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Dosimetry and Epidemiology: Validation of RBE values for alpha particles

James Marsh, Dominique Laurier, Alan Birchall, Eric Blanchardon and Margot Tirmarche.

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Structure of talk

- Introduction

- Comparison of risks from alpha and external radiation

  - Lung cancer

    — French uranium miner studies
    — Plutonium workers study (Mayak nuclear facility, Russia)

    } Dosimetry

  - Liver cancer and leukaemia

    — Studies of thorotrast patients

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Differences between internal and external dosimetry

- The source of irradiation is the decay of radionuclides in one or more of the organs of the body
- Internal doses can’t be measured directly (and so models have to be used extensively)
- Internal doses are protracted over time
- Short range (non-penetrating) radiation (α, β, etc.) make a significant contribution to internal dose
- The distribution of absorbed dose between organs is often very inhomogeneous
- Heterogeneous exposure to organs

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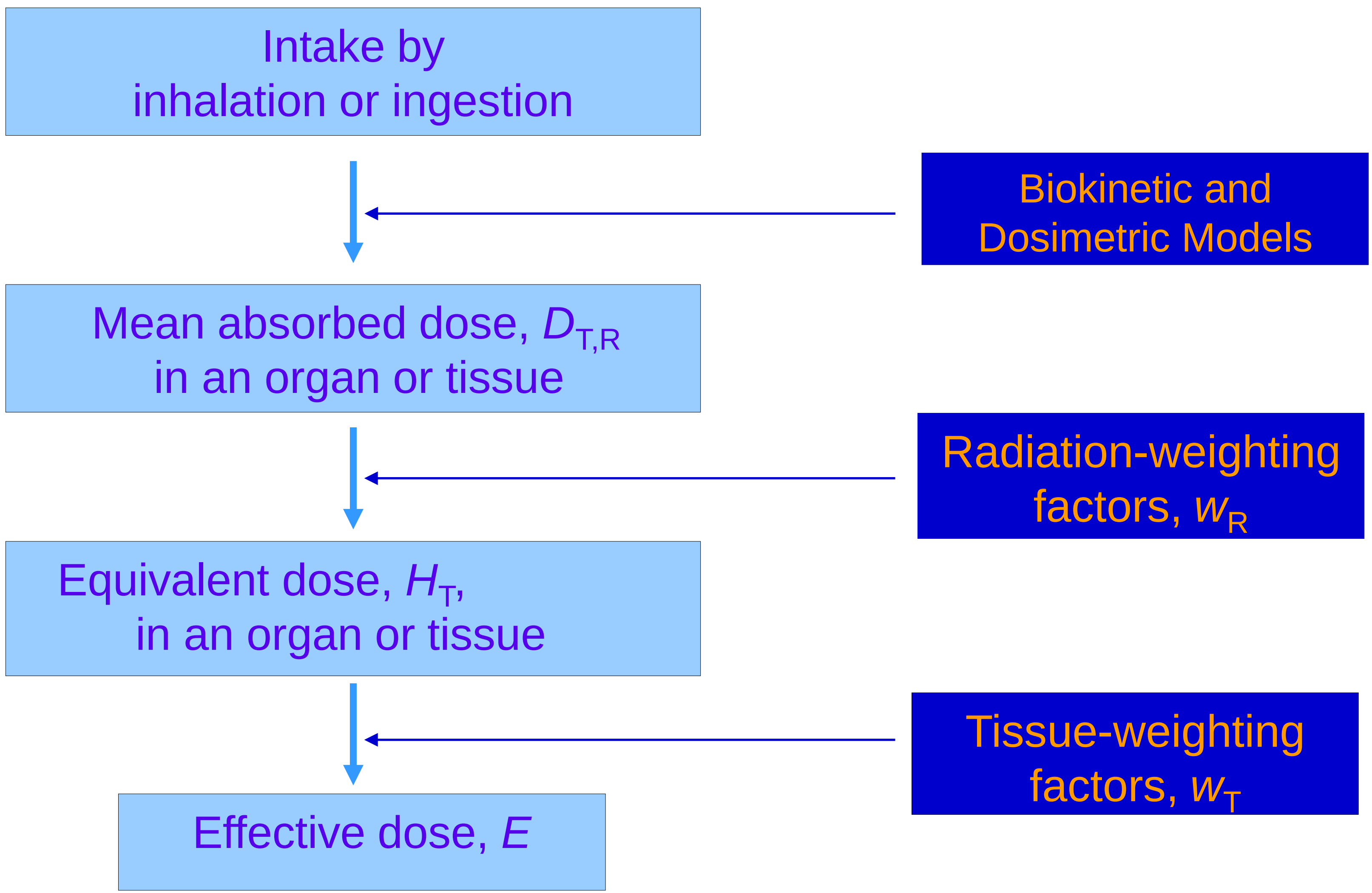
Effective dose

- Applies to stochastic effects only
- Assumes no threshold
- Allows summation of doses from different radionuclides, and with external dose
- Allows comparison with dose limits / constraints

Calculation of equivalent and effective dose for internal emitters



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Weighting factors – simple risk adjustments

Radiation weighting factors, W_R

W_R = 1 for all low-LET radiation (e.g. gamma)

W_R = 20 for alpha particles for all types of cancer.

- Based on relative biological effectiveness (RBE) of alpha particles compared to gamma

Tissue weighting factors, W_T

Simple set of fractions which apply to all ages and both sexes.

- Based on relative detriment of individual organs from stochastic effects

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Comparison of Excess Relative Risk (ERR) values

Japanese A-Bomb survivors

Life Span Study (LSS)

Epidemiological study

Exposed to gammas

Calculation of absorbed dose to organ from internal alpha emitter

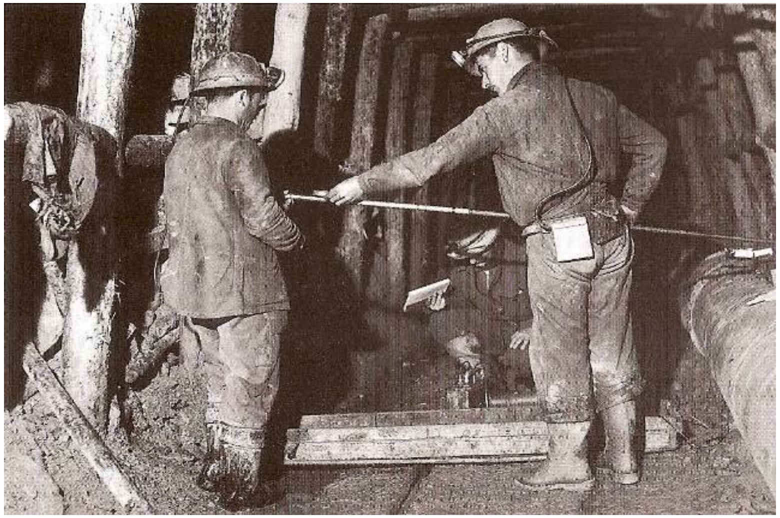
ERR per Sv

ERR per Gy

Estimation of RBE of alpha particles for the induction of a given cancer type

Lung cancer risks

Epidemiological studies have provided values of excess relative risks (ERR) per unit absorbed lung dose from alpha radiation:



- Uranium miners, France

(Rage et al. 2012. Radiation Research 177, 288-297)

- Plutonium workers at the Mayak nuclear facility, Russia

(Gilbert et al. 2013. Radiation Research 179, 332-342)

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Uranium miner dosimetry

A miner is exposed to:

- Radon progeny
- Radon gas
- Long-lived radionuclides (LLR) in the uranium ore dust
  [e.g. ^{238}U, ^{234}U, ^{230}Th, ^{226}Ra, ^{210}Po]
- External gamma radiation

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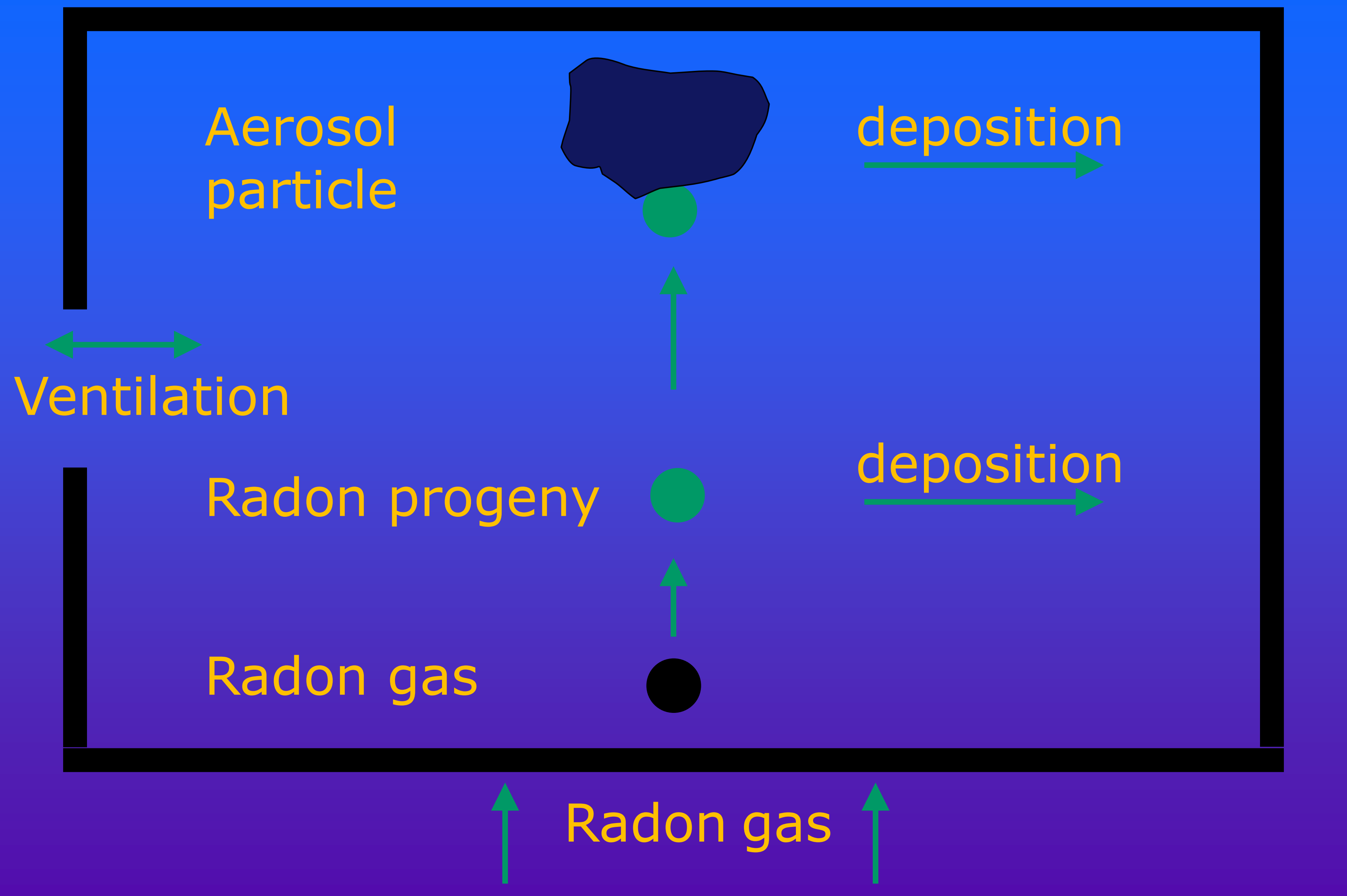
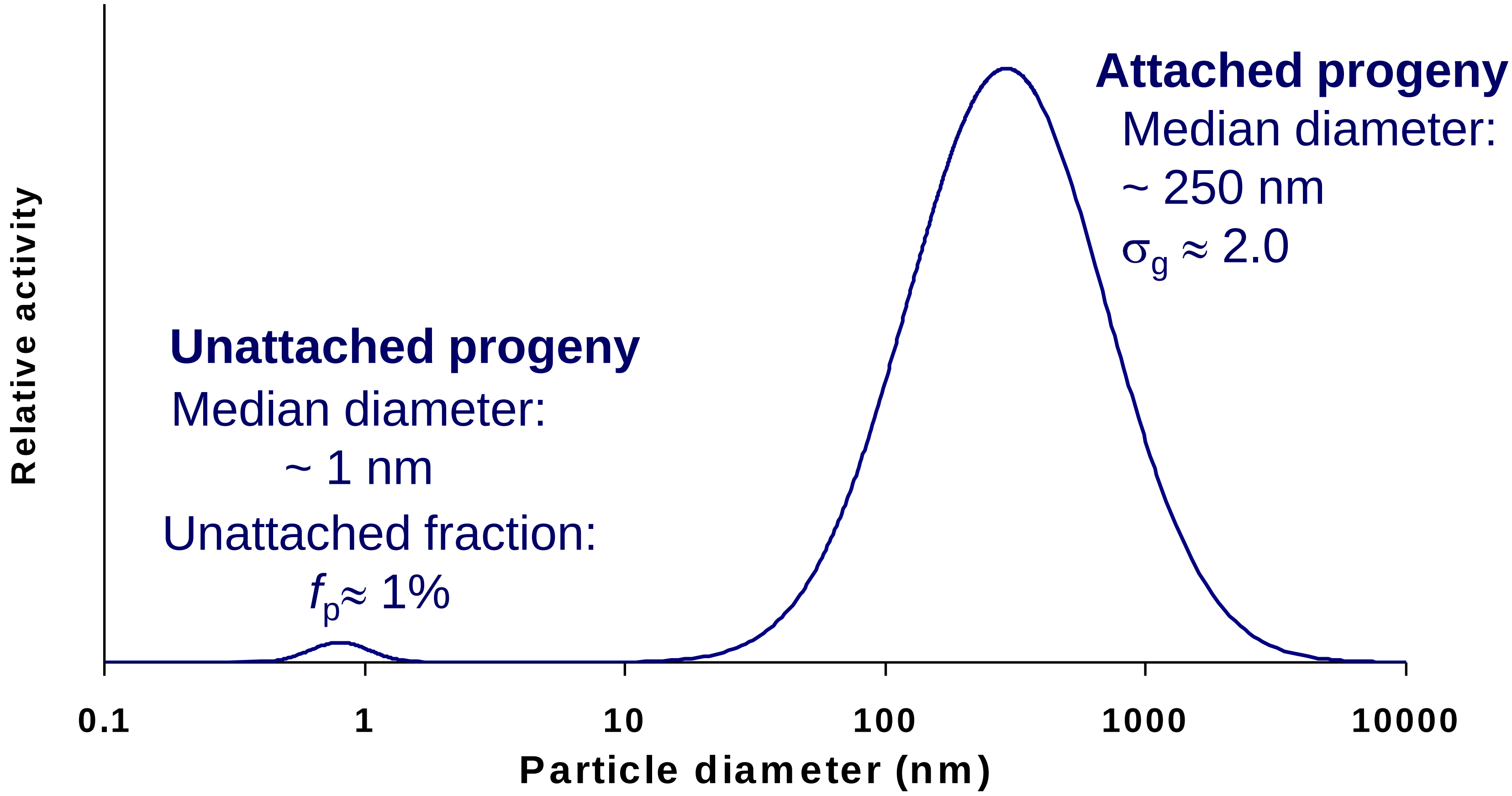
Decay chain

Radon gas	^{222}Rn	3.8 d
	↓	
Polonium	^{218}Po	3 min
	↓ α	
Lead	^{214}Pb	27 min
	↓	
Bismuth	^{214}Bi	20 min
	↓	
	^{214}Po	160 μs
	↓ α	
	^{210}Pb	22 y

Formation of radon progeny aerosol



Activity size distribution of a radon progeny aerosol in a mine



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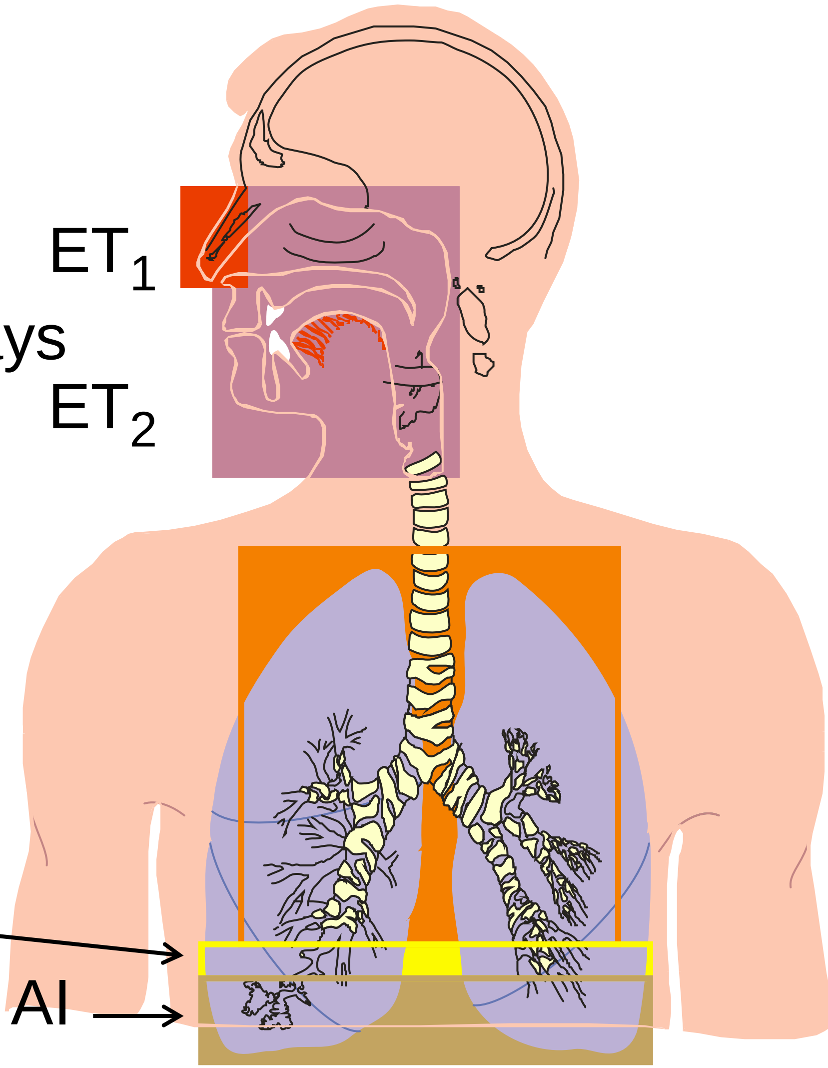
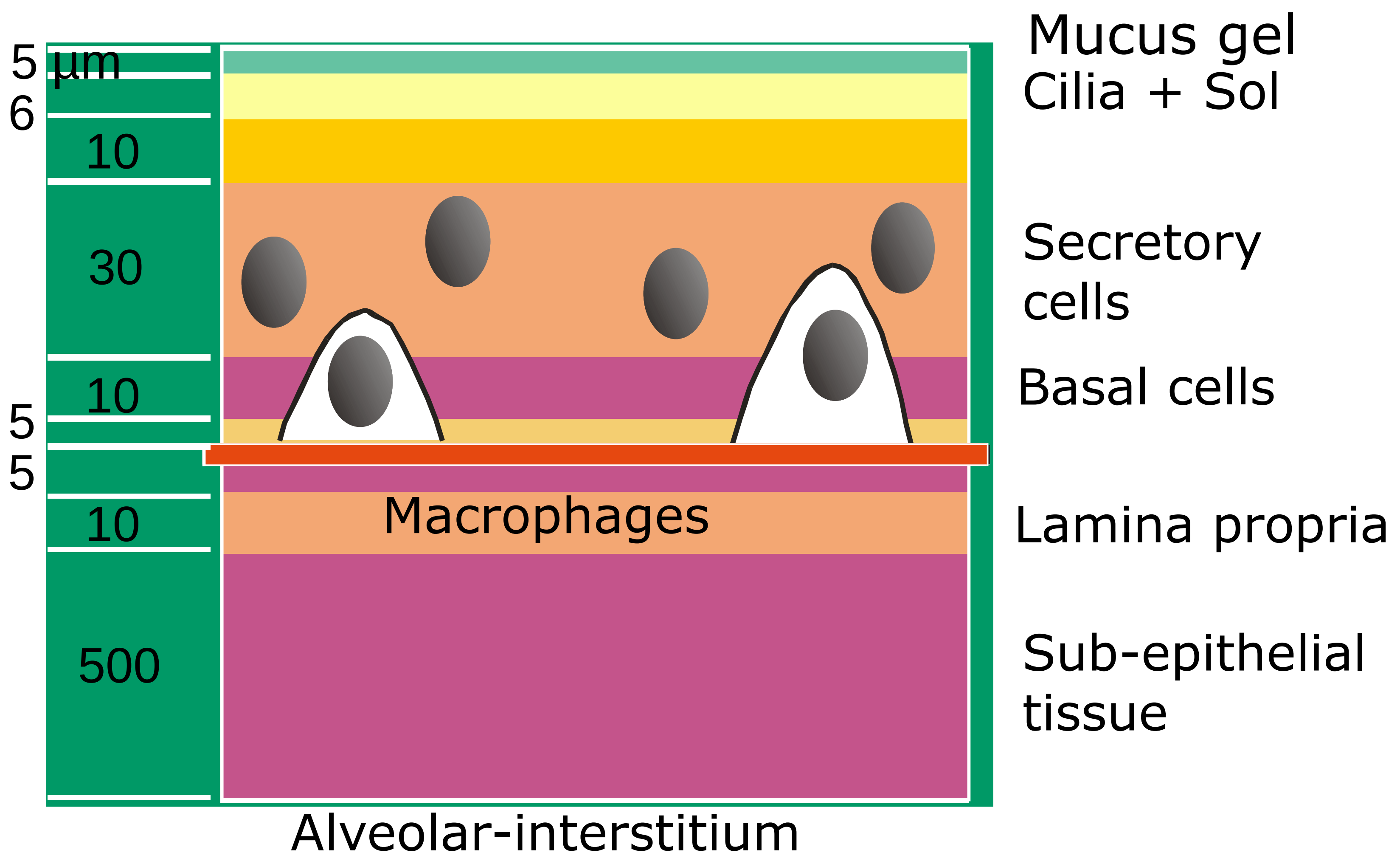
Human Respiratory Tract Model (HRTM), ICRP Publication 66



Bronchial (BB) Wall for Dosimetry



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Absorbed dose to lung

Absorbed dose is calculated to each of the 3 regions

- bronchial region (BB): $D_{BB} = ½ (D_{bas} + D_{sec})$
- bronchiolar region (bb): D_{bb}
- Alveolar-Interstitial region (AI): D_{AI}

Detriment-weighted absorbed lung dose,

- $D_{lung} = D_{BB} A_{BB} + D_{bb} A_{bb} + D_{AI} A_{AI}$

Where A_i = the apportionment factor representing the regional's estimated sensitivity to radiation induced lung cancer relative to that of whole lung.

Regional distribution of spontaneous lung cancers in general population is:
0.6 for BB; 0.3 for bb; 0.1 for AI (ICRP 66, para. 113)

$A_{BB} = 0.333$; $A_{bb} = 0.333$; $A_{AI} = 0.333$

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Detriment-weighted absorbed lung dose from inhalation of radon progeny for a miner

Region	Absorbed dose (mGy/WLM)	Fractional contribution
Bronchial ($D_{BB} = 0.5\ D_{sec} + 0.5\ D_{bas}$)	6.7	48%
Bronchiolar (D_{bb})	7.0	49%
Alveolar interstitial (D_{AI})	0.40	3%
Detriment-weighted absorbed lung dose	4.7	

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Uncertainties in radon dosimetry

For a given radon exposure there are dosimetric uncertainties associated with:

- Breathing rates
- Activity size distribution of the inhaled aerosol (including f_p)
  - ➢ Highly variable conditions in mines
    - ➢ Different ventilation rates in mines,
    - ➢ Use of diesel or electrical powered equipment
    - ➢ Type of heating: - Ventilation air is heated by burning propane gas
- Dosimetric model of the respiratory tract
  - ➢ Depth and location of target cell regions
  - ➢ Variability in bronchial airway dimensions and filtering efficiency of nasal passages

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Mean absorbed lung doses for the French uranium miner cohort (Rage, et al. 2012)

Cohort: 3,377 miners; 66 lung cancer deaths

	Absorbed dose, mGy	% of total	% of alpha dose
External gamma (low-LET radiation)	56	42%	
Alpha radiation	78	58%	
Radon gas	1.5		2%
Radon progeny	76		97%
Long-lived radionuclides in uranium ore dust	1.0		1%

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Estimation of RBE values of alpha particles for induction lung cancer

Comparison with risk estimates from life span study (LSS) of Japanese A-bomb survivors

French uranium miner cohort (Rage, et al., 2012)

Alpha: ERR per Gy: 4.5 (95% CI: 1.3 – 11)

	ERR per Sv	Inferred RBE
Gamma		
LSS mortality data	0.48 (0.23-0.78)	9
LSS incidence data	0.28 (0.12-0.49)	16

Large uncertainties in the Life Span Study estimates

- **Data also consistent with a large range of RBE values (e.g. 3 and 30)**

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Mayak workers dosimetry system 2008 (MWDS-2008)

Assessed intakes and doses from urine data only

- Assumed urine data were lognormally distributed with a given GSD

Models:

- Leggett's plutonium systemic biokinetic model
- Modified ICRP Publication 66 Human Respiratory Tract Model (HRTM)
  - Autospy data showed greater activity in pulmonary lymph nodes than expected
    - ➢ Revised particle transport rates to lymph nodes

Separate calculations for smokers and non-smokers.

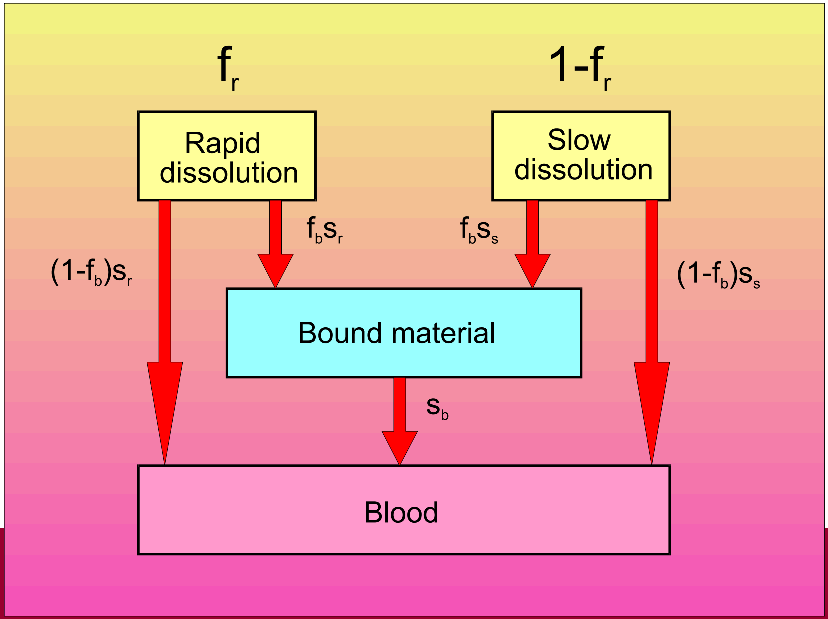
- Modified particle transport rates for smokers as suggested in ICRP Publication 66

Mayak workers dosimetry system 2008 (MWDS-2008)

Absorption parameter values for plutonium

Obtained absorption parameter values for nitrates, oxides and 'mix' compounds based on in-vitro & autopsy data

- Used bound state to account for the long term retention in lung
  - bound fraction: f_b = 2-4% for nitrate, f_b = 35-40 % for oxides
  - However, long term retention maybe due to material sequestered in the alveolar interstitium.
  - Also some Pu may have been encapsulated in scar tissue



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Mayak workers dosimetry system 2008 (MWDS-2008)

Absorbed dose to lung calculated as:

$$= \frac{\text{Energy deposited in whole lung}}{\text{Mass of lung (1.1 kg)}} \approx \text{Dose to AI region}$$

The dose to BB and bb regions are ignored

ie, mass-weighted absorbed lung dose of D_{BB}, D_{bb}, D_{AI}

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Uncertainties in plutonium dosimetry

Assessments based on urine measurements have uncertainties associated with:

- Urine measurements
- Absorption characteristics of the inhaled aerosol
- Route and time pattern of intake
- Biokinetic and dosimetric models
  - Structure of model
  - Particle transport clearance rates from the respiratory tract
  - Parameters used to estimate the deposition and clearance of systemic organs

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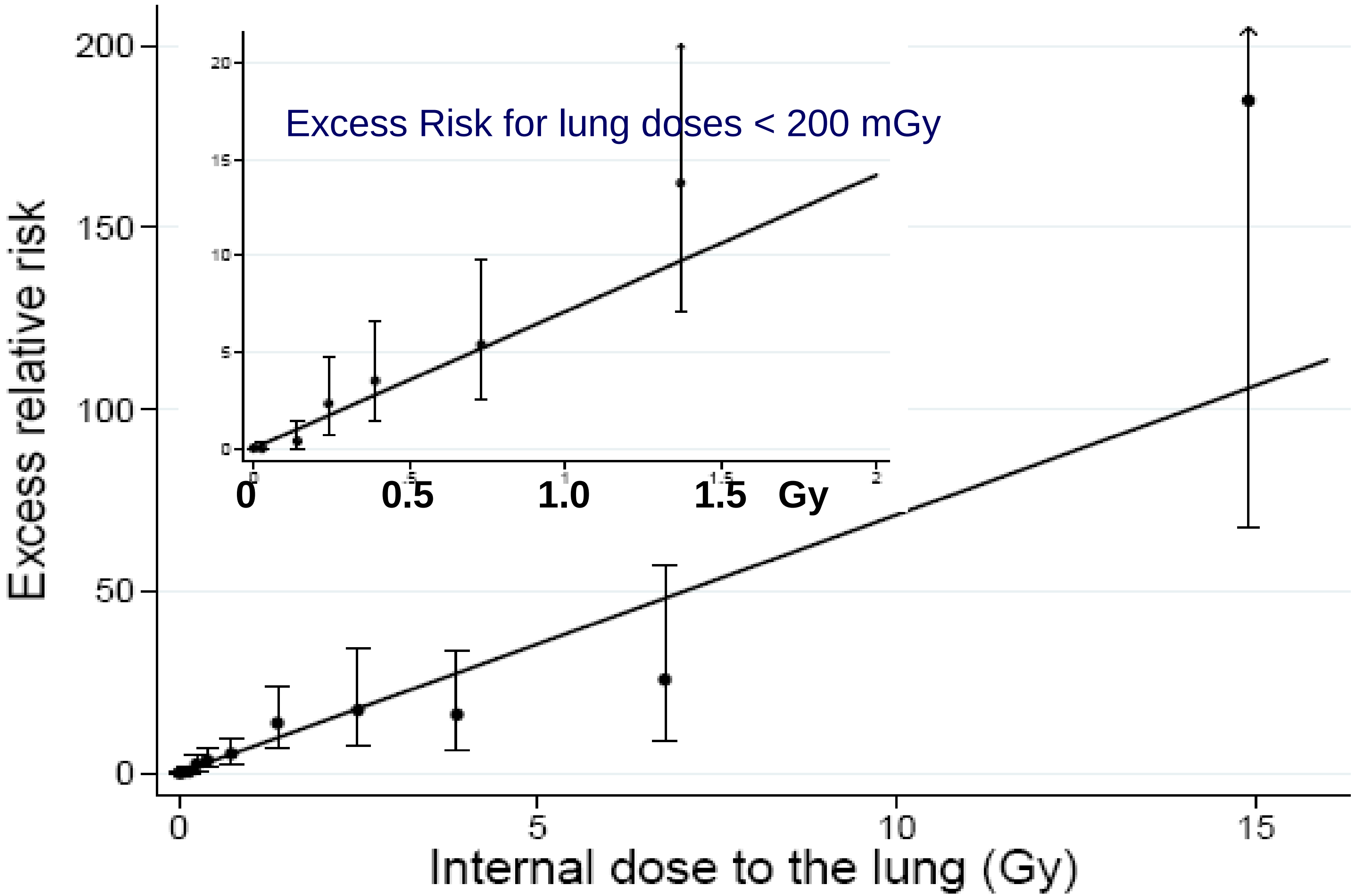
Mean absorbed lung doses for Mayak workers (Gilbert, et al. 2012)

Mayak worker cohort: 25,757 workers hired between 1948 to 1982
Lung cancer deaths: 486

	Mean absorbed dose, mGy
External gamma (low-LET radiation)	400
Plutonium dose (Alpha radiation)	115

Excess Relative Risk (ERR) of lung cancer for male Mayak workers at age 60 (Gilbert, et al. 2012)



Estimation of RBE values of alpha particles for induction lung cancer

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Comparison with risk estimates from life span study (LSS) of Japanese A-bomb survivors

Mayak Workers (MWDS-2008) (Gilbert et al. 2013)

Alpha: ERR per Gy at age 60*: **7.0** (95% CI: 4.8 – 10)

	ERR per Sv*	Inferred RBE
Gamma		
LSS mortality data	0.36 (0.04-0.78)	19
LSS incidence data	0.34 (0.05-0.72)	21

*Based on analyses with common attained age parameter for Mayak and LSS

Large uncertainties in the Life Span Study estimates

- **Data also consistent with a large range of RBE values**

Calculation of lifetime absolute risks. Example: Radon

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- **Lifetime:** cumulative risk up to age 90 (ICRP, 1993)
- **Exposure scenario:** 2 WLM per year from age 18 - 64
- **Background rates, R_o:** ICRP reference population (ICRP, 2007)
  Euro-American/ Asian population
  Smoking included
- **Risk model:** (ERR per WLM) Obtained from miner epidemiological studies
  Time dependent modifying factors
- **Projection model:** multiplicative model

$$\text{absolute risk, } R(w) = \mathbf{R_o}\,.(1 + \beta.\, w)$$

ERR per WLM → β

Exposure, WLM → w

Calculation of lifetime detriment for low-LET radiation.

- **Lifetime:** cumulative risk up to age 90 (ICRP, 1991)
- **Exposure scenario for worker:** chronic from age 18 – 64 y
- **Background rates, R_o:** ICRP reference population (ICRP, 2007)
  Euro-American/ Asian population
- **Risk model:** Obtained from A-bomb survivors incidence study using additive (EAR) and multiplicative models (ERR) with modifying factors
- **Projection model:** weighted average of a multiplicative and additive projection models

Multiplicative: absolute risk, $R(w) = \mathbf{R_o} + \mathbf{R_o}.\,\beta.\,w$

ERR per Sv (β) — dose (w)

Additive: absolute risk, $R(w) = \mathbf{R_o} + \beta.\,w$

EAR per Sv (β)

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Calculation of lifetime detriment for low-LET radiation.

- **Extrapolation to low doses**
  - ➢ Risk per unit dose is **lower** at low doses and low dose rates compared with that at high doses at high dose rates
    - ➢ Estimates are reduced by a dose and dose rate effectiveness factor (DDREF)
      - → DDREF = 2

- Detriment quantifies harmful effects of radiation exposure taking account:
  - ➢ fatal and non-fatal cancers
  - ➢ lethality of cancer
  - ➢ Quality of life
  - ➢ Years of life lost

Comparison of lifetime excess absolute risk (LEAR) estimates

		Alpha		Gamma	
Risk model	Exposed population (ICRP, 2007)	Lifetime lung cancer risk (WLM^{-1})	Lifetime lung cancer risk (Gy^{-1})	Lung detriment[(a)] (Sv^{-1})	Inferred RBE
Miner studies ICRP, 2010	Sex-averaged	5.0×10^{-4}	0.12 [(b)]	1.21×10^{-2}	10
Smoking	Males	7.0×10^{-4}	0.16[(b)]	8.00×10^{-3}	21
Mayak workers Gilbert, et al., 2013	Males		0.15	8.00×10^{-3}	19

a) Values taken from ICRP Publication 103, (ICRP, 2007).

b) A detriment-weighted absorbed lung dose of 4.3 mGy WLM^{-1} was calculated with the revised HRTM for a miner.

Mayak calculations

LEAR up to age 90 y following a constant chronic intake of ^{239}Pu oxide between the ages 18 y- 64 y.

Interaction of risks from alpha radiation and smoking

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Miner studies and the Pu worker Mayak study showed:
(BEIR VI; Hunter et al 2013; Leuraud et al 2011; Gilbert et al 2013)

- a sub-multiplicative interaction of risks from smoking and alpha radiation (i.e. intermediate between additive and multiplicative).

  - That is, the ERR per Gy was **higher** for **non smokers** than for smokers under a relative risk model.

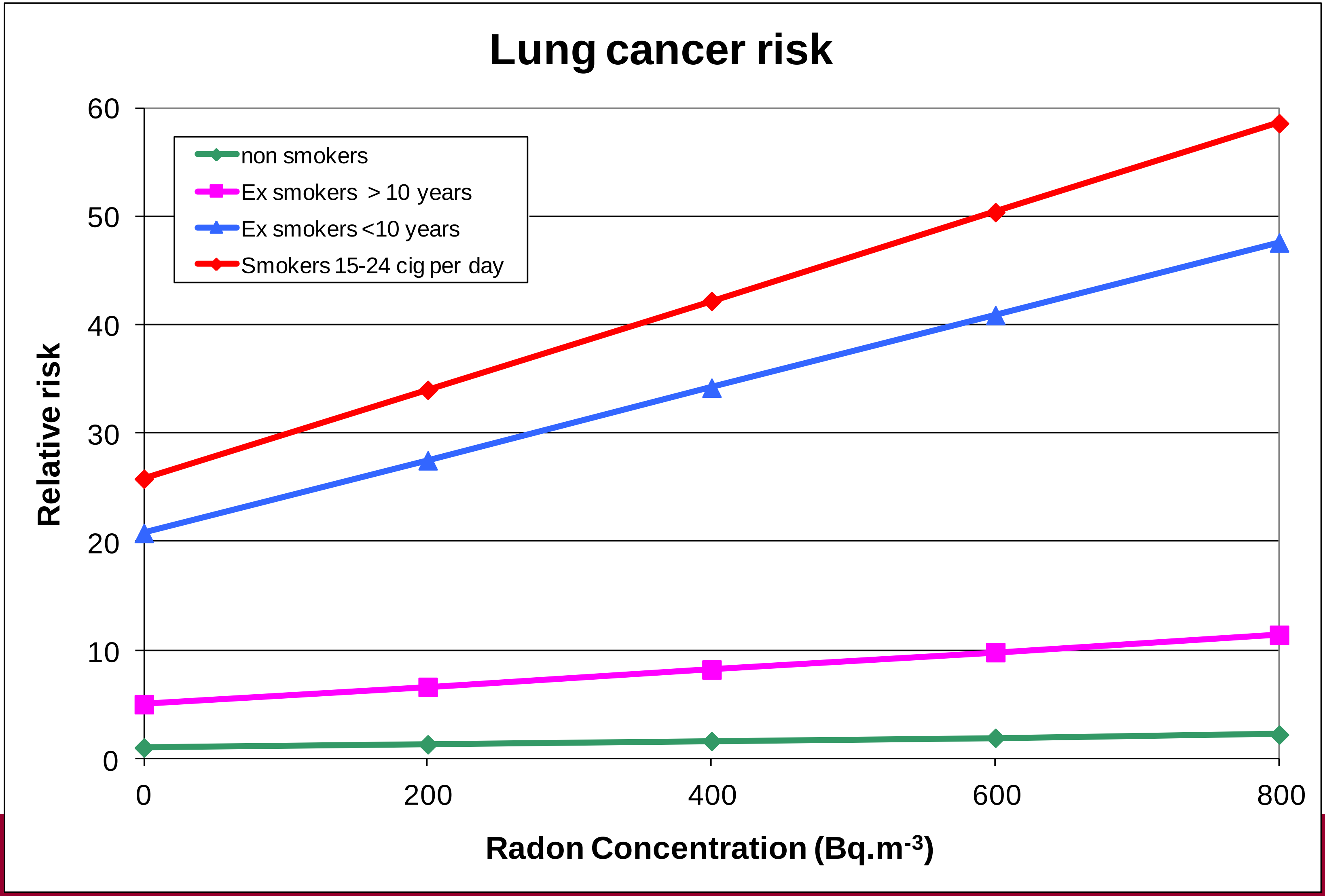
- *Absolute* risk for smokers > never smokers because baseline risk for smokers is greater

  - absolute risk, $R(w) = \mathbf{R_o}\,.(1 + \beta .\, w)$

ERR per WLM → β

Exposure, WLM → w

European residential study: Risk of lung cancer relative to lifelong non-smoker with no radon exposure (Darby, et al., 2006)



Effect of smoking

- Calculation of lifetime absolute lung cancer risk to a population following exposure to internal alpha emitters depends on:
  - the smoking prevalence
  - the type of interaction of risks from alpha radiation and smoking (additive, multiplicative or sub-multiplicative)

- Should protection standards be set for smokers and non-smokers?
  - To do so may lead to discrimination that could cause ethical and social problems.
  - Would also introduce complexity in the protection system.

- Current protection system does not distinguish between smokers and non-smokers.

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New dosimetry system for the Mayak workers: MWDS-2013

- Use revised HRTM of the forthcoming Occupational Intakes of Radionuclide document (OIR)
  - New particle clearance model for AI region
  - Greater retention in AI region for insoluble particles

- New estimates of absorption parameters (f_r, s_r, s_s, f_b, s_b)
  - Bound fraction f_b to model long term retention of soluble plutonium (i.e. Binding of dissociated material)

- Detriment-weighted absorbed lung dose

$$= \frac{1}{3} \times (D_{BB} + D_{bb} + D_{AI})$$

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MWDS-2013
Detriment-weighted absorbed lung dose

Assume detriment is equally apportioned between the 3 regions of lung:

- Detriment-weighted absorbed lung dose (Gy) = ⅓ × (D_{BB} + D_{bb} + D_{AI})

Region	Plutonium nitrate		Plutonium oxide	
	Absorbed dose ($\mu Gy\ Bq^{-1}$)	Fractional contribution	Absorbed dose ($\mu Gy\ Bq^{-1}$)	Fractional contribution
Bronchial ($D_{BB} = 0.5\ D_{sec} + 0.5\ D_{bas}$)	0.85	12%	0.51	3%
Bronchiolar (D_{bb})	2.4	33%	2.5	17%
Alveolar interstitial (D_{AI})	4.0	55%	12	80%
Detriment-weighted absorbed lung dose	2.4		5.1	

Comparison of doses from MWDS-2008 and MWDS-2013

Exposure regime:

A constant chronic intake of ^{239}Pu by inhalation over 7 years (1950-1957)

Urine measurement:

1 mBq d^{-1} sampled at 30 years (1980) after start of intake.

Absorbed lung dose per urinary excretion rate
(mGy per 1 mBq d^{-1})

	Pu nitrate			Pu oxide		
	MWDS-2013	MWDS-2008	**Ratio**	MWDS-2013	MWDS-2008	**Ratio**
Non-smoker	6.0	4.7	**1.3**	34	32	**1.1**
Smoker	6.0	2.4	**2.5**	34	50	**0.69**

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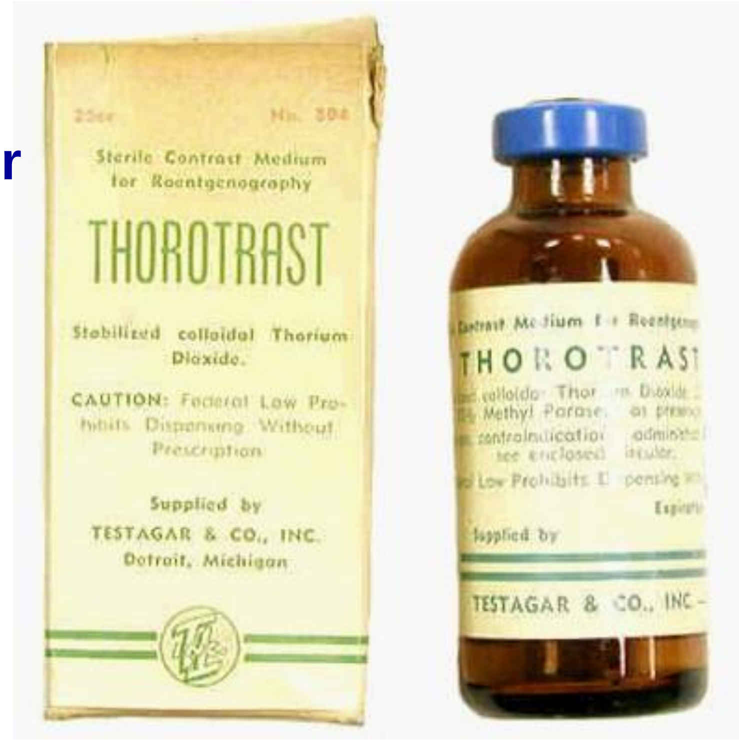
Thorotrast

A thorium dioxide colloid – **An alpha emitter**



- Excellent X-ray absorber
- Used as a radiographic contrast medium in 1930s and 1940s
- Injected for the visualisation of vascular structures, mostly for cerebral arteriography.
- Retained in liver, spleen and bone marrow

Studies of German, Danish and Japanese patients have shown raised risks of cancer:

- ➢ 100-fold increase for liver cancer
- ➢ 20-fold increase for leukaemia

Thorotrast patients: Comparison of lifetime risks (Harrison and Muirhead, 2003)

Liver Cancer:

		Risk
Thorotrast:	Alpha	40 – 80 10^{-3} Gy^{-1}
A-bomb survivors:	Gamma	3 10^{-3} Sv^{-1}
	RBE	~10 - 30

Leukaemia:

		Risk
Thorotrast:	Alpha	14 – 18 10^{-3} Gy^{-1}
A-bomb survivors:	Gamma	5 – 8 10^{-3} Sv^{-1}
	RBE	~2 - 4

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Main points (1)

- RBE values for alpha particles can be validated by comparing risk estimates per Gy of alpha dose with risk estimates for low-LET radiation for a given organ.

- Studies of thorotrast patients gave RBE values for alpha particles of:

  - 10 - 30 for liver cancer

  - 1- 4 for leukaemia:

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Main points (2)

- Lung cancer risk estimates per Gy of alpha dose can be obtained from uranium miner studies and plutonium worker studies

- RBE values around 10 and 20 were obtained by comparing ERR values, but with wide uncertainty ranges
  - Comparing lifetime risks of a reference population gave similar values.

- Regional lung dose distribution differs
  - Radon progeny: most to bronchial and bronchiolar regions (97%)
  - Plutonium: most to alveolar-interstitial region (55% nitrates; 80% oxides)

- **Calculate detriment-weighted absorbed lung dose**

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Main points (3)

- ERR per unit ‘absorbed lung dose’ of alpha radiation is similar for French uranium miner and Mayak worker studies

		ERR per Gy
Miner studies;	Radon progeny;	4.5 (95% CI: 1.3 – 11)
Mayak Workers (MWDS-2008);	Plutonium	7.4 (95% CI: 5.0 – 11)

- New dosimetry system for Mayak workers give doses that are a factor of ~2.5 higher for plutonium nitrates.
  - this **may** lead to lower risks.
  - but still in agreement with risks estimates from radon progeny

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Thank you for your attention