Some remarks to the current debate about the validity of the Linear-No Threshold (LNT) model of radon risk

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GARRM

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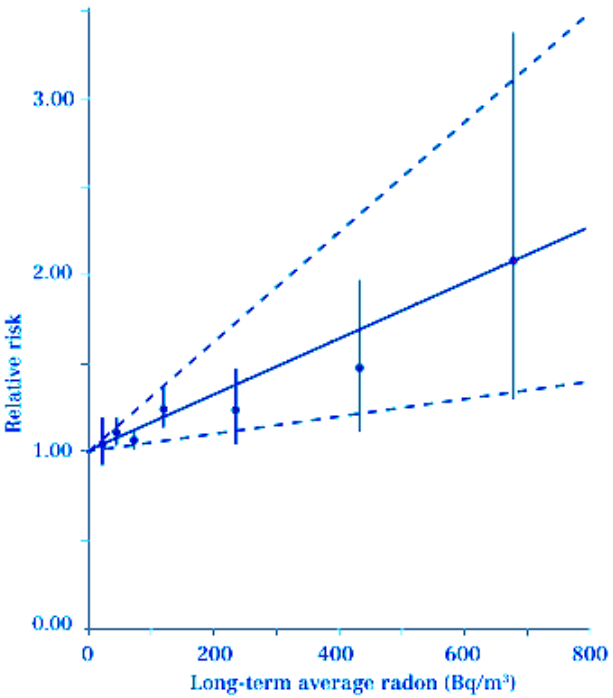
The question:

- Most models of radiation risk assume the linear no-threshold (LNT) hypothesis.
- It seems conservative, therefore reasonable for practical radioprotection.
- How correct is it?
  - What do data say?
  - How would estimates of collective detriment, based on alternative models, look like in comparison?
- Discussed on the example of radon.

Just to make sure:

- This talk is not about radio-biology!
- We do not present new data!
- We don’t take any decision about correctness or applicability of particular risk models! We also do not discuss their plausibility on radio-biological grounds.
- **This talk is about investigation of a possible effect of the choice of models on estimation of the detriment caused by radon.**
- We think that it is important to emphasize this, because the subject is very controversial and almost a matter of faith!

The main LNT reference for radon



Source: Darby et al. 2005
Relative risks and 95% confidence intervals are shown for categorical analyses and also best fitting straight line. Risks are relative to that at 0 Bq/m³.

Darby et al. 2005: [1]
Analysis of pooled studies.

Main results:

- Compatible with LNT model;
- The risk of lung cancer increased by 8.4% (95% confidence interval 3.0% to 15.8%) per 100 Bq/m³ increase in measured radon (P = 0.0007)
- Also for Rn<200 Bq/m³
- Risk for smokers ca. 20 × the one of non-smokers. Relative risk about the same for both.

(taken from the abstract)

Gaskin et al. 2018 [2] reports lung cancer mortality attributable to Rn, based on the LNT.

[1] Darby S. et al. (2005): Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ doi:10.1136/bmj.38308.477650.63 ; technical supplements in Scand J Work Environ Health 2006;32(1):1-84; www.sjweh.fi/article/982
Graph taken from Zeeb H. and Shannoun F., eds., (2009): WHO handbook on indoor radon: a public health perspective. https://apps.who.int/iris/handle/10665/44149
[2] Gaskin et al. (2018): Global Estimate of Lung Cancer Mortality Attributable to Residential Radon. https://doi.org/10.1289/EHP2503

Recent results, similar: PUMA study

Richardson D.B. et al. (2022): Lung Cancer and Radon: Pooled Analysis of Uranium Miners Hired in 1960 or Later; incl. suppl. material, https://ehp.niehs.nih.gov/doi/suppl/10.1289/EHP10669 (open)

Kelly-Reif K. et al. (2023): Radon and lung cancer in the pooled uranium miners analysis (PUMA): highly exposed early miners and all miners, http://dx.doi.org/10.1136/oemed-2022-108532 (paywall)

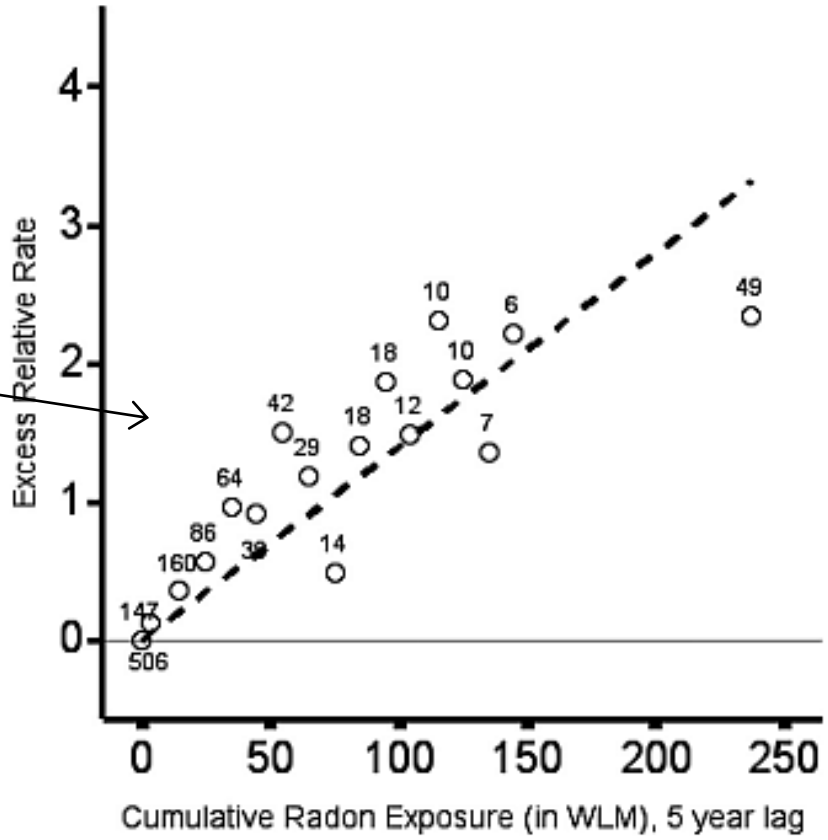


Figure 1. Excess relative rate of lung cancer mortality (circles) and observed number of lung cancer deaths (numbers), by categories of cumulative exposure to radon progeny (category-specific estimates of excess relative rate of lung cancer mortality are reported in Table S1). Simple linear model for the association between cumulative exposure, lagged 5 y, and lung cancer mortality [dashed line: ERR/100 WLM = 1.33 (95% CI: 0.89, 1.88)]. Background stratified by study cohort, attained age, calendar period, and duration of employment as a uranium miner. Pooled Uranium Miners Analysis (PUMA) of uranium miners in Canada, Czech Republic, France, Germany, and the United States, male miners hired in 1960 or later. Note: CI, confidence interval; ERR, excess relative rate; WLM, working level months.

Apparent deviation from linear discussed in the paper!
Quadratic (superlinear) model does not provide great improvement

Scepticism against the LNT

Critique:

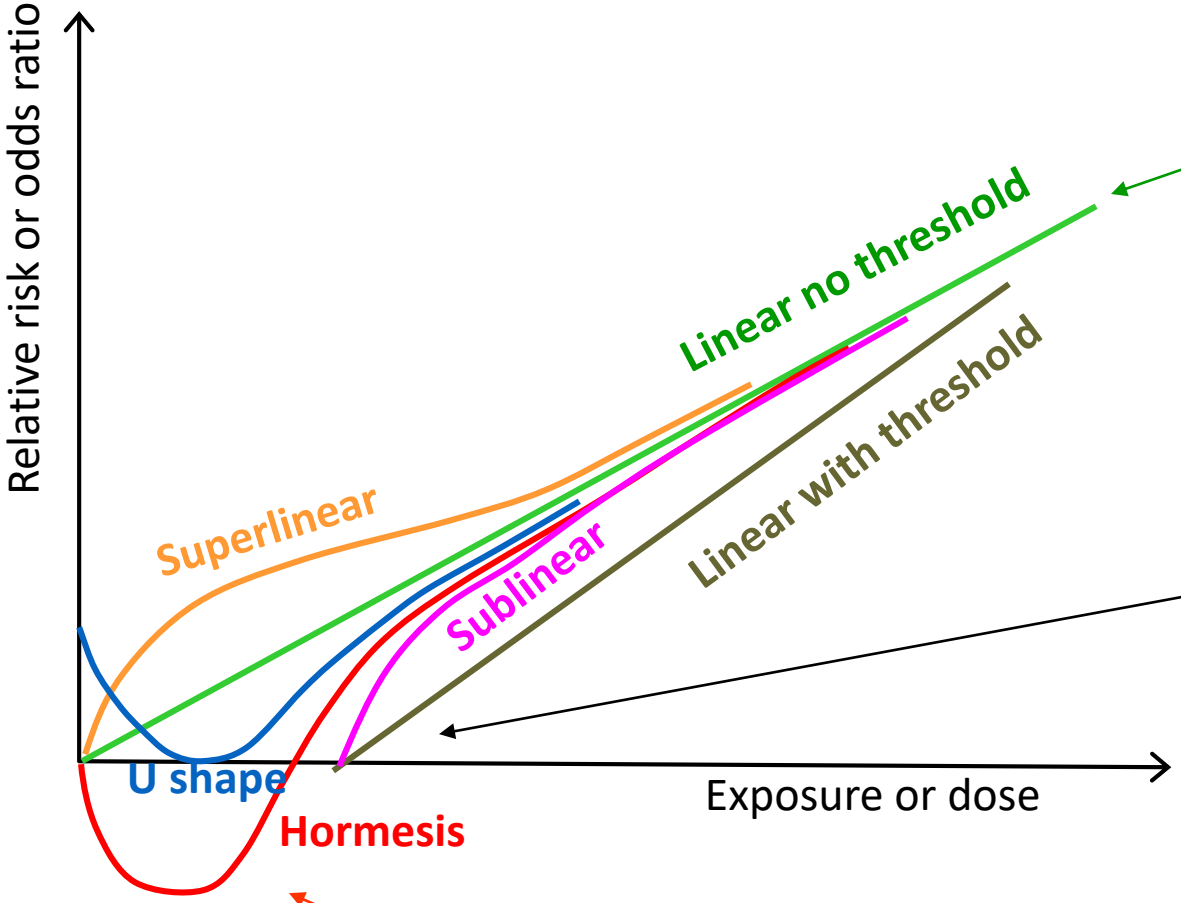
- That a model is compatible with data does not say that the model represents the truth.
- New statistical evaluation of existing data suggests deviation from LNT
- New data and evidence suggests deviation from the LNT
- H. Friedmann 2004: according to current risk models, in some regions of Austria, Rn alone would cause more lung cancer fatalities among women than actually registered [1].

Apparently most favoured alternatives:

- Linear with threshold (LT) or sub-linear
- Hormesis for low dose
- U shaped

[1] Friedmann H. (2004): Radon, Rauchen und Lungenkrebs. Radon-Fachgespräch des BfS, Berlin 14.-15.10.2004. (In German)

Alternative models



Currently most accepted and applied: ≈8%* percent increase of relative lung cancer fatality risk per 100 Bq/m³ (long term) increase (Darby and other studies)

Proposals for possible threshold: long-term exposure to 50 – several 100 Bq/m³

Hormesis means that low doses are healthy

* 16% if accounted for uncertainty of exposure

Terminology

"contingency or confusion table"
RR and OR are measures of association between exposure of given size and assumed effect of the exposure.

	no exposure (control group)	exposure	
no effect	true negatives TN	false negatives FN	negatives N
effect	false positives FP	true positives TP	positives P

relative risk

$$RR = \frac{\frac{effect\,in\,the\,exposed\,group}{all\,exposed}}{\frac{effect\,in\,the\,non\text{–}exposed\,group}{all\,non\text{–}exposed}} = \frac{\frac{TP}{TP+FN}}{\frac{FP}{TN+FP}}$$

RR-1 = excess relative risk

odds ratio

$$OR = \frac{odds\,of\ having\,effect\,if\ exposed}{odds\,of\ having\,effect\,if\ not\,exposed}$$

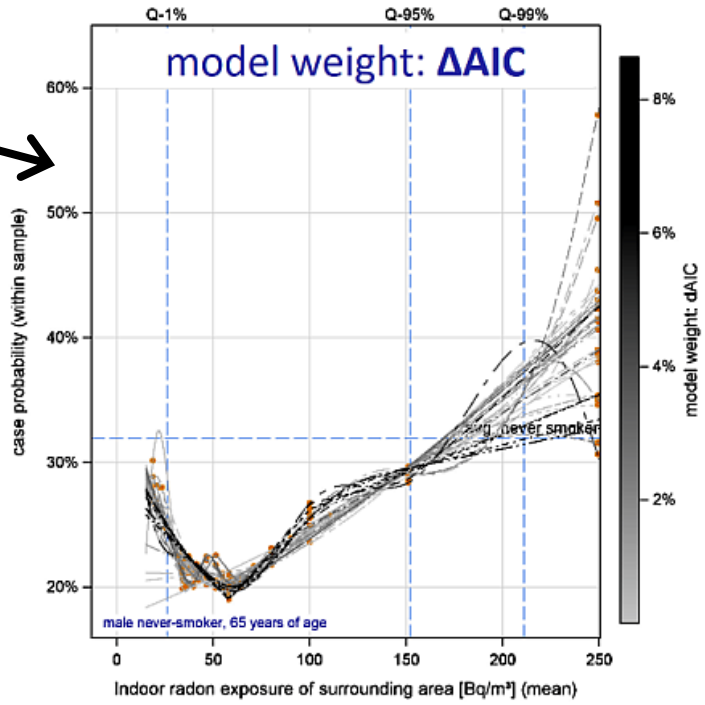
$$= \frac{\frac{exposed\,with\,effect}{exposed\,without\,effect}}{\frac{non\text{–}exposed\,with\,effect}{non\text{–}exposed\,without\,effect}} = \frac{TP/FN}{FP/TN}$$

"rare disease assumption": low prevalence of an effect, i.e., P/all=small and TP/(TP+FN)= small $\Rightarrow$ **RR ≈ OR**

Good explanation in Wikipedia, "Relative Risk", "Odds Ratio"

Non-linearity: Some references, 1

- Latest: Rosenberger A. et al.[1] propose U-shaped relationship but no hormesis
- Meta-analysis by Duan et al.[2] showed evidence of non-linear response, partly sub-, partly super-linear; no hormesis.
- Studies in the region of a Rn spa in Japan showed no effect of elevated Rn; possibly bio-positive effect (hormesis).



[1] Rosenberger A. et al. (preprint 2022): On the non-linearity of radon-induced lung cancer; DOI: https://doi.org/10.21203/rs.3.rs-1933741/v2

[2] Duan et al. (2015): Nonlinear dose – response relationship between radon exposure and the risk of lung cancer: evidence from a meta-analysis of published observational studies. DOI: 10.1097/CEJ.0000000000000066

Non-linearity: Some references, 2

- Some say that **LNT < 100 mSv is not proven**, e.g., Kino (2021)[1].
  Very roughly, 100 mSv ≅ 20 years with 100 Bq/m³.
- Nilsson & Tong (2020): No detrimental effect proven below 100-200 Bq/m³; "Clear risk" above 200-300 Bq/m³ [2].
- Tubiana et al. (2009): "No convincing epidemiologic data support the LNT relationship."[3]
- Comment:
  While it is true that the LNT for low dose is not proven – actually **it cannot be proven for deliberately low dose** – it is also a fallacy to suggest that therefore an alternative model must be true. This cannot be proven for the same reason. Decision between models that all fit to data is a difficult task!

[1] Kino et al. (2021):Considering Existing Factors That May Cause Radiation Hormesis at <100 mSv and Obey the Linear No-Threshold Theory at ≥100 mSv. Challenges 2021, 12,33 https://doi.org/10.3390/challe12020033
[2] Nilsson & Tong (2020): Opinion on reconsideration of lung cancer risk from domestic radon exposure. https://doi.org/10.1016/j.radmp.2020.01.001
[3] Tubiana et al. (2009): The Linear No-Threshold Relationship Is Inconsistent with Radiation Biologic and Experimental Data; 10.1148/radiol.2511080671

Hormesis ??

- Frequent argument: **Radon spas**
  - It seems that controlled exposure to Rn in water or in a defined atmosphere is useful for certain diseases, such as rheumatism and related.
  - Lung dose is not so high in such treatment; skin dose? other exposure?
- Experience in **Ramsar** / Iran: high doses due to Ra in building material: apparently positive effect.
- Possibility of **adaptive response** to ionizing radiation ??
- Classical papers by **B. Cohen** (1980s, 1990s); ecological studies, criticized for problematic design, missing confounders, but apparently qualitatively confirmed by more exact re-analysis.
- **The "Polish school"**: L. Dobrzyński†, K. Fornalski, J. Reszczyńska, M. Janiak, P. Waligórski, M. Pylak, P. Kukulski, etc: Statistical re-analysis of existing data shows that Rn < some 100 Bq/m³ has no detrimental effect or is even beneficial. Summary paper [1].
- A fierce advocate of hormesis is Sanders (2010) [2]; many examples; quite polemic at times, not really convincing. A rather funny argument in the preface: *"The author acknowledges that the Lord made ionizing radiation to benefit his creation."*
- **Sceptical position: BfS** [3]: "Possible positive effects of ionising radiation refer to individual cases and must not be transferred to the population."

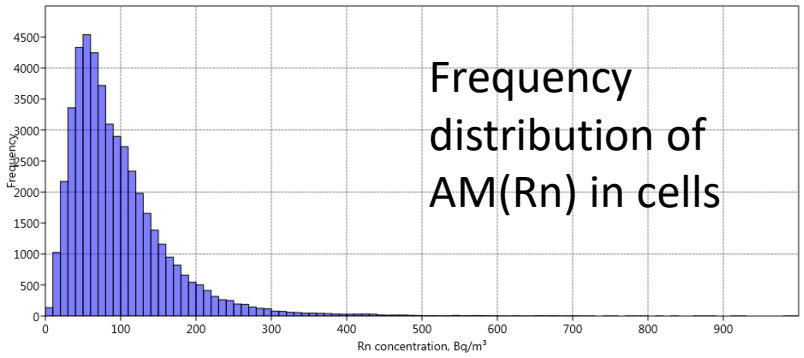
[1] Janiak et al. (2023): Can Low-Level Ionizing Radiation Do Us Any Harm? DOI: 10.1177/15593258221148013
[2] Sanders (2010): Radiation Hormesis and the Linear-No-Threshold Assumption; Springer. DOI: 10.1007/978-3-642-03720-7. Chapter 9 about Rn.
[3] www.bfs.de/EN/topics/ion/effect/hormesis/hormesis.htm

Possible consequences

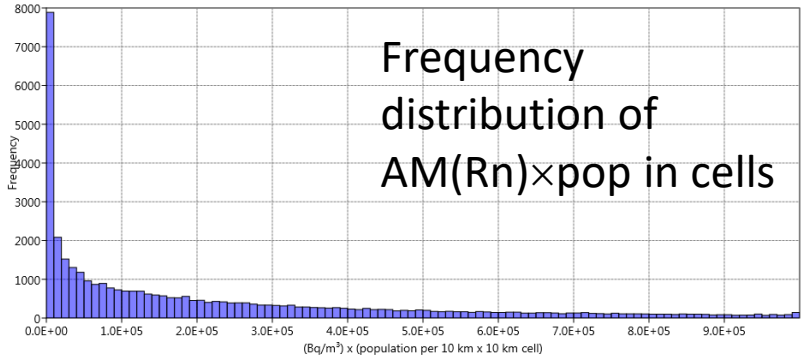
- Little consequences related to high exposure, i.e., exposures above reference level 300 Bq/m³ (as long as the linearity threshold is not assumed > RL). Therefore, also Rn priority areas (RPAs) would be little modified.
- Large consequences for estimating attributable risk or total detriment = number of lung cancer fatalities in a region or country, because most of collective exposure is due to low individual exposure.

Why is it relevant?

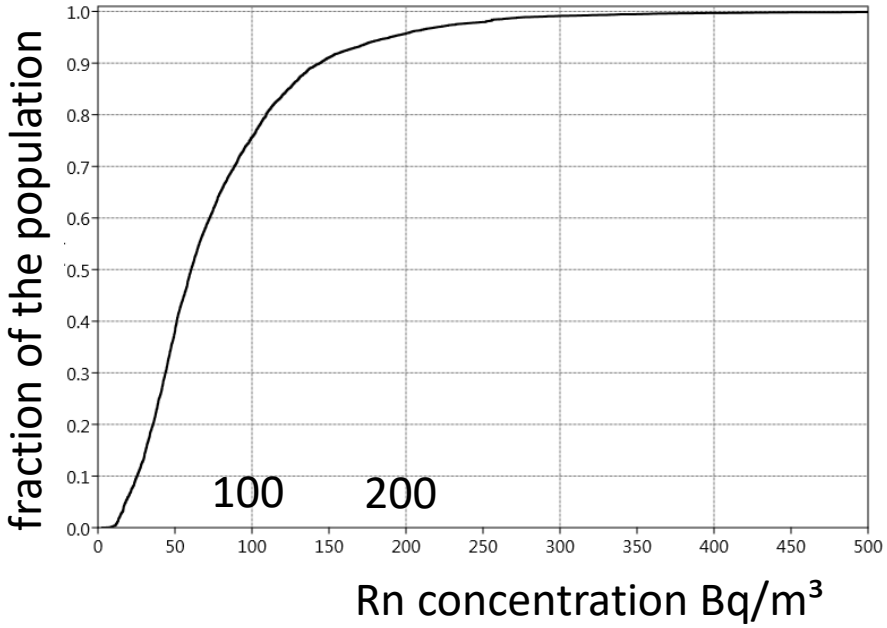
- Most Europeans are exposed to Rn < 100 Bq/m³
- ⇒ for the majority of the European population the risk model is uncertain!



Frequency distribution of AM(Rn) in cells



Frequency distribution of AM(Rn)×pop in cells



Hazard, risk, detriment

- Individual exposure and risk is related to the Rn hazard
- Risk = hazard × vulnerability × people × risk factor
- H(x) = hazard at location (x), e.g.,
  - Rn concentration under standard condition (ground floor, standard house etc.) or
  - the geogenic Rn potential (GRP) or
  - proxies such as U in the ground, ambient dose rate (ADR)
- V(i) = Vulnerability of a person (i) at a location due to conditions or factors, such as
  - floor level
  - building / construction type, presence of basement,…
  - ventilation
  - exposure time
- IE(i,x) = individual exposure of person (i) at (x) = H(x) ×V(i)
- Presence of people exposed to IE(i,x) = number of persons in building at (x) under conditions V(i) = N(i,x), quantified e.g. as population density under condition V = ρ(x,V)
- RF = risk factor, e.g. chance of lung cancer fatality per exposure = RF(IE)
- Σ_i IE(i,x) RF(IE(i,x)) = collective risk at location (x) = CR(x)
- Σ_x CR(x) = detriment = collective risk = number of lung cancer fatalities in a region. (Usually per year)

Example

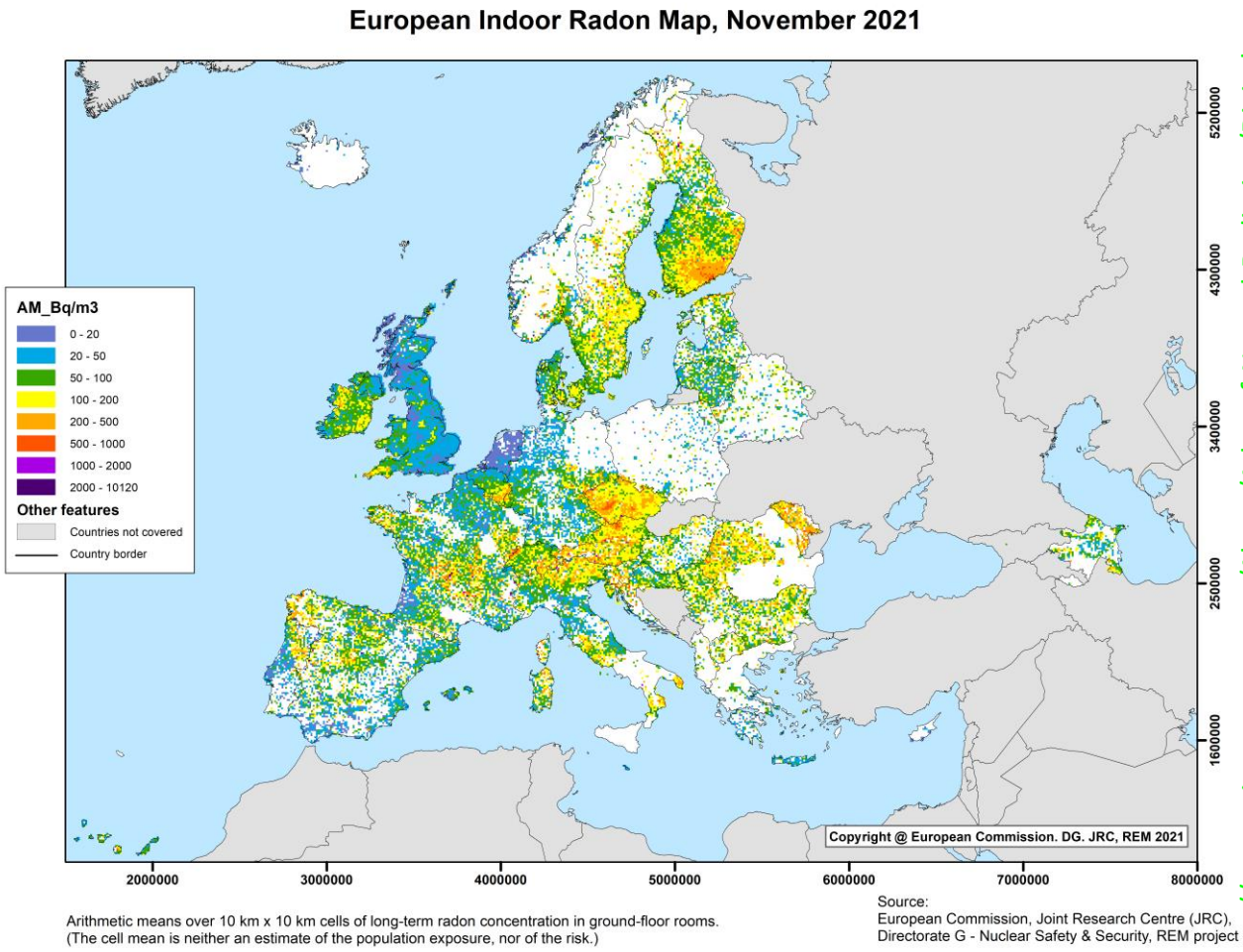
- Strongly simplified, only to visualize the consequences of different risk models!
- European indoor radon map, interpolated based on the European Atlas of Natural Radiation [1] and covariates, values C(x) = mean Rn concentration per cell (x) for ground floor rooms only $\Rightarrow$ V(i) = 1 = const.
- Presence of people: map of population density
- Relative risk RR: according to the different models RF_k
- additional individual risk due to Rn = background risk * (RR-1)
- background risk (r_0) of lung cancer depends on fraction of smokers; here simplistically assumed geographically const.
- additional risk due to Rn in one cell = N(cell)*r_0*[RR(Rn(cell)-1], Rn(cell)=mean Rn conc. in the cell. (Note that RR(mean Rn) $\neq$ mean(RR(Rn)) which would be more correct. But we do not have the individual data.)
- additional risk for model (k) normalized to the additional risk according to the LNT model (k=0).
- Resulting quantity:
  Detr(k) = $\int_x dx\ \rho(x)\ RF_k(C(x)) \approx \sum_{\text{cells } x} N(x)\ RF_k(C(x))$,
  N(x)=number of persons in cell x.
- Relative detriment = Detr(k) / Detr(0)

[1] https://remon.jrc.ec.europa.eu/About/Atlas-of-Natural-Radiation

European indoor radon map

European indoor radon database, from the European Atlas of Natural Radiation (2019):

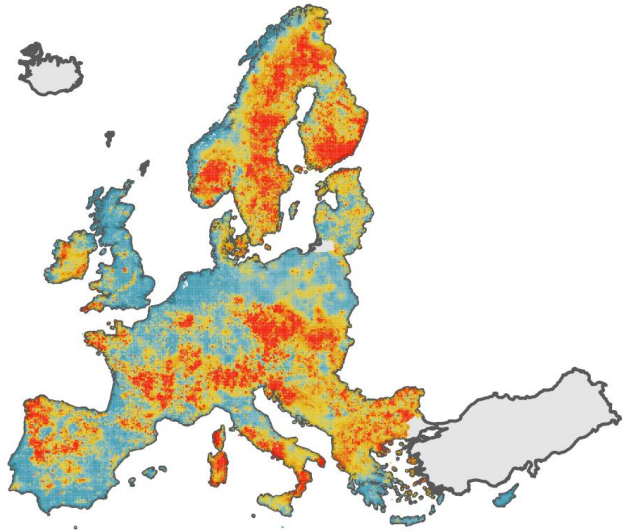
- about 1.2 mill. measurements, ground floor rooms, aggregated into 10 km × 10 km cells.
- Statistics: AM, SD*, AM and SD of ln-transformed data, min, median, max, N (data per cell). n=29,539 cells
- Exceedance probability prob(IRC>RL)* can be calculated under log-normal assumption in cells.

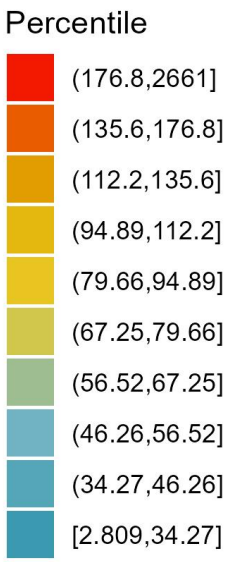


https://remon.jrc.ec.europa.eu/About/Atlas-of-Natural-Radiation/Digital-Atlas/Indoor-radon-AM/Indoor-radon-concentration

* AM, SD – arithmetical mean, standard deviation; RL – reference level

Interpolated radon map





Regression kriging, 4 steps:

- **Linear regression:** $log(AM) = X\beta + \varepsilon$

  Dependent variable (AM): mean IRC in ground floor rooms over 10 km × 10 km cells

  Independent variables: Geology (1:5 Million), and U and K_2O in topsoil.

- **Spatial distribution of the residual (ε):** Ordinary Kriging

- **Final estimates:**

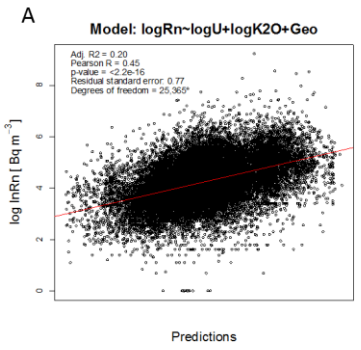
  μ = sum of the regression estimates and the ordinary kriging estimates

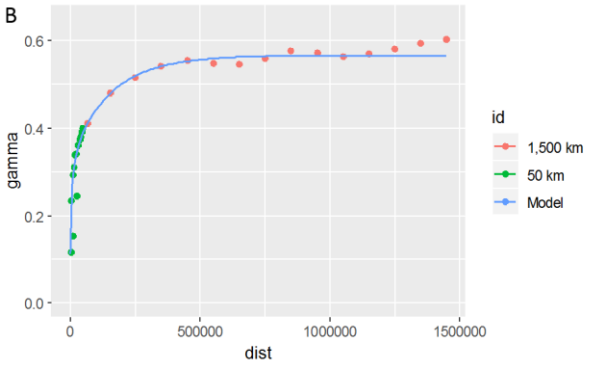
  σ = kriging variance

- **Back-transform to original scale:**

$$\mathbf{E}[X] = e^{(\mu + \frac{\sigma^2}{2})}$$

$$\mathbf{var}[\mathbf{X}] = \mathbf{e}^{(2\mu + \sigma^2)} \cdot \left(\mathbf{e}^{\sigma^2} - \mathbf{1}\right)$$





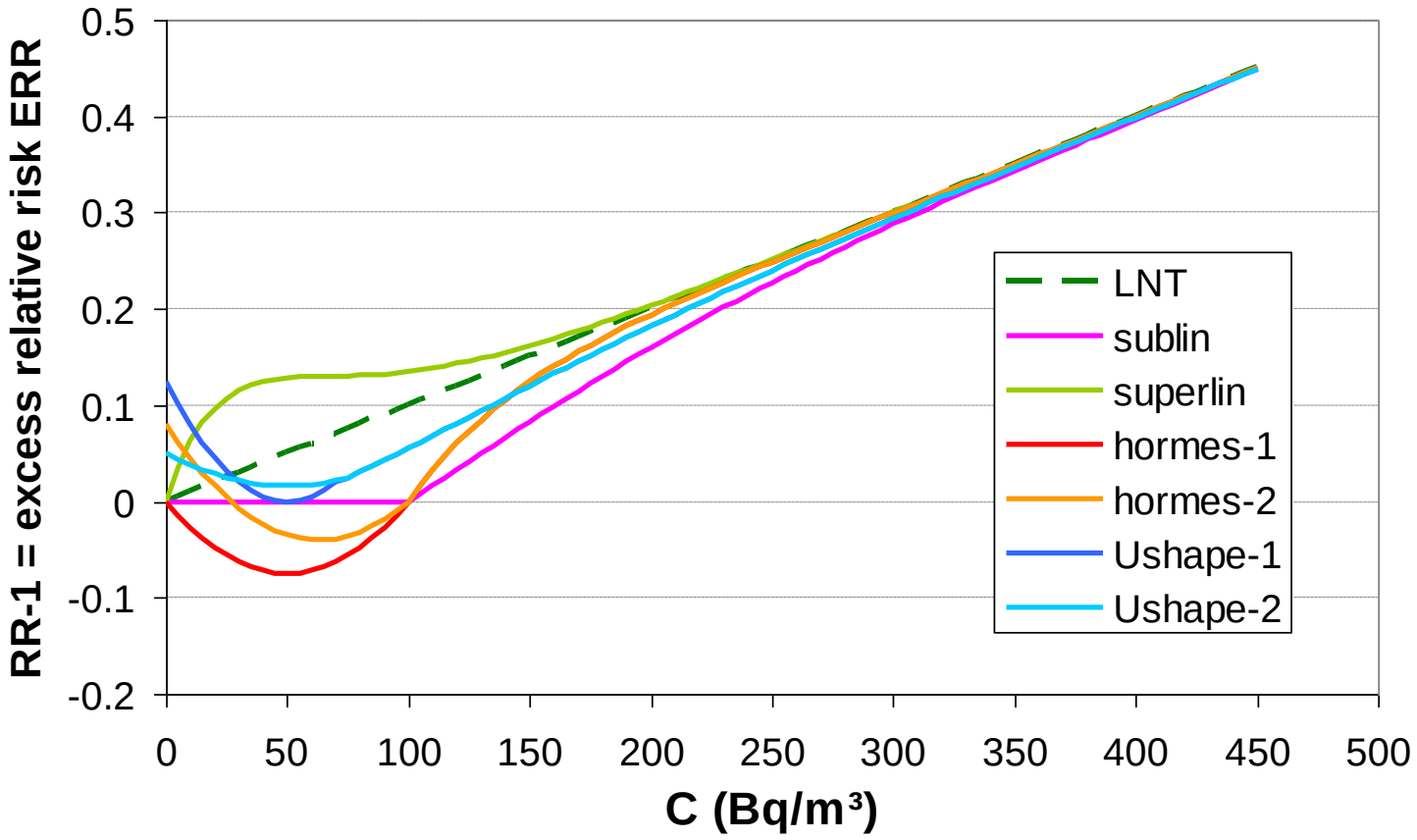
Elio et al: The first version of the Pan-European Indoor Radon Map, NHESS, 19, 2451–2464, 2019

Risk models

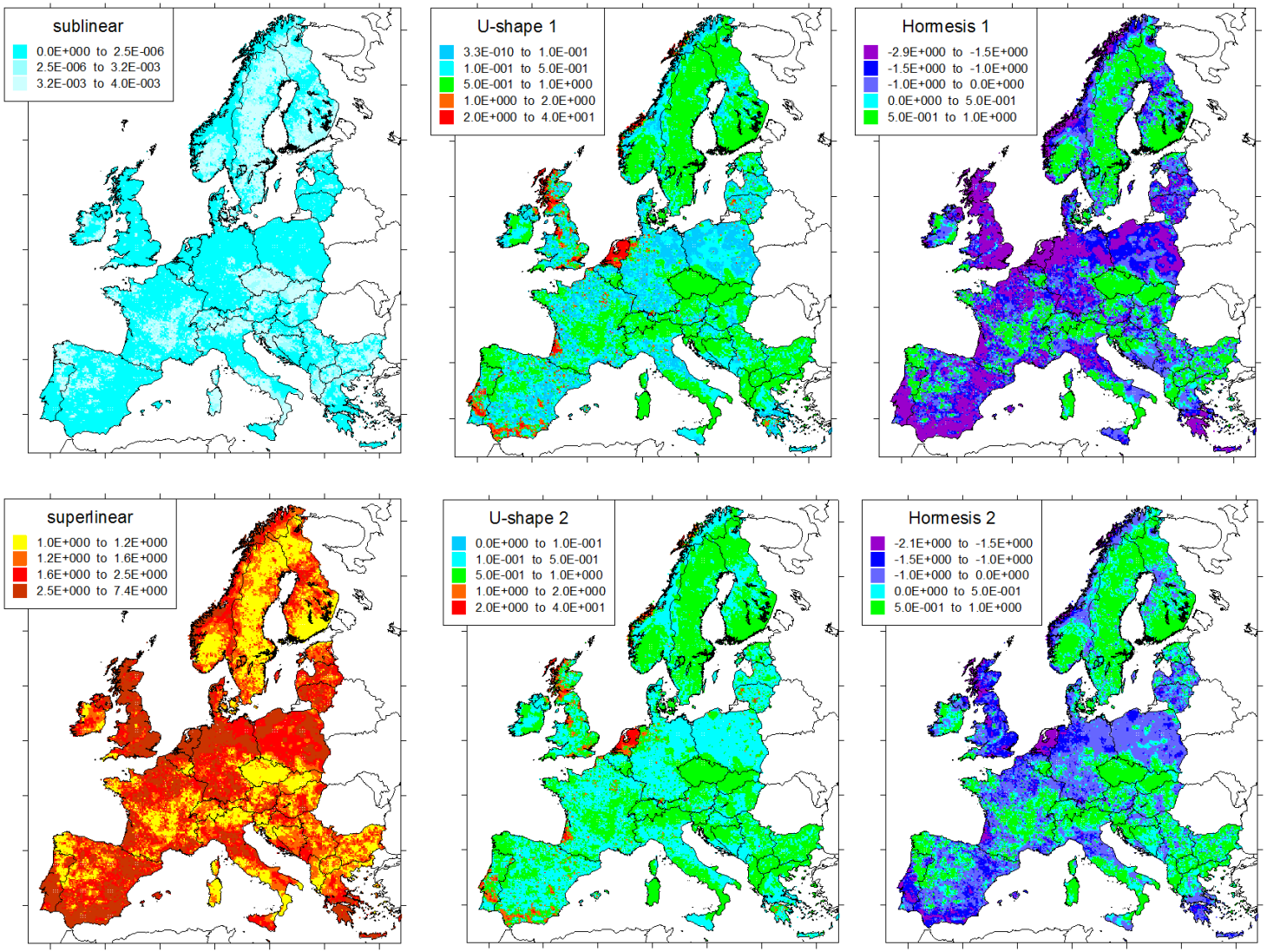
Assumed definitions of risk models – only for the sake of the example, neither functional forms nor parameters are based on epidemiological data!

LNT: $RR_0(C)-1 = \alpha\, C$, $\alpha=0.001 \leftrightarrow$ 10% per 100 Bq/m³

(Other models: parameterization not shown here)



Result 1



additional risk due to Rn for different models of relative risk, relative to the LNT model

purple – dark blue: Rn healthy! / light blue - green: little Rn risk < LNT / yellow – red: Rn risk > LNT

Result 2

Relative detriment = Total additional risk over Europe due to Rn according to different models, relative to LNT

According to numbers (means) in Gaskin et. al. (2018), Tab.2, https://doi.org/10.1289/EHP2503

missing: RS, BiH, MK, MT, XK, LV

numbers to be taken with many grains of salt!

model	relative detriment	detriment fatalities / a, Gaskin
LNT	1	44,574
sublinear	0.0014	63
superlinear	1.74	77,694
hormesis-1	-0.23	-10,270
hormesis-2	0.18	7,845
Ushape-1	0.59	26,212
Ushape-2	0.63	27,951

All models about compatible with the data.

This variability reflects the component of the uncertainty budget related to the choice of model (epistemic uncertainty).

Conclusions & To-do

- **For the majority of the Europen population: risk model uncertain.**
- **Choice of the risk model has large influence on the detriment attributable to radon.**
- **If the community should come to the conclusion that an alternative risk model should be used, this would have consequences on regulation and on Rn Action Plans! – In other words, a highly political matter.**
  If hormesis exists, Rn protection policy would even be counter-productive in the hormetic dose range.
- **But we think that the discussion should not be suppressed for reasons of political or ideological unease – what ever the outcome in the future.**
- **One may have to revise the frequent statement that Rn is the second cause, or one of the leading causes of lung cancer after smoking.**
- **It has been proposed to replace "LNT hypothesis" by "LNT concept"** [2]
- <u>To do</u>
- Specification of alternative models according to literature;
- Accurate consideration of individual exposure, e.g., like in Petermann et al. (in work)[1], where floor levels are accounted for.
- Uncertainty budget: several sources of different type, probably not easy to handle.

[1] Petermann et al. (2023): Estimating national indoor radon exposure at a high spatial resolution – improvements by a machine learning based probabilistic approach. EGU, https://doi.org/10.5194/egusphere-egu23-6423
[2] Gellermann & Brechow, Strahlenschutzpraxis 1/2023, p.81

Thank you!