Quantitative Modeling of Radon-Induced Lung Cancer Incorporating Targeted and Non-Targeted Effects

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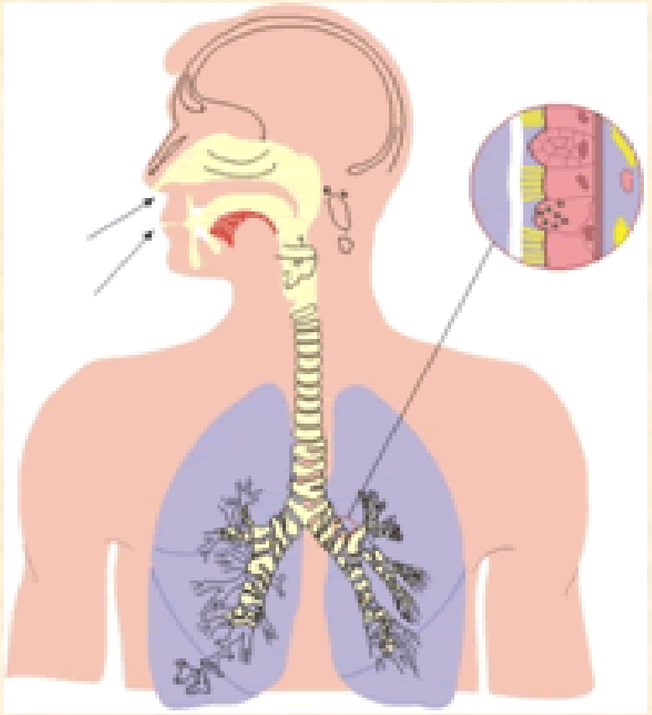
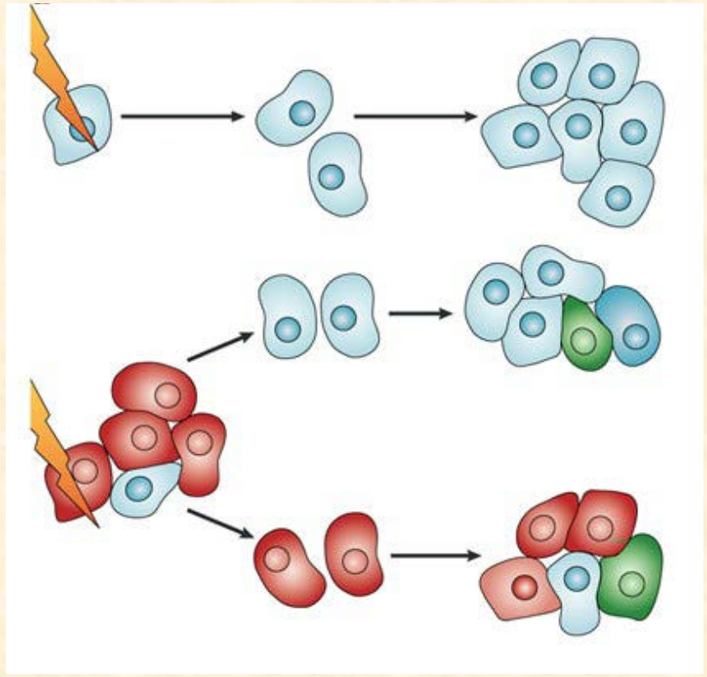
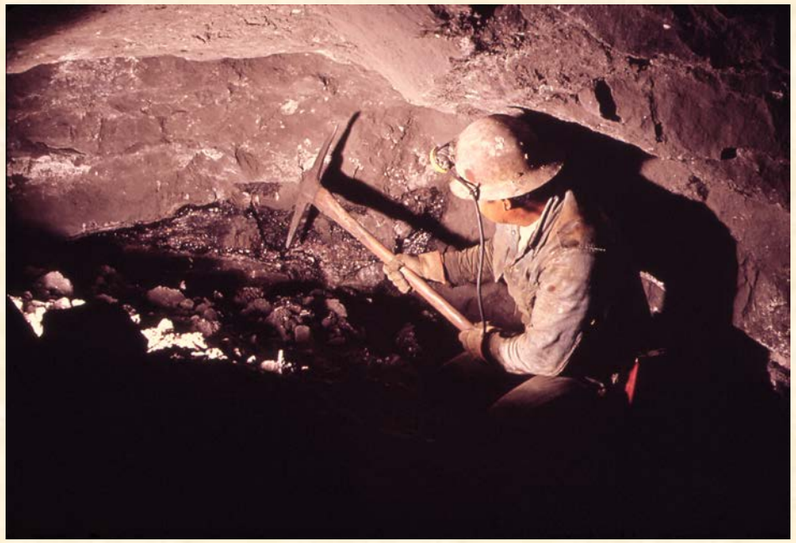
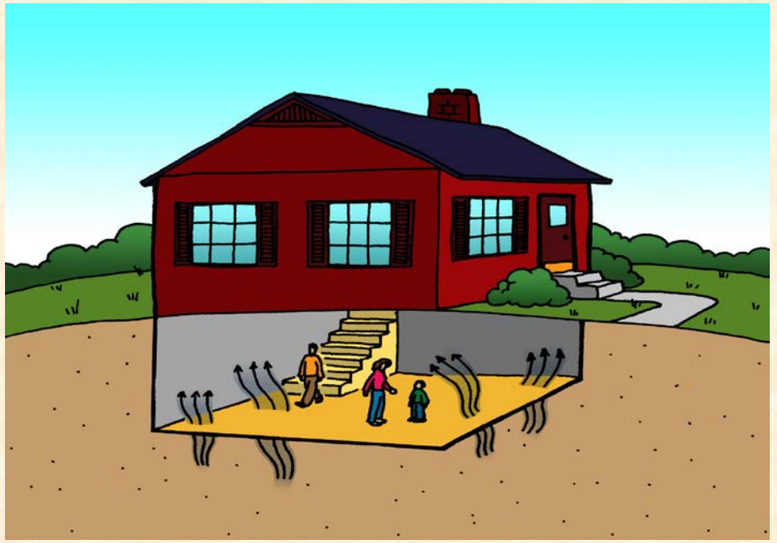




Radon: High-LET radiation effects at very low dose rate



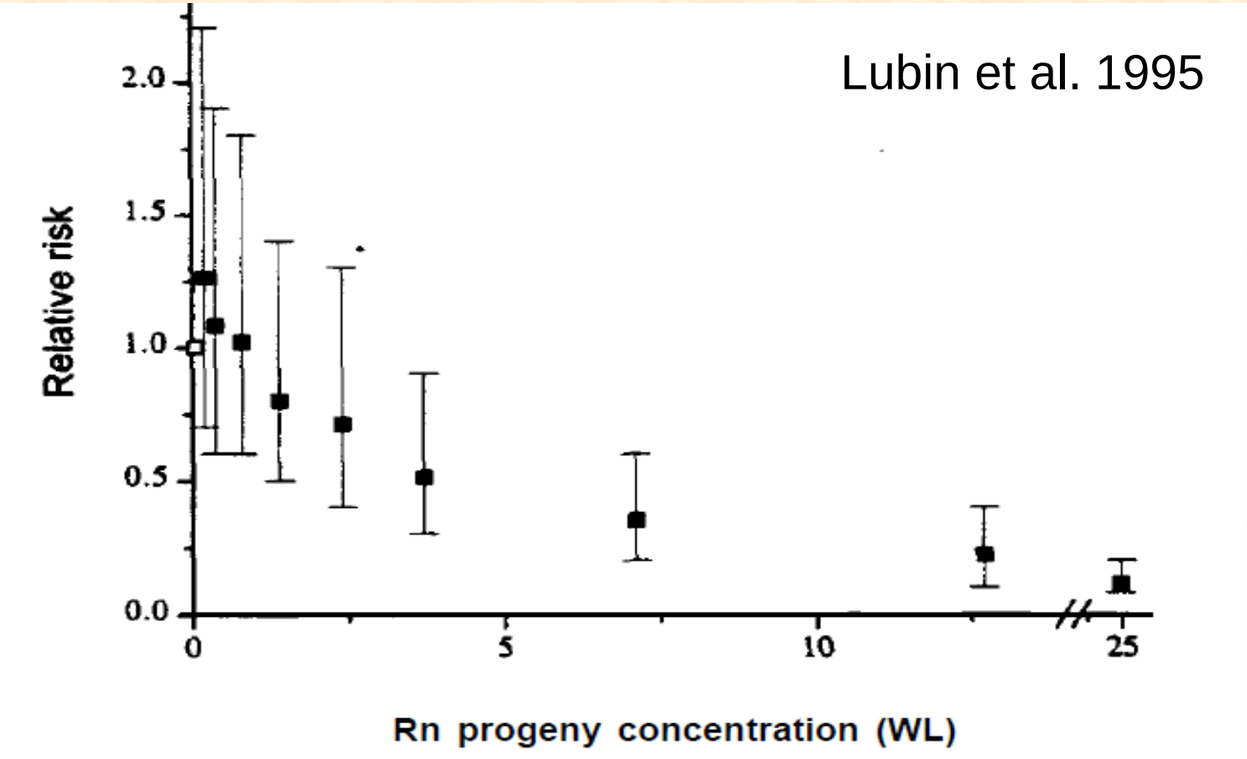
Typical uranium miner dose rates ~ 3 WL
(~ 3 mGy/d to bronchial epithelial cells)



In homes, corresponding radon dose rates are typically several orders of magnitude lower

- The combination of very low radon doses and very low radon dose rates present in homes is difficult to study epidemiologically or in the laboratory
- Quantitative mechanistic models are needed…..

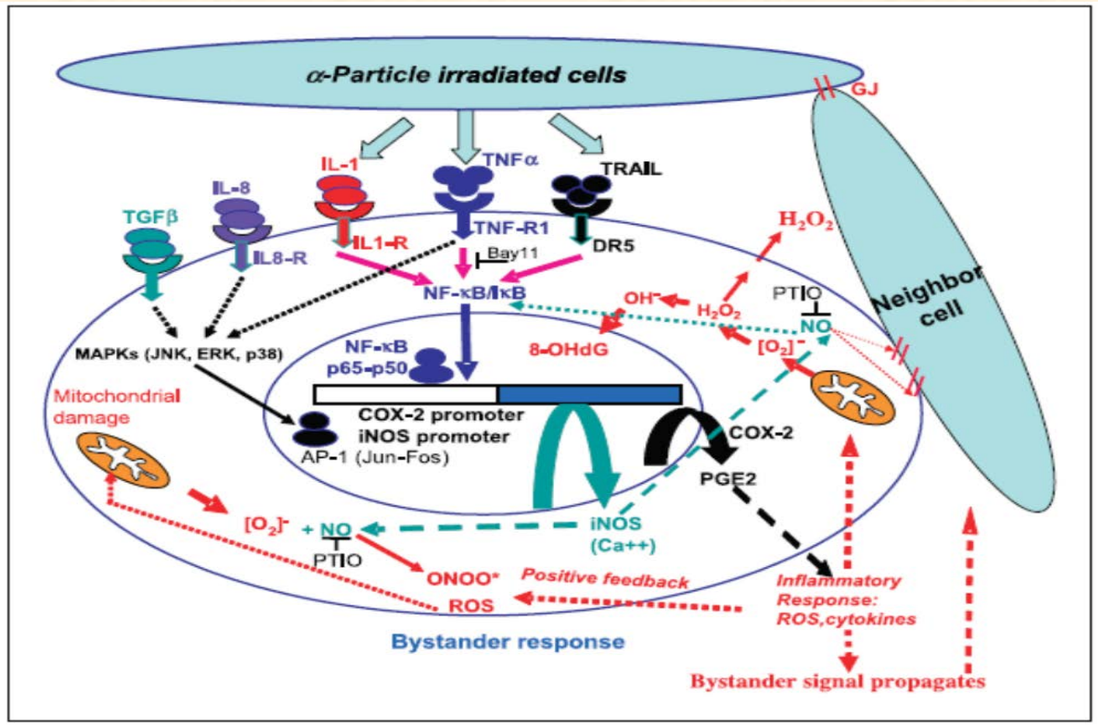
- **Radon dose responses for lung cancer are generally close to linear**
- **Effects of dose rate are more complicated:**
  - **Inverse dose-rate effect**
  - **Reducing the dose rate (WL) ➔ more (not less) cancer risk**



Due to Non-Targeted Effects?

Non-Targeted Effects (NTE)

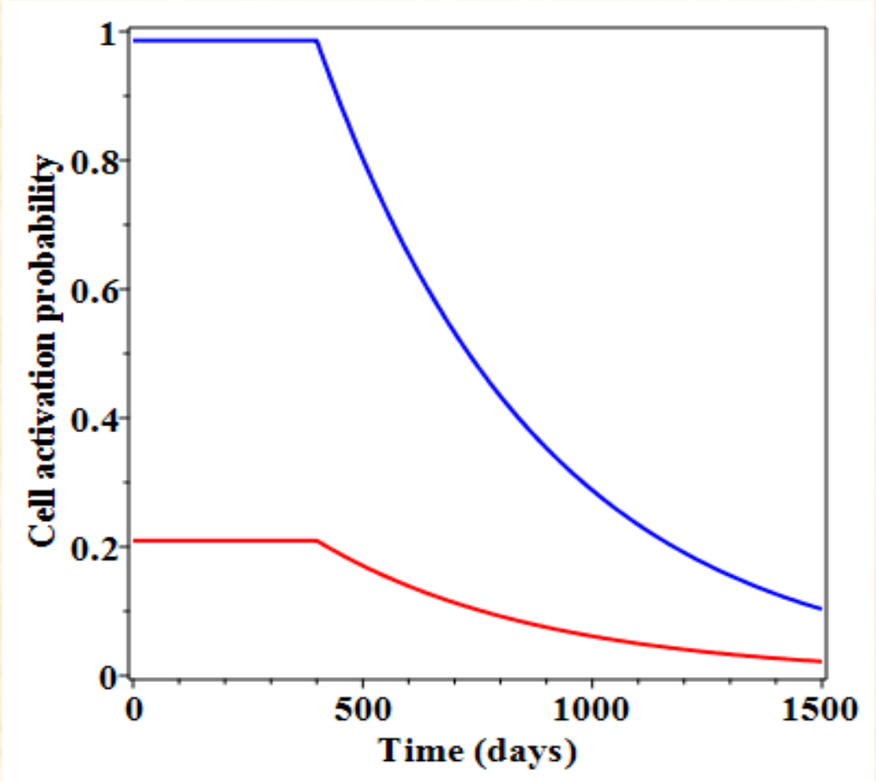
- ☑ **Also called “bystander effects”**
- ☑ **Unirradiated cells respond to signals emitted by nearby irradiated cells**
- ☑ **First quantified by Nagasawa & Little (1992): Cells exposed to low doses of alpha particles: ~1% of cells were hit, but ~30% of cells showed increased chromosomal aberrations**
- ☑ **NTE reported for many endpoints (*e.g.* cell killing, mutagenesis), mainly after high-LET radiation**
- ☑ **Many signaling pathways and reactive oxygen species (ROS) appear to be involved, shifting cells into an “activated” stressed state**



Zhou et al. *Cancer Res*, 2008

Modeling High-LET Non-Targeted Effects

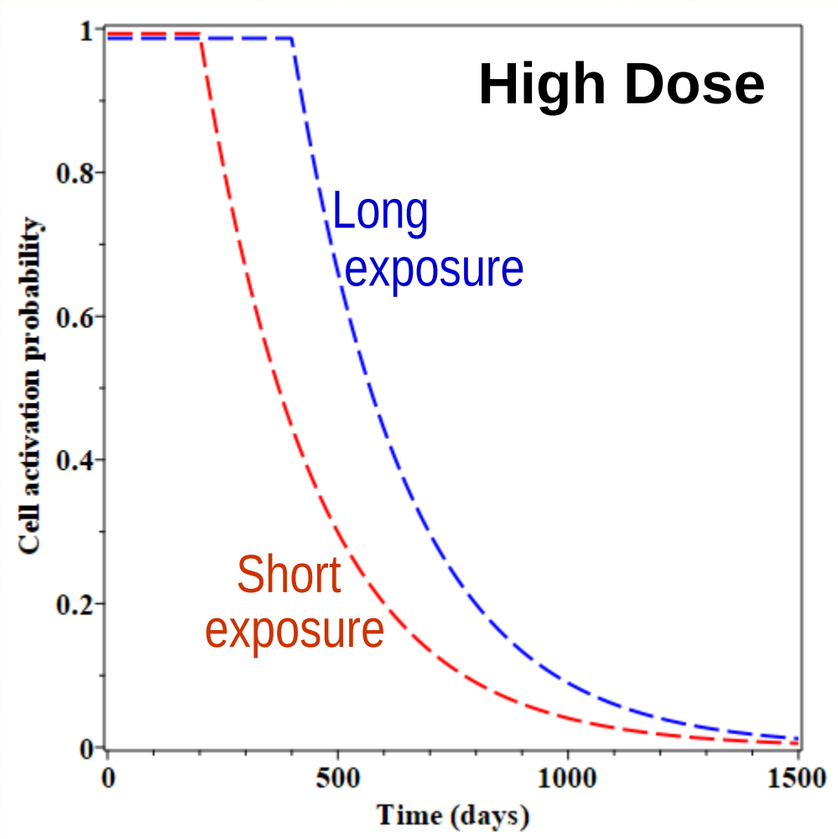
- NTE cell activation probability per unit time proportional to the local concentration of the NTE signals
  - Activation probability during irradiation increases with dose rate
  - Likely to saturate at high doses / dose rates, particularly at high LET
- After irradiation, NTE-activated cells revert to the background state with a constant probability per unit time
- Tumor induction by NTE proportional to time integral of cell activation probability



High-LET NTE Dose-Rate Effects

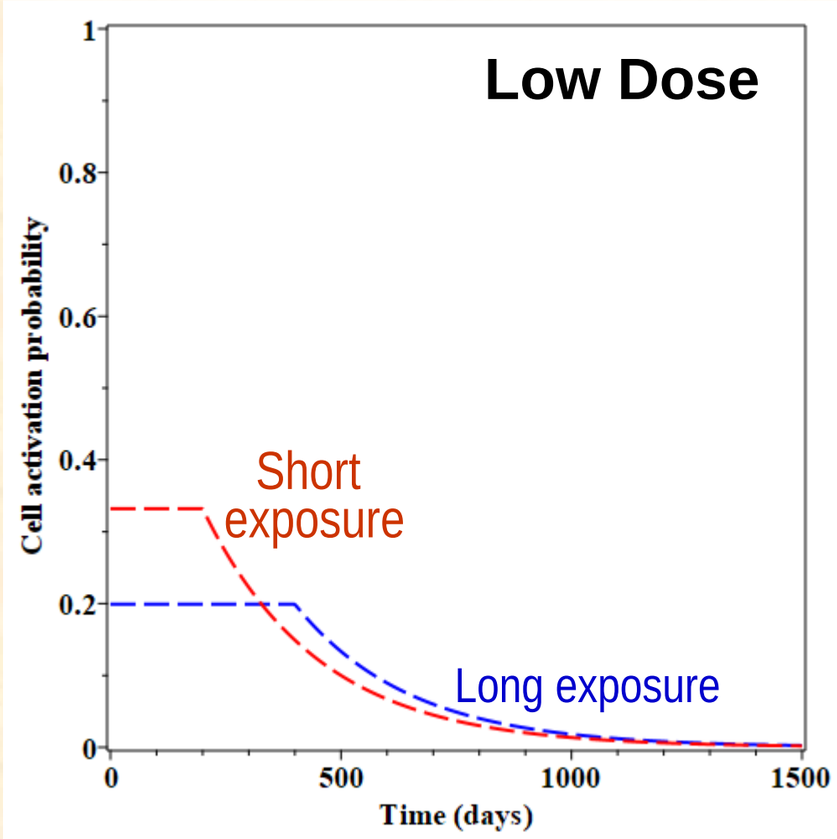
High Dose

Cell activation probability *saturates* during exposure, so longer exposure at lower dose rate leads to more NTE activation



Low Dose

Cell activation probability *does not saturate* during exposure, so longer exposure at lower dose rate leads to less NTE activation



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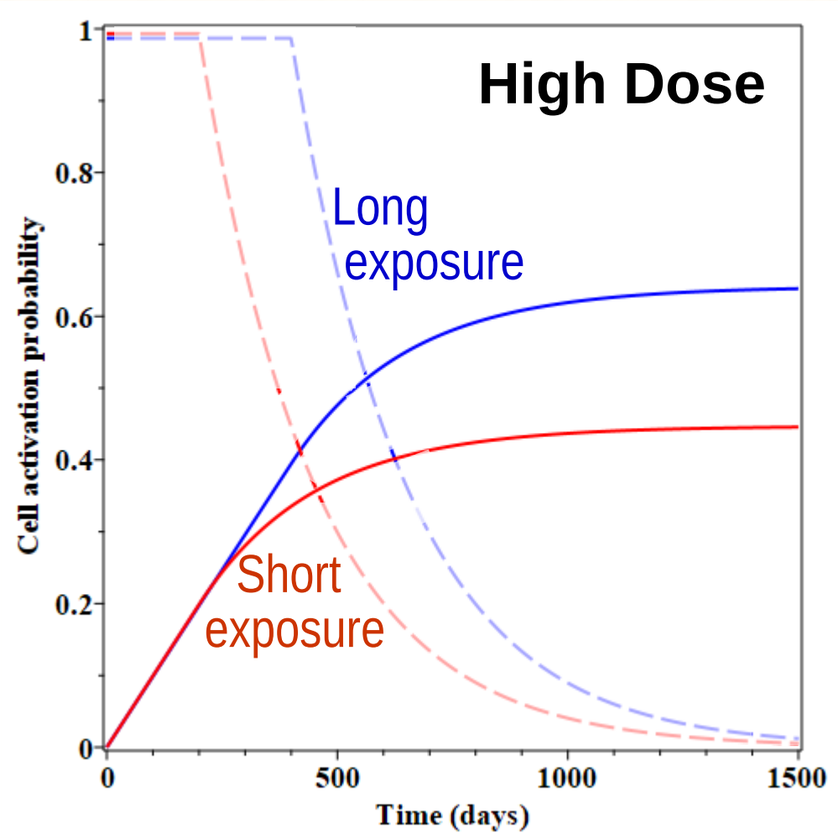

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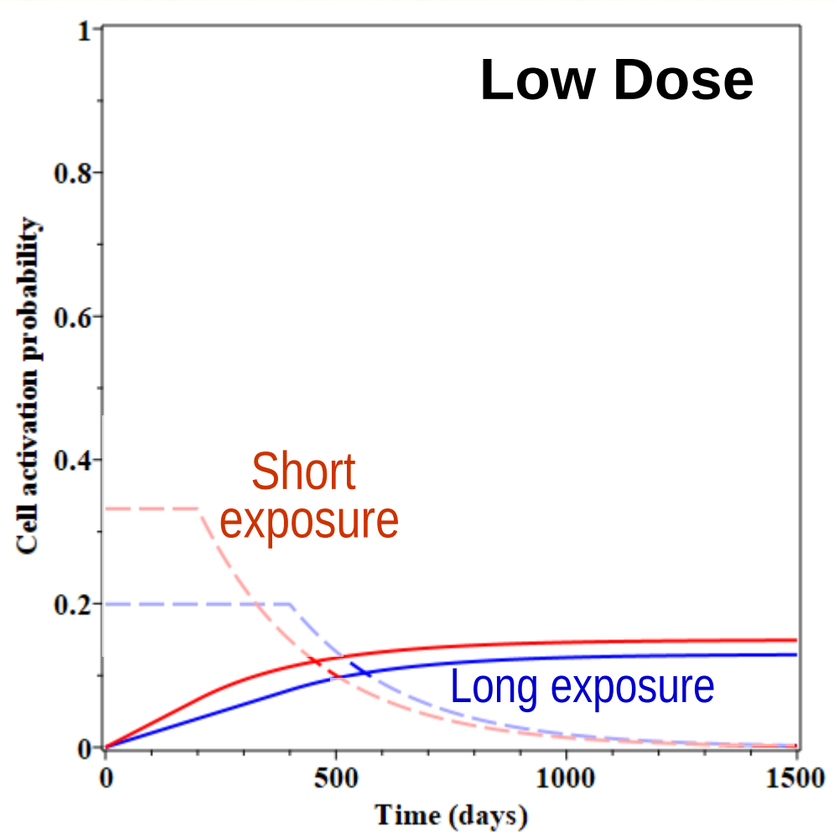
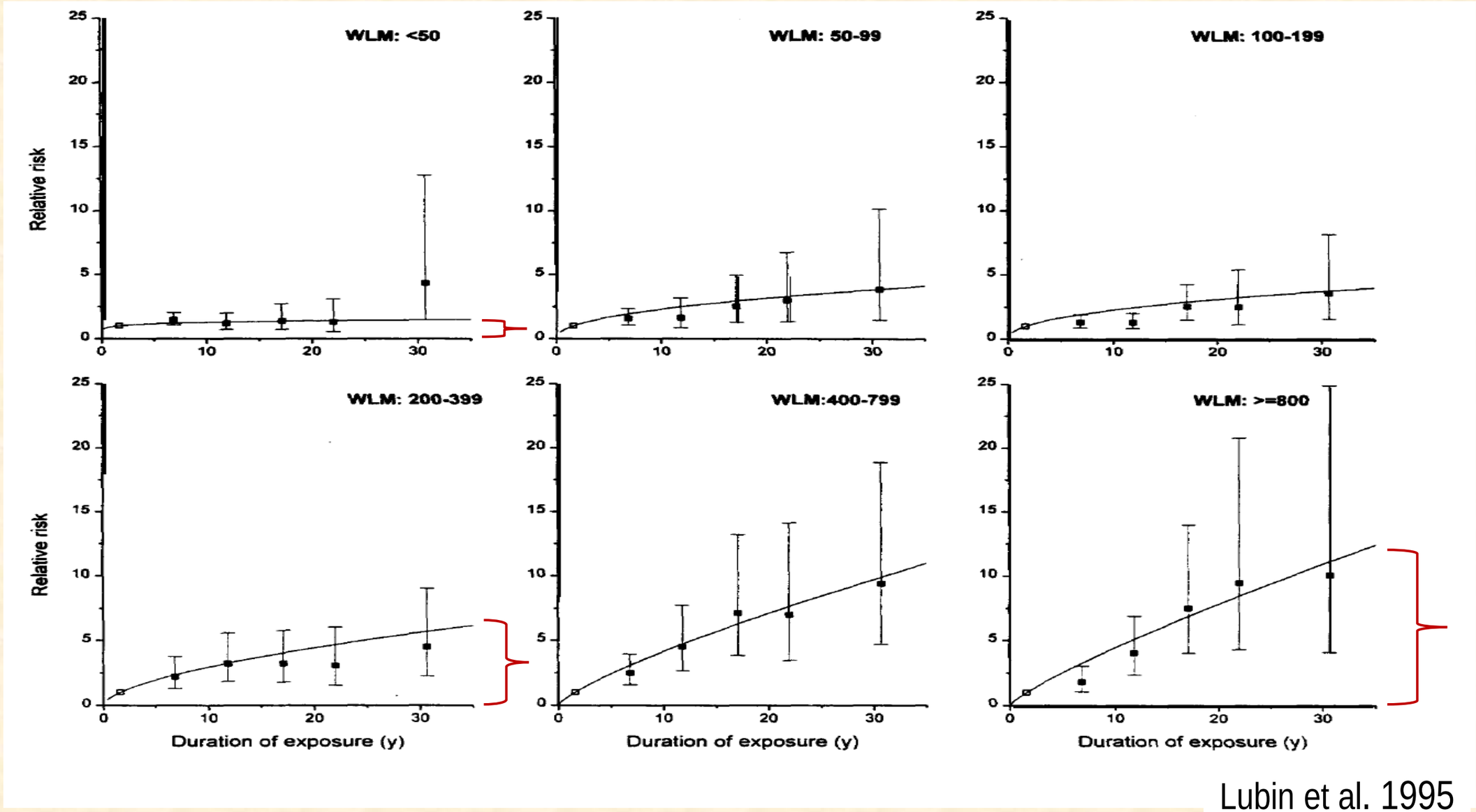


Solid Curves: Time-Integrated Number of Activated Cells

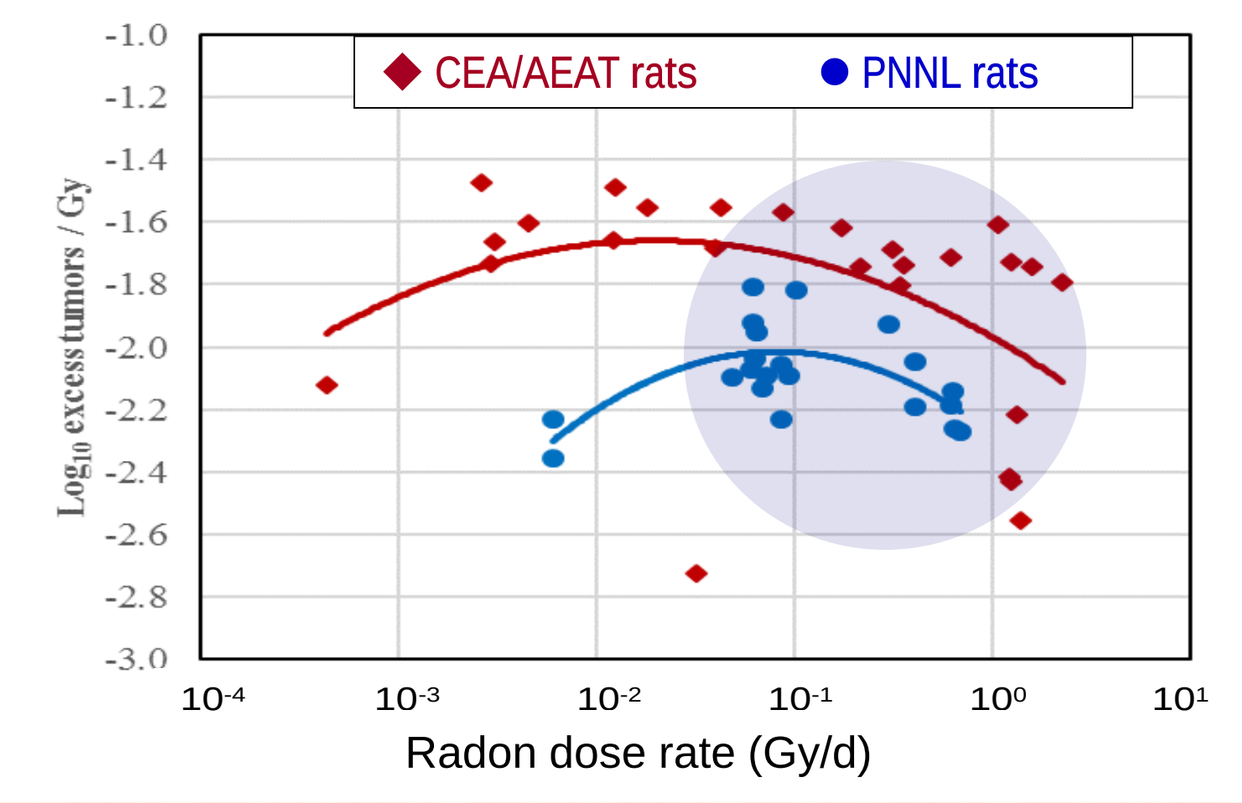
From the uranium miner data, the inverse dose-rate effect is indeed dose-dependent



Lubin et al. 1995

Dose-dependent inverse dose-rate effects…… can also be seen in very large data sets of lung tumor induction in rats exposed to radon over wide ranges of dose and dose rates:

- Inverse dose rates effects at higher doses / doses rates
- No dose rate effects at intermediate dose / dose rates
- Conventional dose rate effects at lower doses / dose rates



From Shuryak et al 2019

Simple (simplistic?) modeling of high-LET dose rate effects for protracted exposures

- **Activation probability per unit time is proportional to the local concentration of the NTE signals (Parameter 1)**
- **NTE activated cells revert to the background state with a constant probability per unit time (Parameter 2)**
- **Tumor induction by NTE is proportional to time integral of cell activation probability (Parameter 3)**

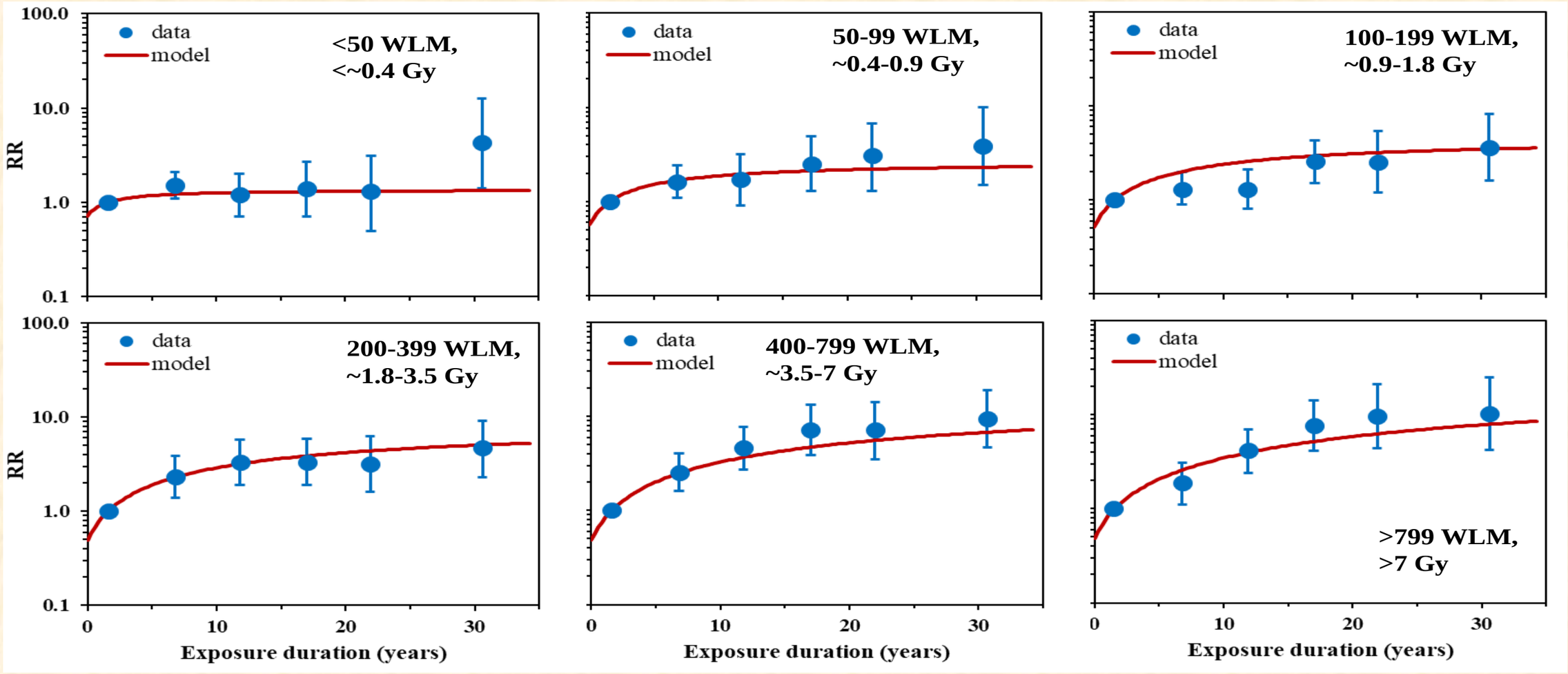
- **Classical high-LET targeted effects proportional to dose (no dose rate effects, Parameter 4)**

- **Background parameter (Parameter 5, cancels out of relative risk equation)**

From Shuryak *et al. Radiat Prot Dosim* 2019

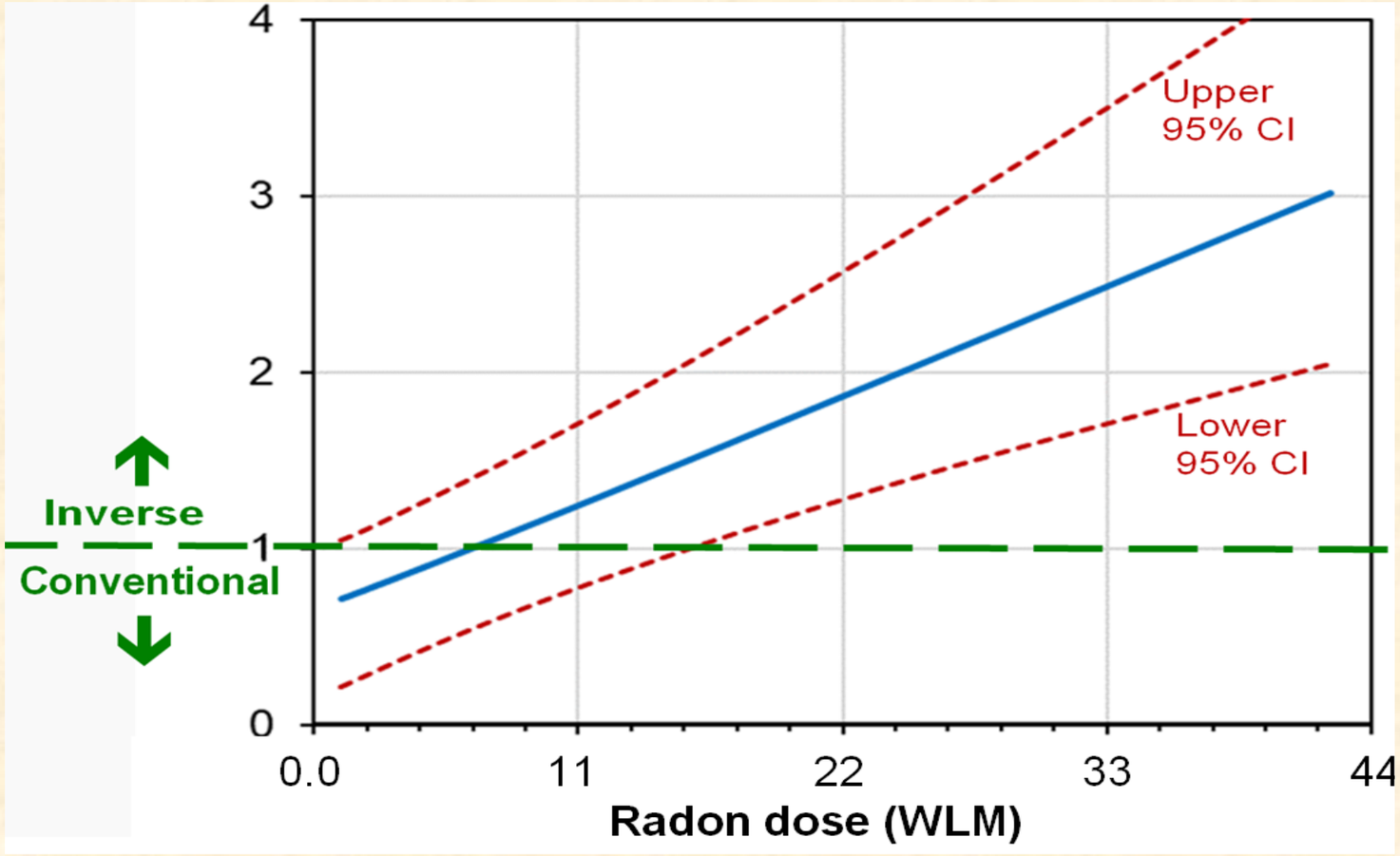
TE / NTE model fits (red curves) to lung carcinogenesis data (blue symbols, Lubin *et al*) from radon-exposed miners

Model was fitted simultaneously to data from all panels combined



Dose dependence of dose-rate effects for radon-induced lung cancer

Dose Rate Effects (1,000 days protracted vs acute) for radon-induced lung cancer



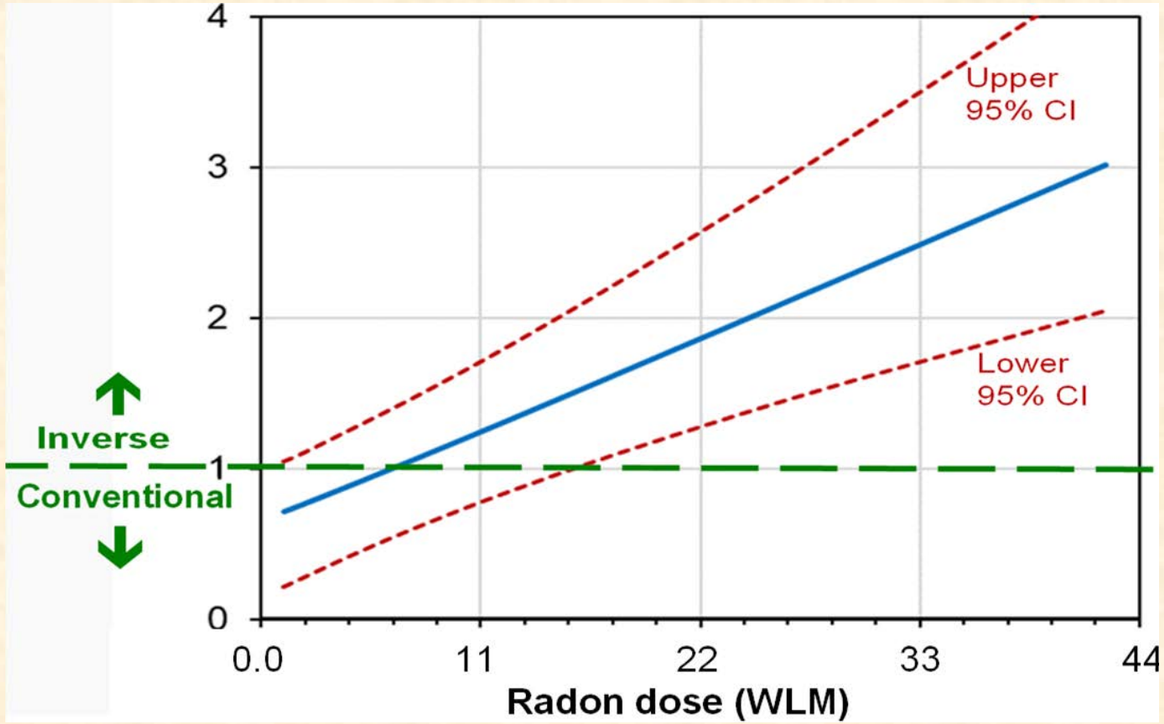
Based on Shuryak *et al.* Radiat Prot Dosim 2019

Where are we now?

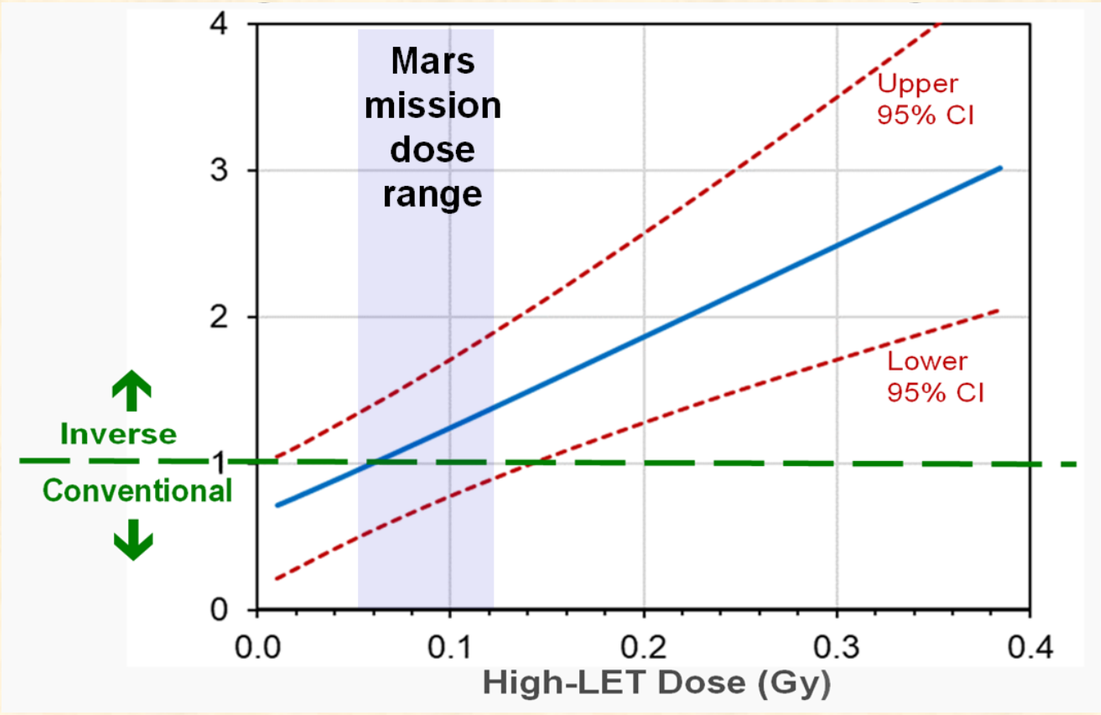
- **A mechanistically-motivated quantitative model of radon-induced lung cancer includes both targeted and non-targeted effects.**
- **The model well describes the observed dose and dose rate patterns in humans and rats, including the inverse dose rate effect and its tendency to increase with dose**
- **Inverse dose rate effects only significant at high radon doses, so potentially not relevant for domestic radon exposure**
- ***Model can be applied to galactic cosmic-ray risks in long-term space flight, and suggests that there will not be significant dose rates effects there***

Applying radon-generated insights to space radiations

Radon

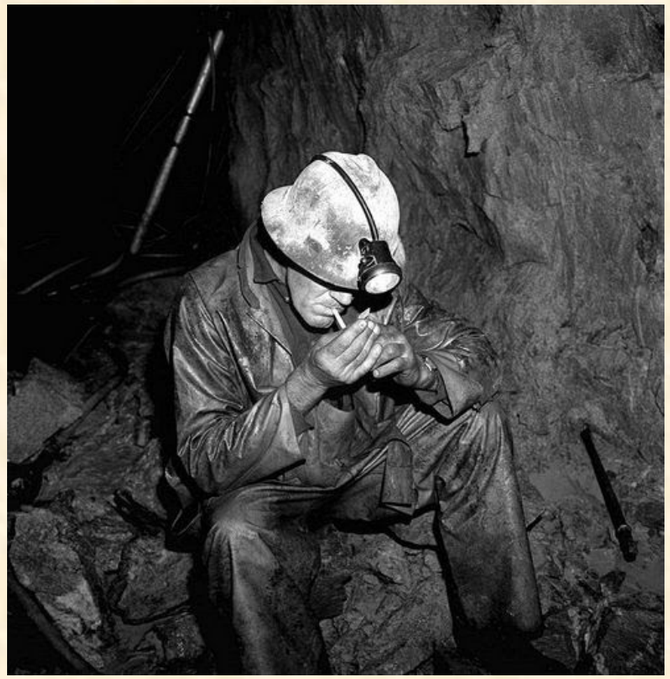


Galactic cosmic rays



The combined effects of radon and tobacco smoking

- **Effects of both carcinogens and interactions between them have been studied in animals and also in human miner cohorts**



- **BEIR-VI analysis of miner data suggested a synergistic sub-multiplicative interaction between radon and smoking (more than additive, less than multiplicative)**

- ***BEIR-VI predicted radon-related US lung-cancer deaths:***

Non-smokers: 1,200 - 2,900 /y

Smokers: 14,200 - 18,900 /y

Incorporating TE+NTE concepts into a Radon + Smoking model

- **Our basic TE+NTE model describes the relative risk of lung cancer due to radon exposure, using a total of 4 parameters**
- **We are extending our TE+NTE radon models to allow various possible interactions of radon with smoking - to be assessed separately (and potentially differently) for TE and NTE effects**
- **Examples are simple multiplicative models as well as geometric mixture models (GMM) models that can be intermediate between additive and multiplicative smoking + radon interactions**

Next step: Apply these methodologies to state-of-the-art uranium-miner data sets

- **A potential opportunity for epidemiologists and mechanistic modelers to collaborate…..**

PUMA – pooled uranium miners analysis: cohort profile

Estelle Rage [1], David B Richardson,[2] Paul A Demers,[3] Minh Do,[3] Nora Fenske,[4] Michaela Kreuzer,[4] Jonathan Samet,[5] Charles Wiggins,[6,7] Mary K Schubauer-Berigan [8,9], Kaitlin Kelly-Reif,[9] Ladislav Tomasek,[10] Lydia B Zablotska,[11] Dominique Laurier[1]

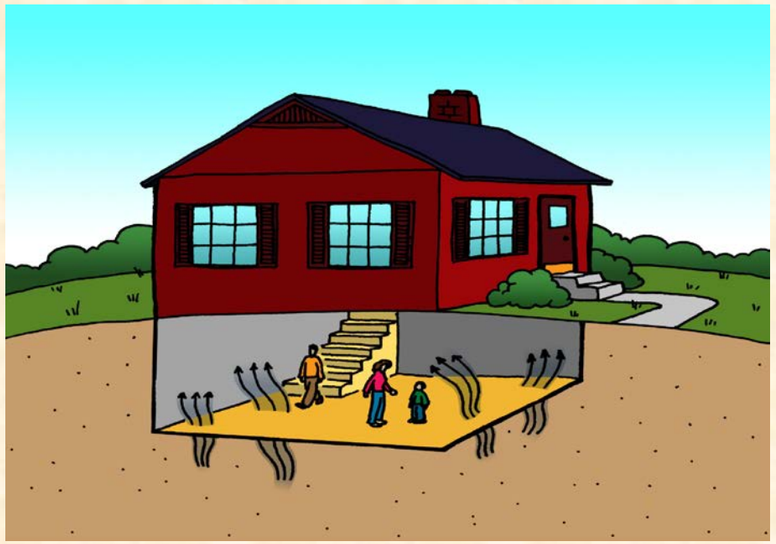
Rage E, et al. Occup Environ Med 2020

Table 3 Smoking exposure assessment methods and distribution, by cohort in the PUMA study

Study (reference)	Assessment methods	Prevalence of smoking
Eldorado*[27]	Nested case-control data derived from interview	96% (cases)/88% (controls)
Ontario[46]	Medical records, interview, and mail survey	~80%
Czech Republic[47]	Nested case-control data derived from medical files and interview	92% (cases)/72% (controls)
France[48]	Nested case-control data derived from medical files and a questionnaire	90% (cases)/73% (controls)
Wismut[49]	Nested case-control data derived from medical files and interview	95% (cases)/75% (controls)
Colorado Plateau[23]	Cigarette use: duration, rate, cessation from surveys in the 1950s, 1960s and 1985	77%
New Mexico[22]	Cigarette use: duration, rate, cessation (at last exam) from medical files	79%

CONCLUSIONS

Extrapolations from uranium miners to domestic radon exposure



High radon doses / dose rates / Mostly smokers → Domestic radon risks

- Extrapolation from miner-based risks to domestic radon risks is non trivial
- We need to understand effects of changing dose, dose rate and smoking patterns
- Quantitative mechanistically-based models can help!