]TiO_2-NP uptake studies in plants



Sunflower

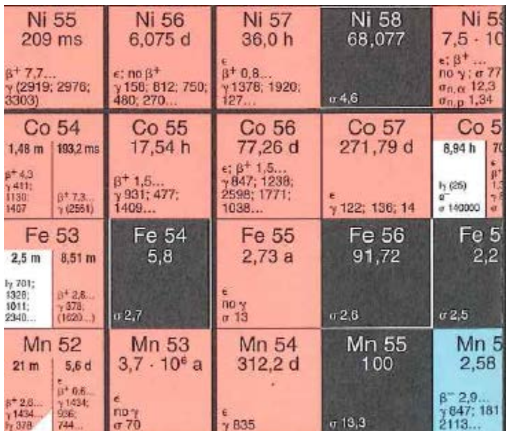
QNANO Research Infrastructure

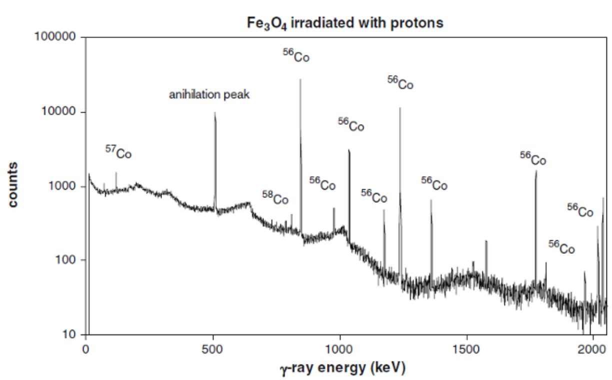
Stanislav Smrček
Jan Kozempel

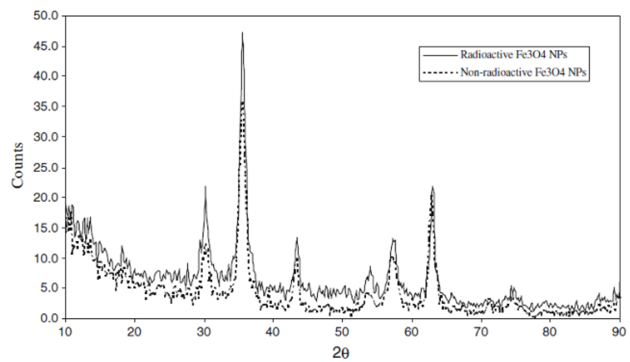
Charles Univ. in Prague

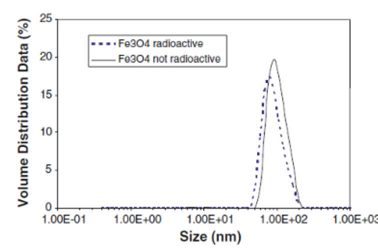
Joint Research Centre

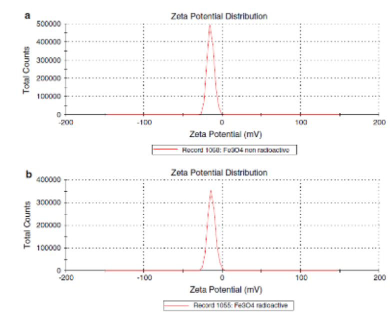
Direct proton activation of Fe_3O_4 nanoparticles











[^{56}Co]Fe_3O_4-NP
activity of
1 MBq/mg possible

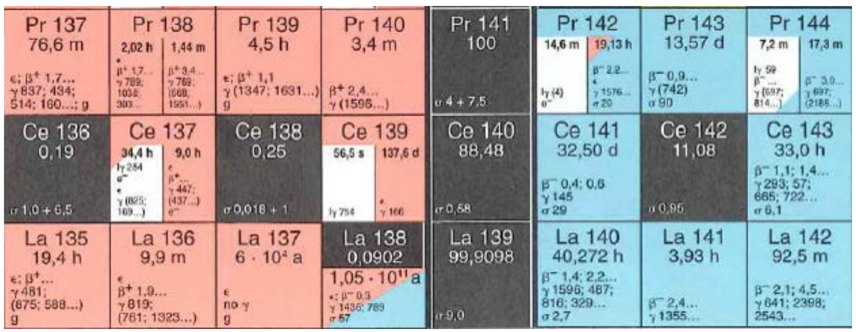
J Nanopart Res (2011) 13:6707–6716
DOI 10.1007/s11051-011-0577-7

RESEARCH PAPER

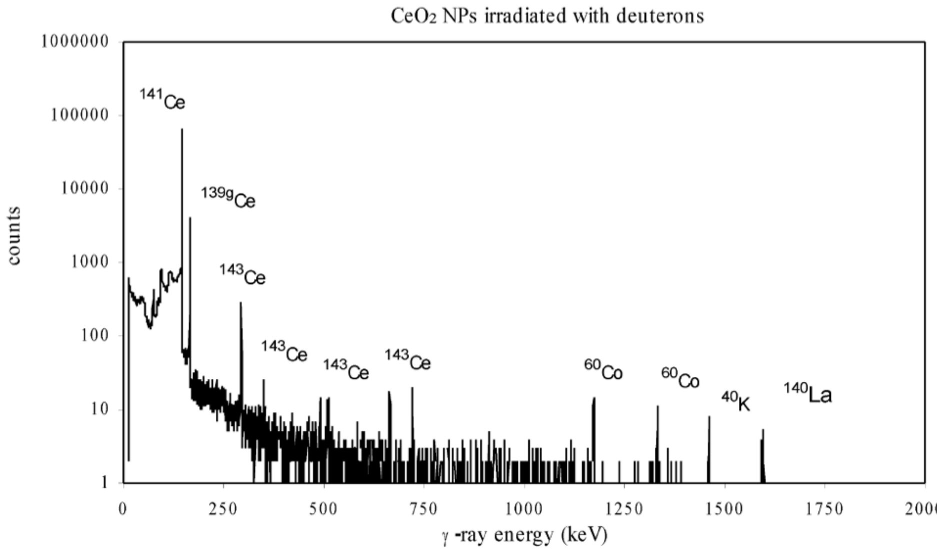
^{56}Co-labelled radioactive Fe_3O_4 nanoparticles for in vitro uptake studies on Balb/3T3 and Caco-2 cell lines

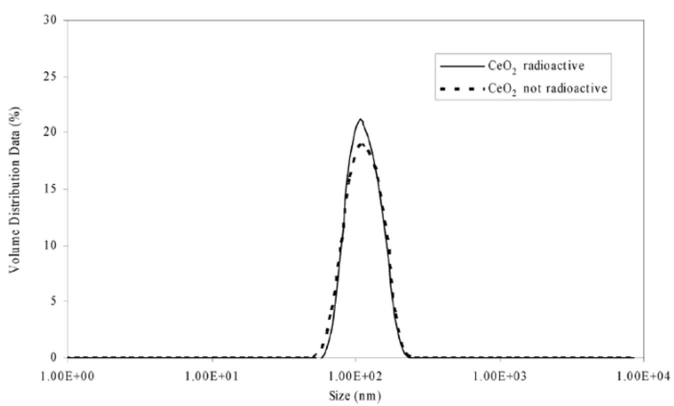
P. Marmorato · F. Simonelli · K. Abbas ·
J. Kozempel · U. Holzwarth · F. Franchini ·
J. Ponti · N. Gibson · F. Rossi

Direct activation with deuterons of CeO_2 nanoparticles



Deuteron irradiation used:
reactions: (d,p), (d,dn), (d,2p)





Deuteron irradiation requires lower currents to limit thermal effects, and chilled He instead of water cooling is necessary, so the activity concentration achievable is limited to about 200 kBq/mg.

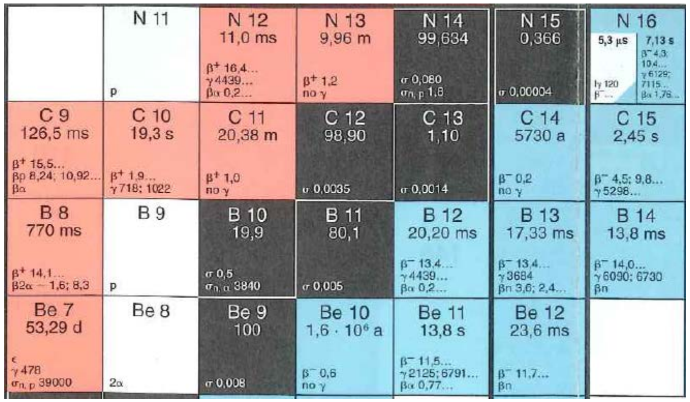
IEEE TRANSACTIONS ON NANOBIOSCIENCE, VOL. 10, NO. 1, MARCH 2011

Cyclotron Production of Radioactive CeO_2 Nanoparticles and Their Application for *In Vitro* Uptake Studies

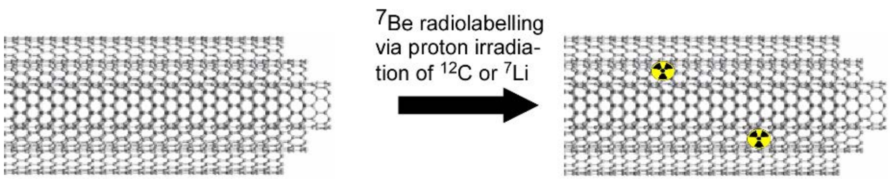
Federica Simonelli*, P. Marmorato, K. Abbas, J. Ponti, J. Kozempel, U. Holzwarth, F. Franchini, and F. Rossi

Joint Research Centre

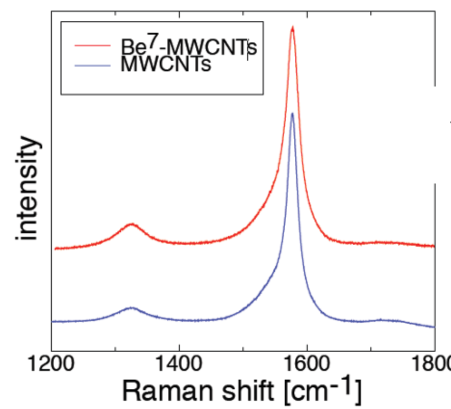
Direct activation of carbon-based nanoparticles



The (p,3p3n) or (p,3d) reaction has a reasonable cross section at high proton energies, creating ^{7}Be with a half-life of 53 days



Max. activity concentration achievable: few hundred kBq/mg.



Slight changes in D:G Raman band ratio


Applied Radiation and Isotopes 73 (2013) 44–48

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journal homepage: www.elsevier.com/locate/apradiso

ELSEVIER

Feasibility study of production of radioactive carbon black or carbon nanotubes in cyclotron facilities for nanobioscience applications

K. Abbas [a,*], F. Simonelli [b], U. Holzwarth [b], I. Cydzik [b,c], A. Bulgheroni [b], N. Gibson [b], J. Kozempel [d]


Strategies for the Radiolabelling of Carbon Nanoparticles

Stefan Schymura[1], Izabela Cydzik[2], Antonio Bulgheroni[2], Federica Simonelli[2], Uwe Holzwarth[2], Jan Kozempel[2], Karsten Franke[1], Neil Gibson[2]

[1] Institute of Resource Ecology, Reactive Transport Division, Helmholtz-Zentrum Dresden-Rossendorf, Germany
[2] Institute for Health and Consumer Protection, Nanobiosciences Unit (NBS), European Commission, DG Joint Research Centre, Ispra (VA), Italy

Nanosafe 2012
13.- 15. November
Grenoble - France

QualityNano

HZDR

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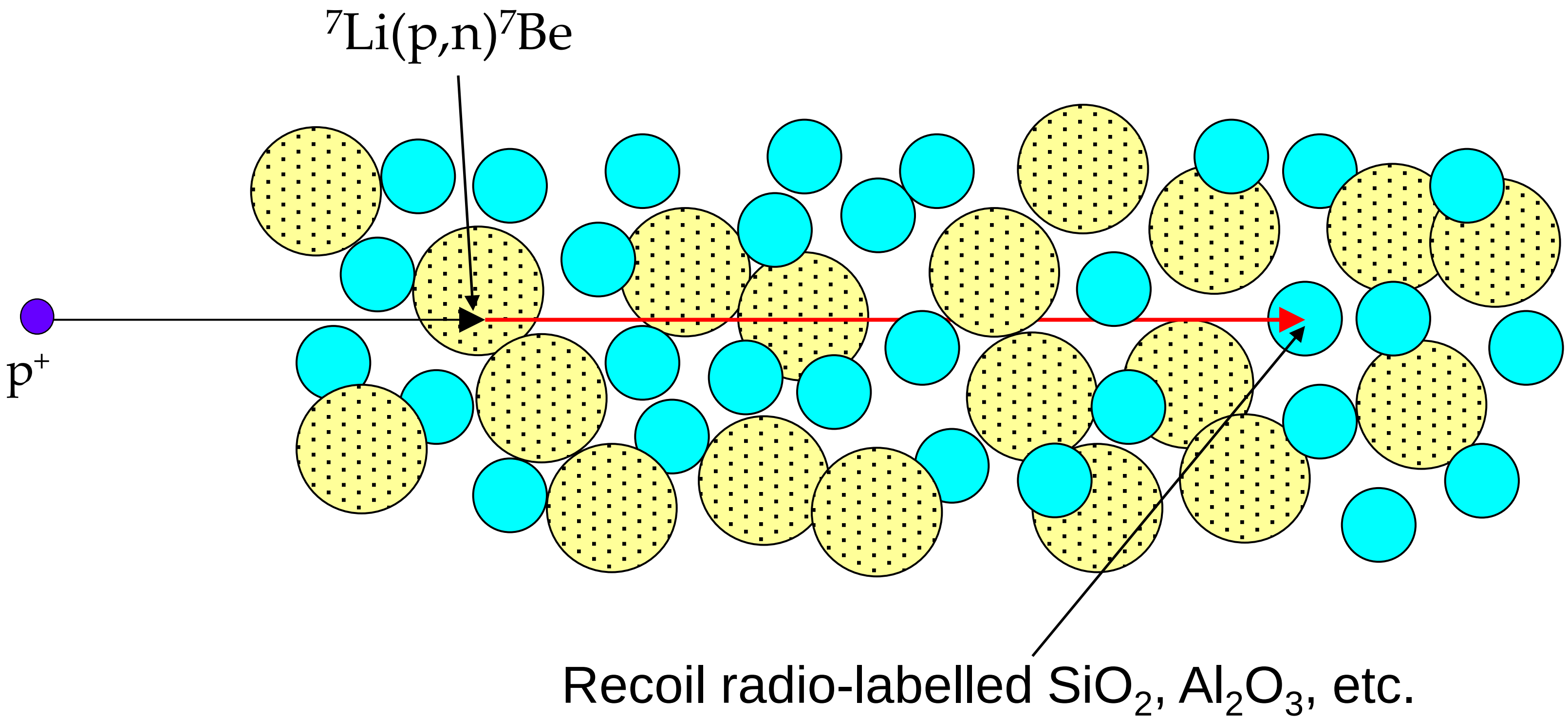
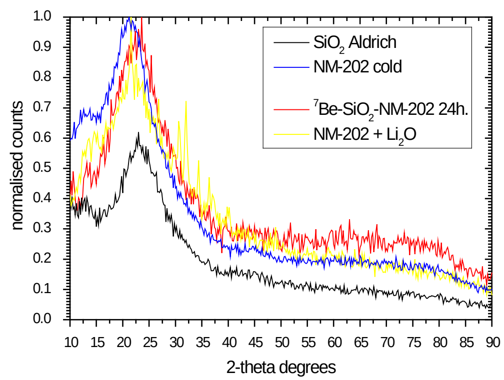
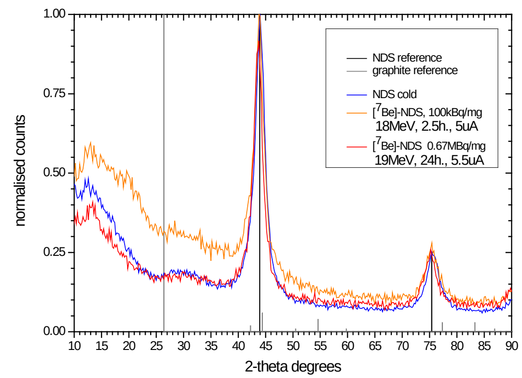
Not all NPs can be radiolabelled directly – e.g. SiO_2, Al_2O_3
→ recoil radio-labelling technique with Li-containing compound

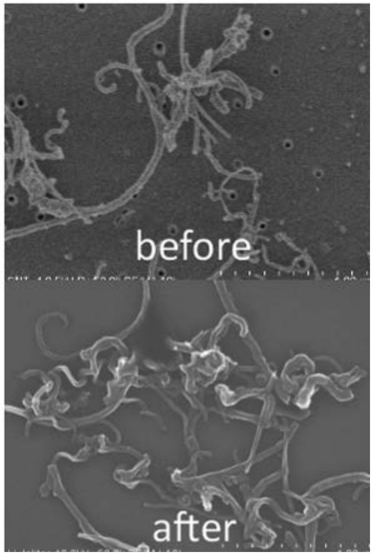


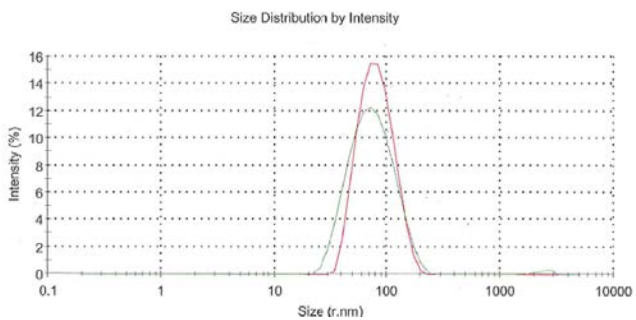
Subsequent separation by dissolution, filtration, centrifugation, ….

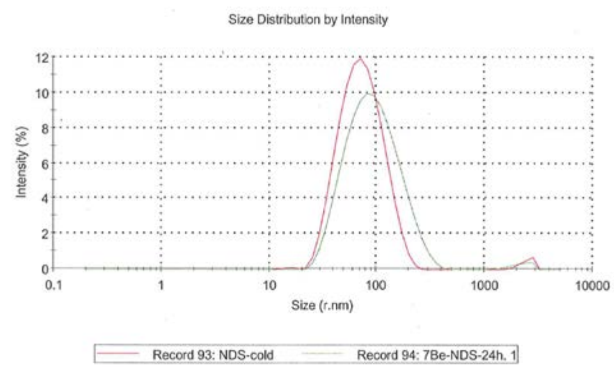
Recoil labelling of SiO_2 , nanodiamonds and MWCNTs

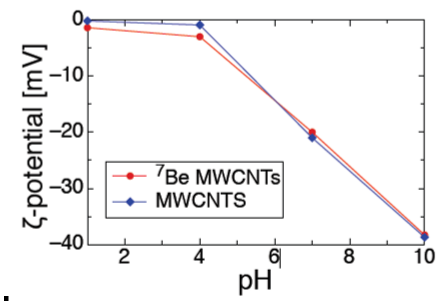












Still under study – labelling to 100 kBq/mg, possibly up to 1 MBq/mg.

European Commission

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DRESDEN concept

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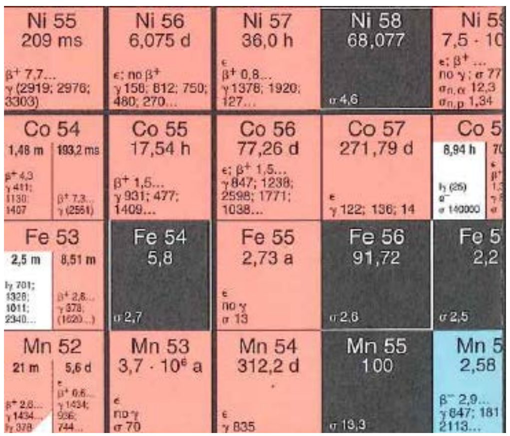
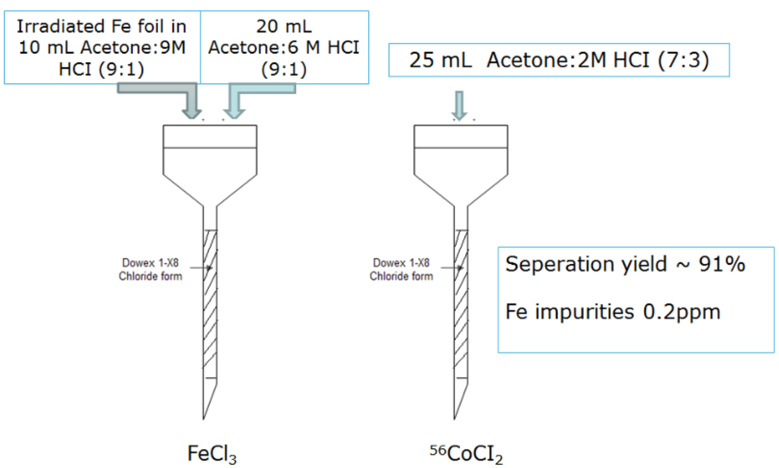
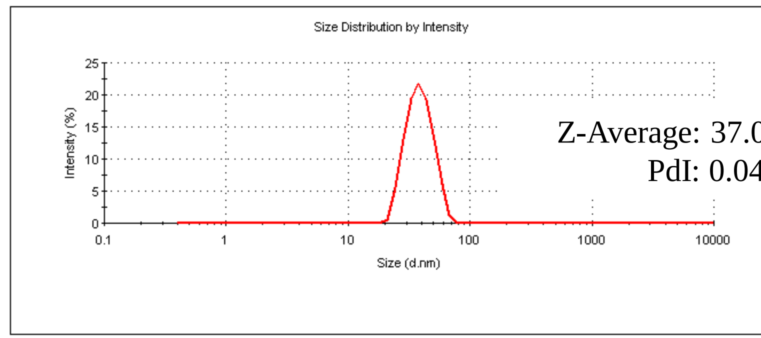
Research Infrastructure QualityNano

$[^{56}Co]SiO_2$ nanoparticles – radiochemical synthesis

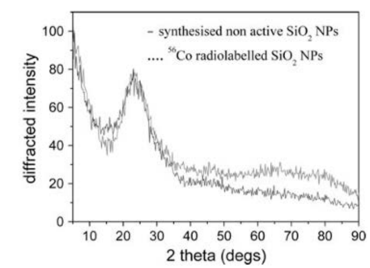




Radiochemical synthesis of SiO_2-NP via the Arginine Catalysis process



Radiochemical synthesis of SiO_2-NP via the Stöber process



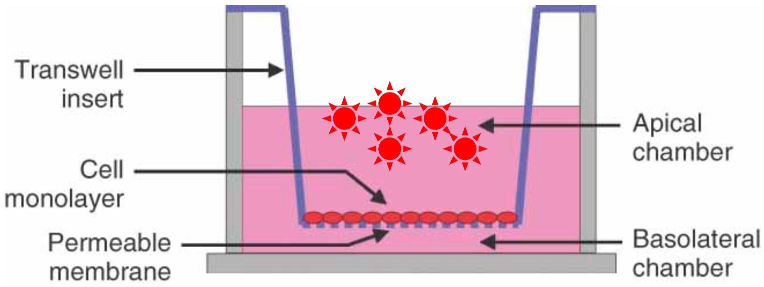
J Nanopart Res (2012) 14:1185
DOI 10.1007/s11051-012-1185-x

RESEARCH PAPER

A novel method for synthesis of ^{56}Co-radiolabelled silica nanoparticles

I. Cydzik · A. Bilewicz · K. Abbas · F. Simonelli · A. Bulgheroni · U. Holzwarth · N. Gibson

NP passage across in vitro intestinal barrier



Nanoparticles: $^{56}Co\text{-}SiO_2$ NPs

Sizes: 20 nm, 40 nm or 100 nm

Conc.: 100 µg/ml

Samples collected at:
2 hrs, 6 hrs, 24 hrs, 48 hrs and 72 hrs.

Fractions analyzed using gamma spectroscopy:

A: medium from apical side

B: medium from basolateral side

C: PBS wash

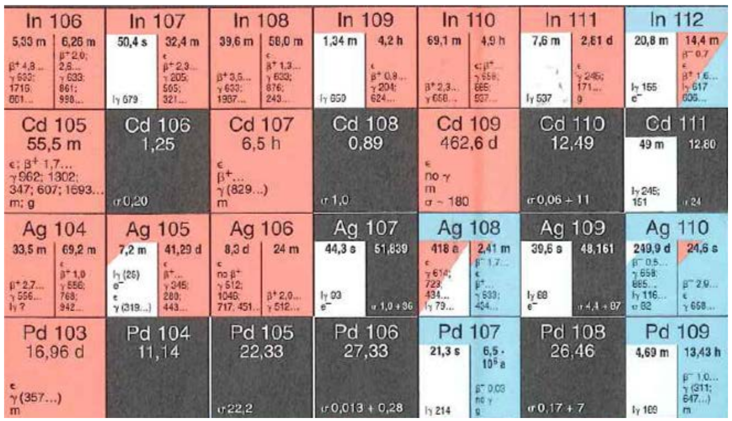
D: whole filter (with or without cells)

Caco-2 is a cell line derived from human epithelial colorectal adenocarcinoma, used as a model for the intestinal barrier

JRC/IHCP Nanobiotechnology Group
Agnieszka Kinsner-Ovaskainen et al.

European Commission

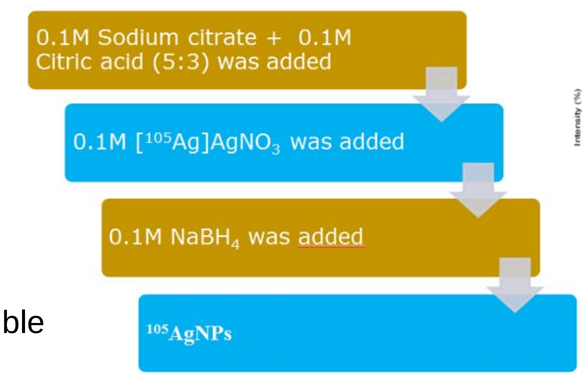
Ag nanoparticles – radiochemical synthesis

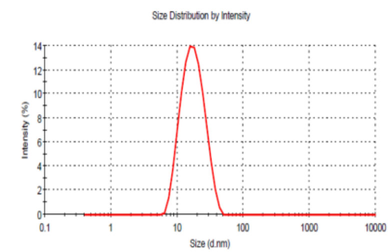


$^{107}Ag(p,3n)^{105}Cd \longrightarrow {}^{105}Ag\ (t_{1/2} = 41.29d)$

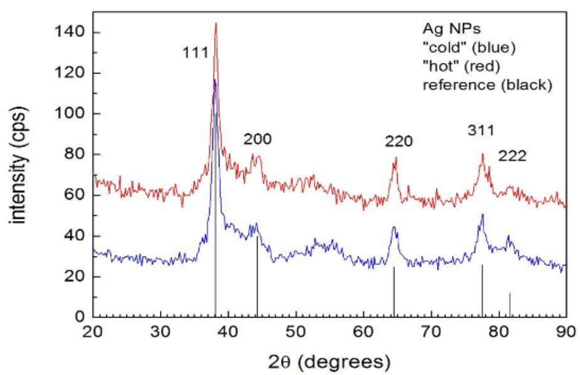
$^{107}Ag(p,p2n)^{105}Ag$

[^{105}Ag]$AgNO_3$ from Ag foil: foil dissolved in nitric acid and left to dissolve forming silver nitrate





[^{105}Ag]Ag-NP in water
Z-Average (nm): 17.20
PdI: 0.215
Zeta Potential: -32.9 mV



[^{105}Ag]Ag-NP activity of >1 MBq/mg possible

J Nanopart Res (2013) 15:2073
DOI 10.1007/s11051-013-2073-8

RESEARCH PAPER

Radiochemical synthesis of ^{105g}Ag-labelled silver nanoparticles

C. Ichedef · F. Simonelli · U. Holzwarth · J. Piella Bagaria · V. F. Puntes · G. Cotogno · D. Gilliland · N. Gibson

Joint Research Centre

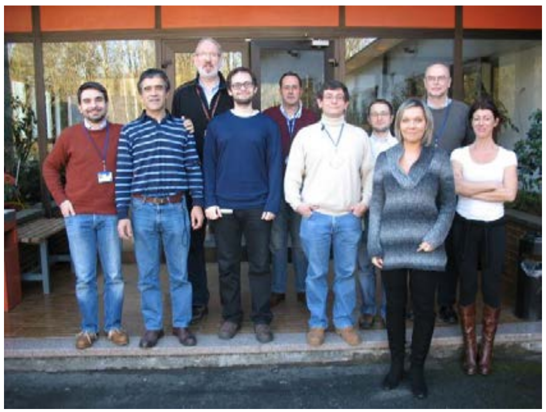
The future

- At the end of 2014 the JRC Ispra Cyclotron Facility will be transferred to the JRC Nuclear Decommissioning Service.
- The IHCP Nanobiosciences Unit intends to keep (at least for some years) an activity running on nanoparticle radiolabelling and in vitro studies – if we can retain access to an appropriately equipped controlled zone.
- In 2014 (and beyond) we will be happy to try to stimulate contacts between “users” and “suppliers” of radiolabelled NPs, and to support potential suppliers to gear up for NP radiolabelling.
- We will probably become a “user” – sometimes requiring directly activated NPs and sometimes irradiated foils or powders with which to synthesise NPs here.

→ opportunities for collaboration?

European Commission

Thanks to all co-workers, past and present!



Kamel Abbas	**Wijbe Horstmann**
Fernando Arroja	**Jan Kozempel**
Izabela Cydzik	**Antonio Bulgheroni**
Federica Simonelli	**Cigdem Ichedef**
Hans Hofman	

Uwe Holzwarth
Giulio Cotogno
Matteo Dalmiglio
Elena Bellido Vera

… and thanks for your attention

Arch Toxicol (2011) 85:751–773
DOI 10.1007/s00204-011-0701-6

INORGANIC COMPOUNDS

Radiolabelling of engineered nanoparticles for in vitro and in vivo tracing applications using cyclotron accelerators

N. Gibson · U. Holzwarth · K. Abbas · F. Simonelli · J. Kozempel · I. Cydzik · G. Cotogno · A. Bulgheroni · D. Gilliland · J. Ponti · F. Franchini · P. Marmorato · H. Stamm · W. Kreyling · A. Wenk · M. Semmler-Behnke · S. Buono · L. Maciocco · N. Burgio

Joint Research Centre