# Biologically-Motivated Mechanistic Models

ICRP TG91

Radiation Risk Inference at Low-Dose and Low-Dose-Rate Exposure for Radiological Protection Purposes

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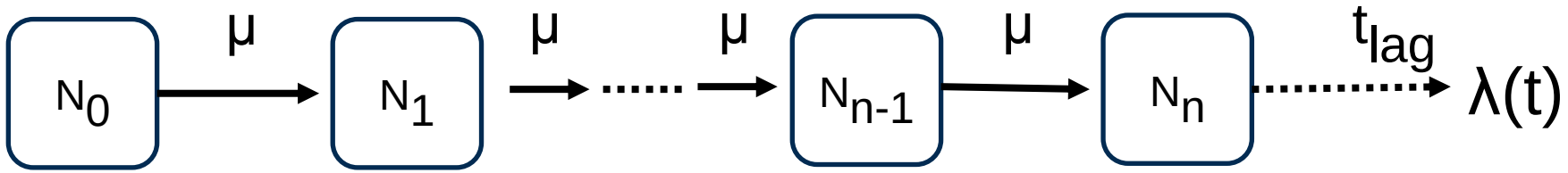
# History in a Nutshell

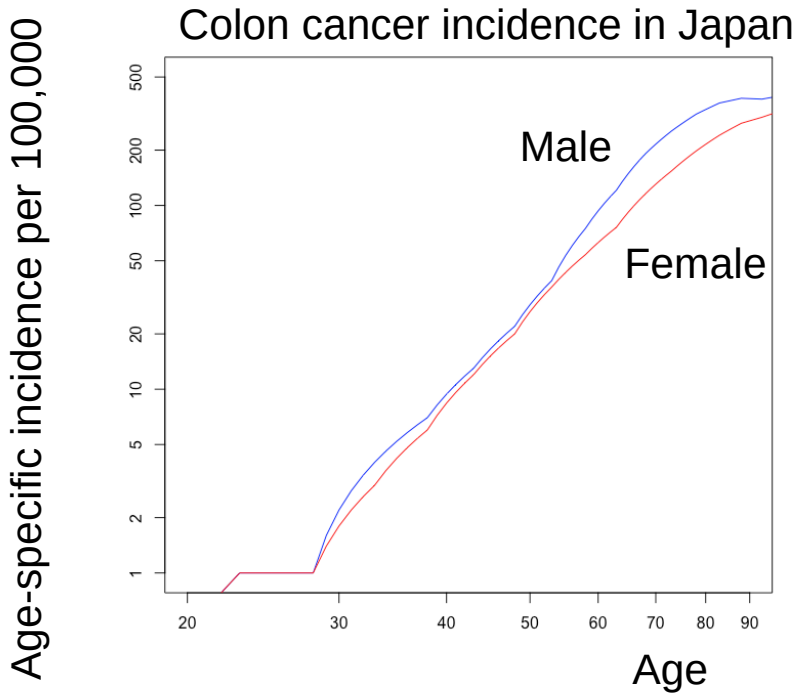
- **Biologically-based mechanistic models (BMD) have been used to discuss the process of carcinogenesis with appropriate quantitative data**
- **In 1950s, Nording postulated six or seven mutational cellular changes to develop cancer among humans.**
- **Armitage and Doll (1954) to develop a mathematical formalism, multistage theory of carcinogenesis to describe the observed cancer mortality.**
- **Armitage and Doll (1957) to develop two-stage model,**
  - the first stage is the production of a mutation in a healthy cell
  - the second stage is a mutation to confer a selective advantage on the changed cells.
- **Knudson (1971) explained the occurrence of retinoblastoma by two mutational events.**
- **Two-stage clonal expansion (TSCE) models were developed by Moolgavkar and Venzon (1979)**

# Multistage theory of carcinogenesis model

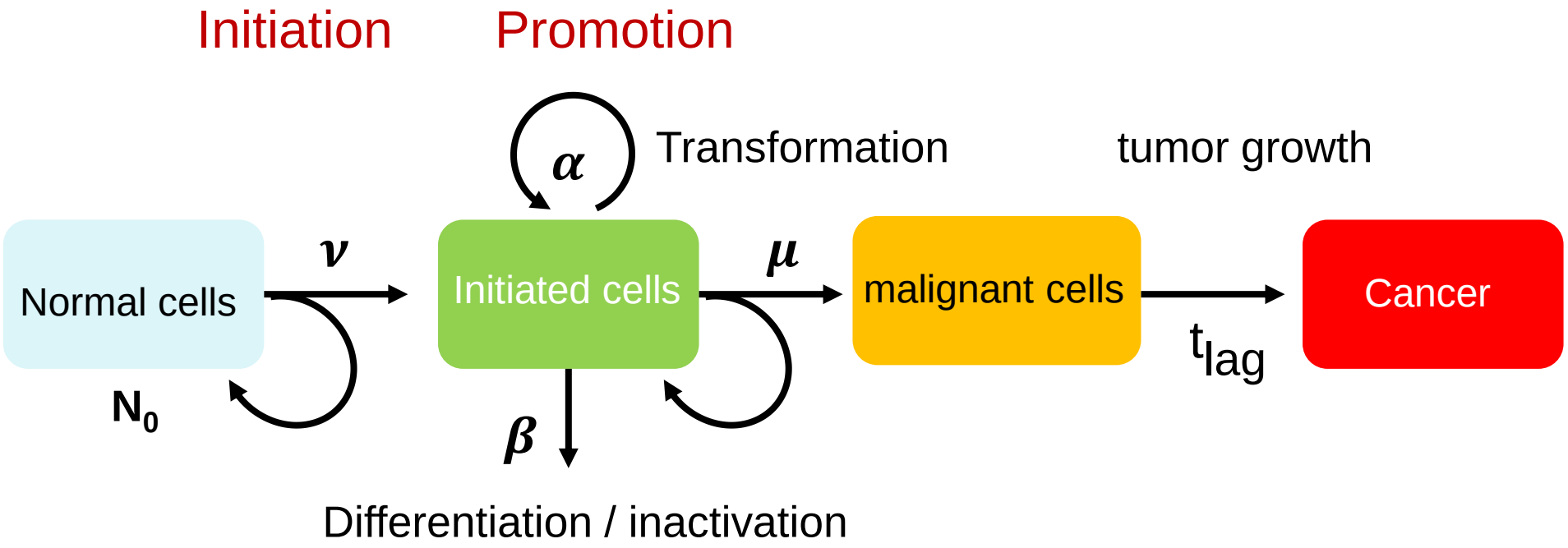



Normal cells Transitional cells Cancer cells Mortality rate

$$\lambda(\mathrm{t} + t_{lag}) = \frac{N_0 \mu^n}{(n-1)!} t^{n-1}$$



# Two-stage clonal expansion (TSCE) model




$$\lambda(\mathrm{t} + t_{lag}) = \frac{\nu N_0}{\alpha} pq\{e^{-qt} - e^{-pt}\}$$

$$p = \frac{1}{2}\left\{(-\alpha + \beta + \mu) - \sqrt{(\alpha + \beta + \mu)^2 - 4\alpha\beta}\right\}$$

$$q = \frac{1}{2}\left\{(-\alpha + \beta + \mu) + \sqrt{(\alpha + \beta + \mu)^2 - 4\alpha\beta}\right\}$$

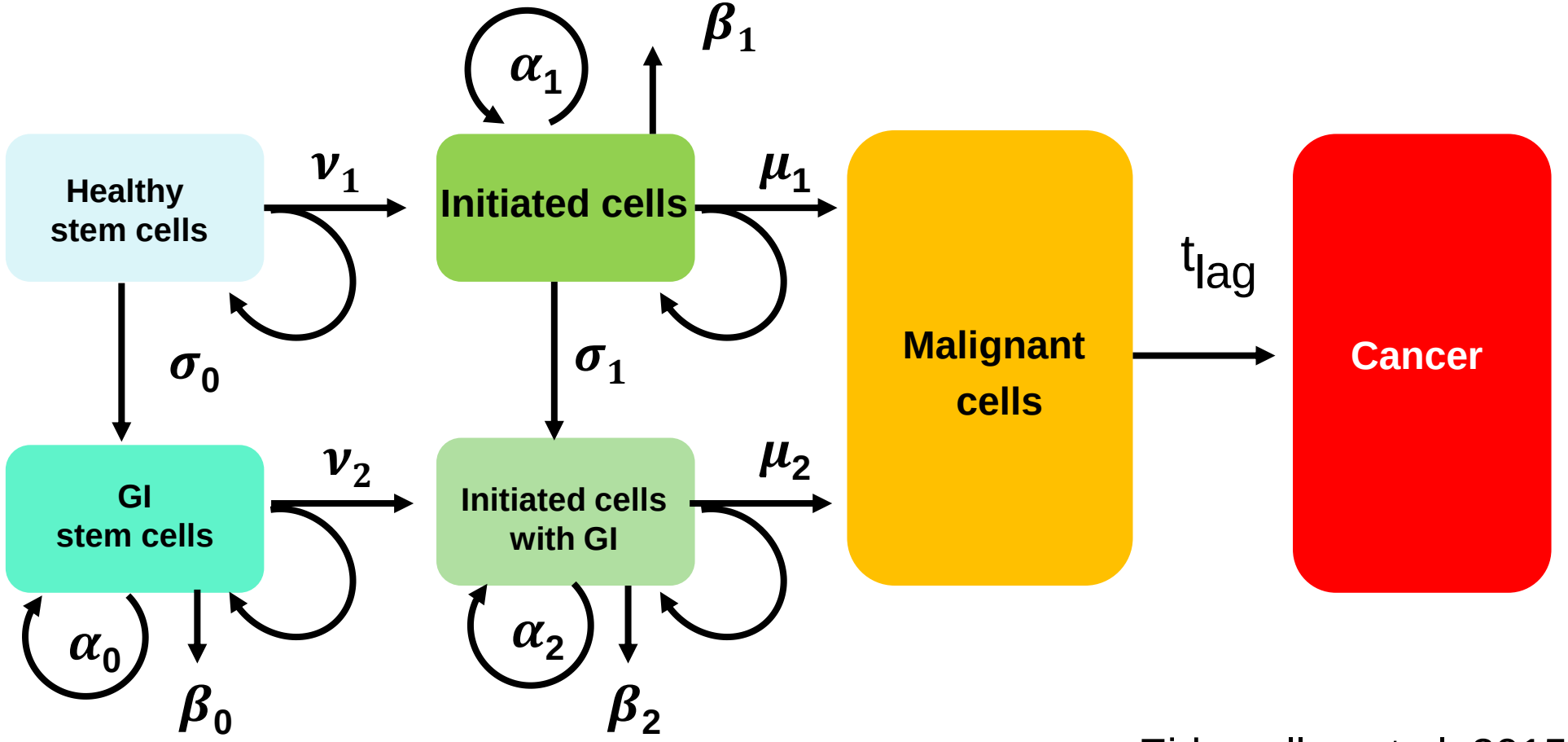
# Atomic Bomb Survivors

- **Fit to solid cancer incidence, Kai et al (1997)**
  - Radiation acts linearly with dose on initiation of healthy cells
  - Fit to Japanese incidence data for lung, stomach and colon cancer (1958 - 1987 incidence follow-up)
- **Comparison among several models, Heidenreich et al (2002),(2007)**
  - RERF data suggest that a number of models including multistage models can describe cancer incidence equally well.
  - Promotion effects of radiation were suggested from protraction.
- **Cell inactivation, Jacob et al (2008)**
  - Examine the possible influence of radiation-induced cell inactivation
  - Radiation acts on initiation / transformation **and** inactivation / promotion
  - Most of the preferred models describe the data better than the preferred empirical (relative or absolute) risk models

# More sophisticated models

- **Age-at-exposure effects, Shuryak, et al. (2010)**
  - A new formalism was developed by assuming radiation initiates, promotes, or kills pre-malignant cells; a pre-malignant cell generates a clone.
  - Promotional processes in radiation carcinogenesis become increasingly important as the age at exposure increases.
- **Genomic instability, Eidemuller, et al. (2015)**
  - Develop an extended TSCE model considering Genomic Instability for colon cancer
  - A radiation-induced transition towards genomic instability was highly significant.
  - Main effect of radiation-induced genomic instability is to increase the rate of transition of non-initiated cells to initiated cells with a proliferative advantage.
- **Kaiser, et al. (2014)**
  - The CIN pathway exhibits a strong radio-sensitivity
  - Among young birth cohorts of both sexes the excess absolute radiation risk related to CIN is larger by an order of magnitude compared to the MSI-related risk.

# Extended TSCE model considering Genomic Instability




Eidemuller, et al. 2015

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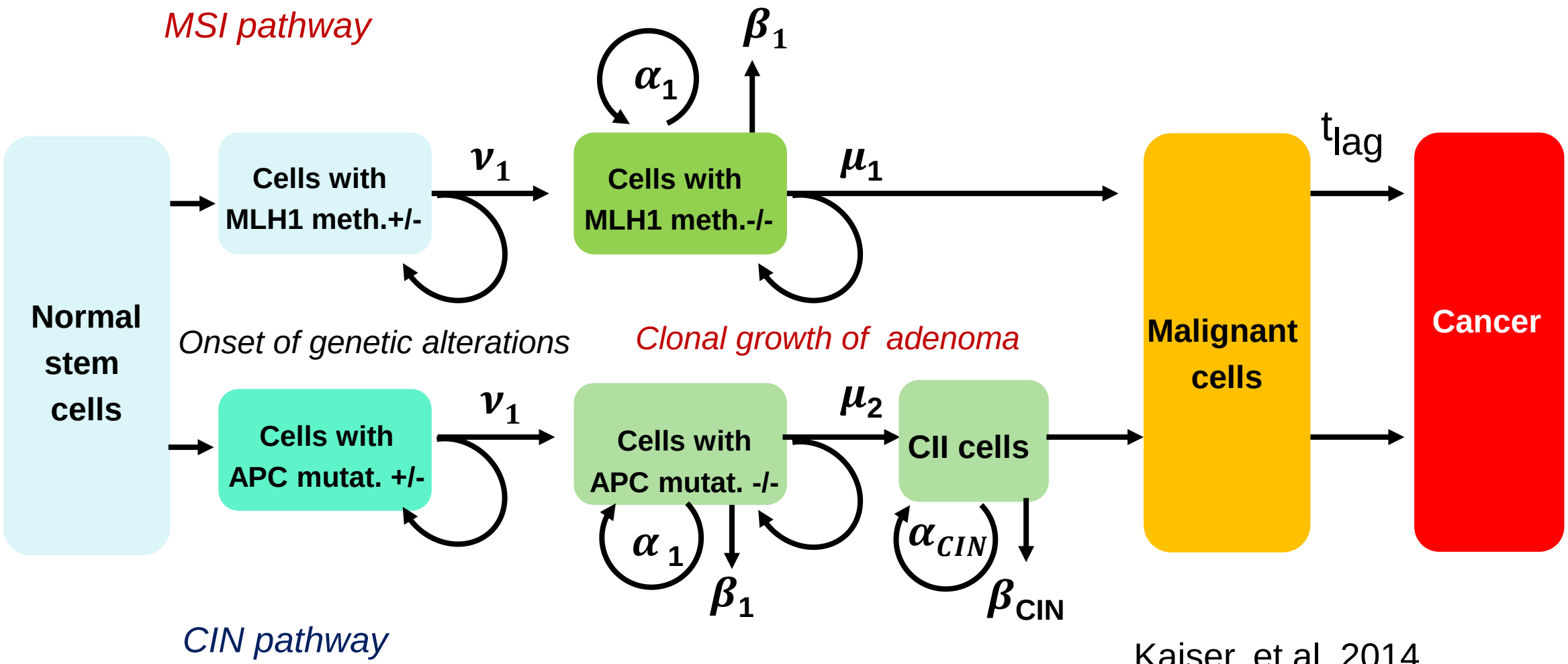
# Extended TSCE model considering MSI and CIN

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# Other model analyses

- **Long-term exposure model, Shuryak, et al. (2009)**
  - A typical radiation dose–response, which is determined by the balance of cell initiation, inactivation (killing), and repopulation.
  - Fractionation of the dose increases cancer ERR because repopulation of both normal and pre-malignant cells during the inter-fraction intervals compensates for much of the cell killing.
- **Techa-River cohort,  Eidemuller et al (2010)**
  - Data could be described equally well by a model incorporating effects of genomic instability using TSCE model.
- **Thyroid cancer in Chernobyl, Kaiser et al (2016)**
  - Propose a mechanistic model motivated by the CLIP2 describes PTC development
  - The model constitutes a unique interface between molecular biology and radiation epidemiology.

# Conclusions - On the Use of Mechanistic Models

- **Arguments that tend to support the use of biologically-motivated models:**
  - The numerical values obtained are in most cases biologically plausible
  - In many cases, they perform similarly or better than descriptive models
  - Good description of investigated endpoints as a function of time since exposure
- **Thus, the assumed mechanisms (initiation, transformation, promotion) might play some role in carcinogenesis**
- **The TSCE model can provide robust risk estimates without additional assumptions, and offers an inherent flexibility to add more stages**
- **Various options of radiation action, including nonlinear processes can be tested**
- **We expect that the approach of using these biologically-based models will continuously benefit in the future from growing knowledge on carcinogenesis**

# Conclusions - On Shape of Dose Response

- **Only very rarely the implications of such models on the shape of dose-response was investigated**
- **Even if the radiation action is assumed linear, the overall dose response is not necessarily be linear**
- **If radiation acts at different process in carcinogenesis, the dose rate effects considering fractionation is needed to be further investigated.**
- **A systematic investigation of the implication of mechanistic models on dose response is needed and currently being performed by the authors**

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