Shape of the dose-response curve and its importance re leukemia risk

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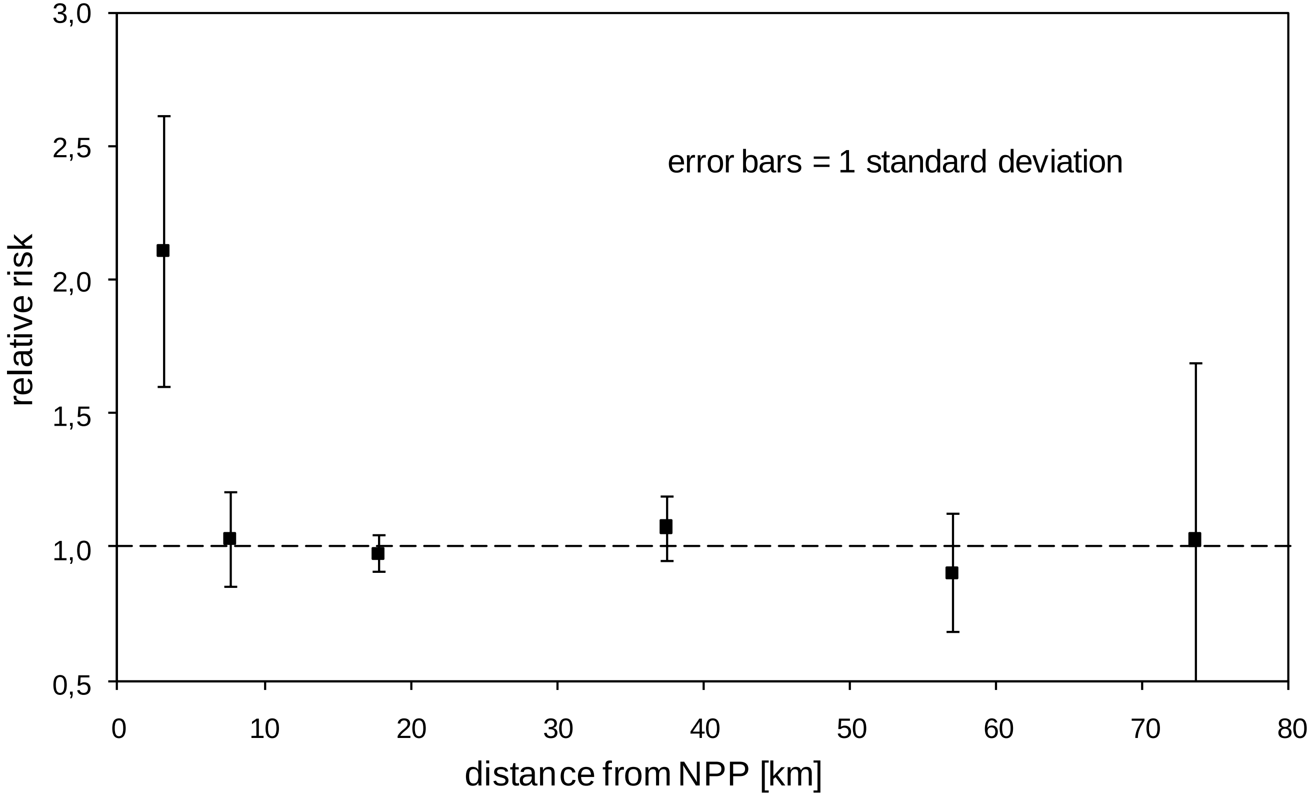
Leukaemia incidence in children < 5 y near German nuclear power plants (KiKK study)

regression model: r < 5 km compared with r > 5 km



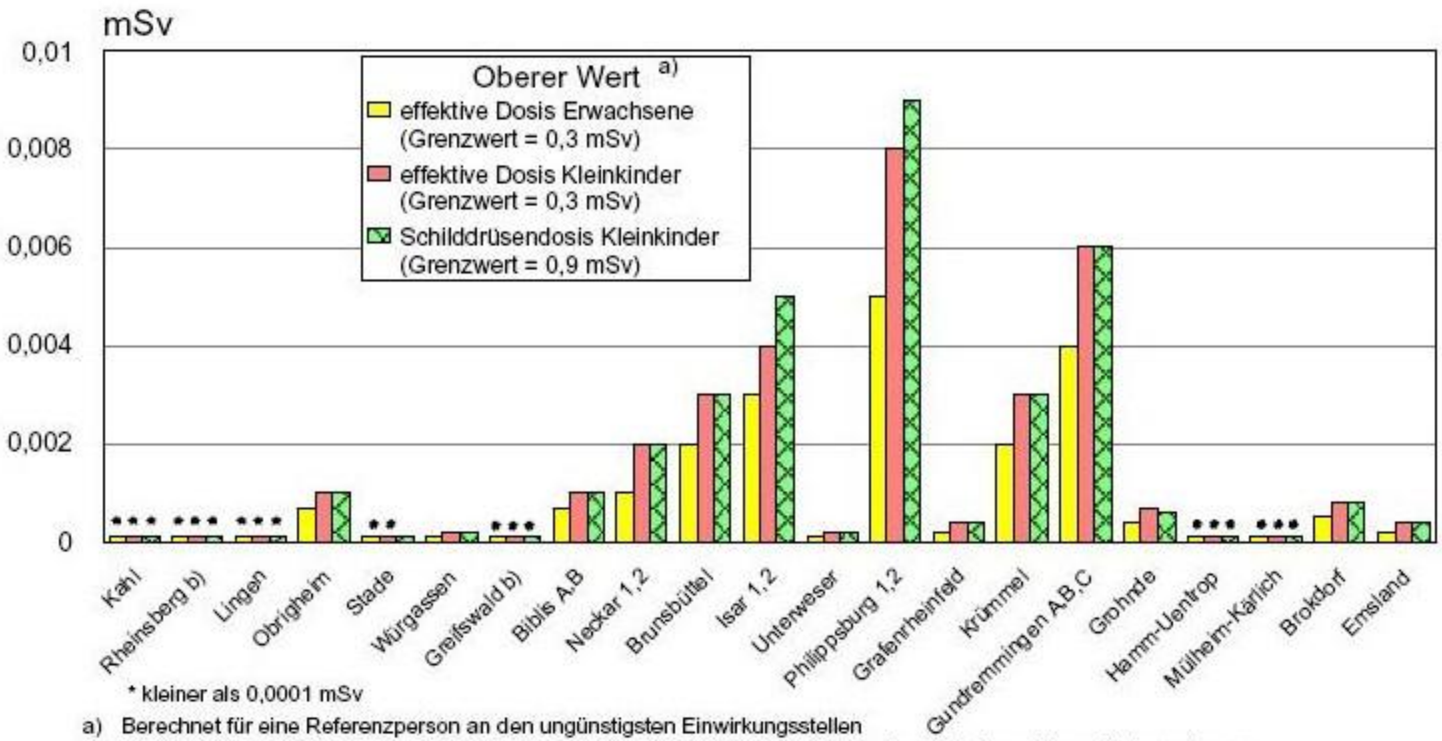
Radiation can cause leukaemia in children - but there is a discrepancy of a factor of 1000!

- KiKK found leukemia risks were ~ doubled (RR=2.19) in children under age 5 near NPPs
- Doubling dose for childhood leukemia:
  some mSv after in utero exposure in first trimester
  according to Stevenson, Strahlenbiologisches Gutachten, page 92
- Official dose estimate for 1 year old children:
  some µSv per year , ie 1000-times smaller than doubling dose
  see: http://dip21.bundestag.de/dip21/btd/16/068/1606835.pdf

Deutscher Bundestag - 16. Wahlperiode - 17 - **Drucksache 16/6835**

Abbildung II. 1-7

Strahlenexposition im Jahr 2006 in der Umgebung von Kernkraftwerken durch die Ableitung radioaktiver Stoffe mit der Fortluft



a) Berechnet für eine Referenzperson an den ungünstigsten Einwirkungsstellen

b) Die Strahlenexposition konnte für Expositionspfade, bei denen Radionuklide in den Vorjahren akkumuliert wurden, nur unvollständig berechnet werden, da bei diesen Kernkraftwerken Werte für die Ableitung radioaktiver Stoffe mit der Fortluft aus den Jahren vor 1990 (Greifswald) bzw. vor 1984 (Rheinsberg) nicht vorliegen

http://dip21.bundestag.de/dip21/btd/16/068/1606835.pdf

Official dose and risk estimates unrealiable

- Official dose calculations use simplified propagation models:
  Two dimensional Gauss model might be in error (up to ± factor 10)

- UK Government's Committee Examining Radiation Risks of Internal Emitters (CERRIE, 2004) concluded uncertainties in INTERNAL radiation doses were considerably greater than in EXTERNAL radiation doses

- Uncertainties accumulate:
  official dose and risk estimates might be low by a factor of 10 to 100!
  -> extra annual dose from NPP could be ~100 µSv/y = 0.1 mSv/y
  ie about 1/10 of background dose (excluding radon)
  (German legal dose limit = 0.3 mSv/y near NPPs)

The official risk estimates might be low
by a factor of 10-100, but
we need to explain a factor of 1000!

How to close the gap?

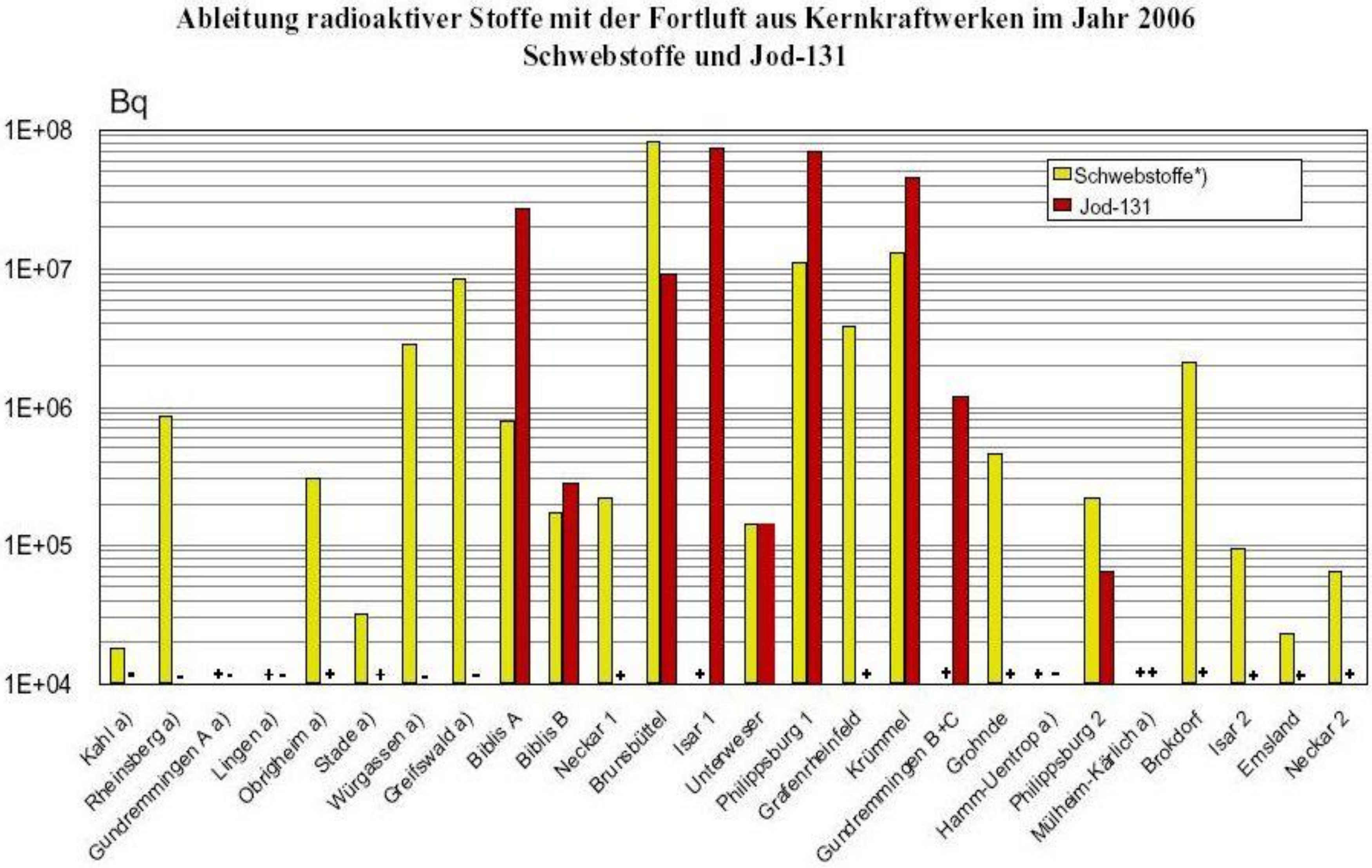
The usual assumption that risk is proportional to average dose is only correct if dose-response relationship is linear.

But:

(1) do we know the shape of the dose-response curve for leukemia induction in-utero?

(2) doses from NPPs show large variations in time and space while dose rate from natural background radiation is rather constant at a given location

Abbildung II.1-1



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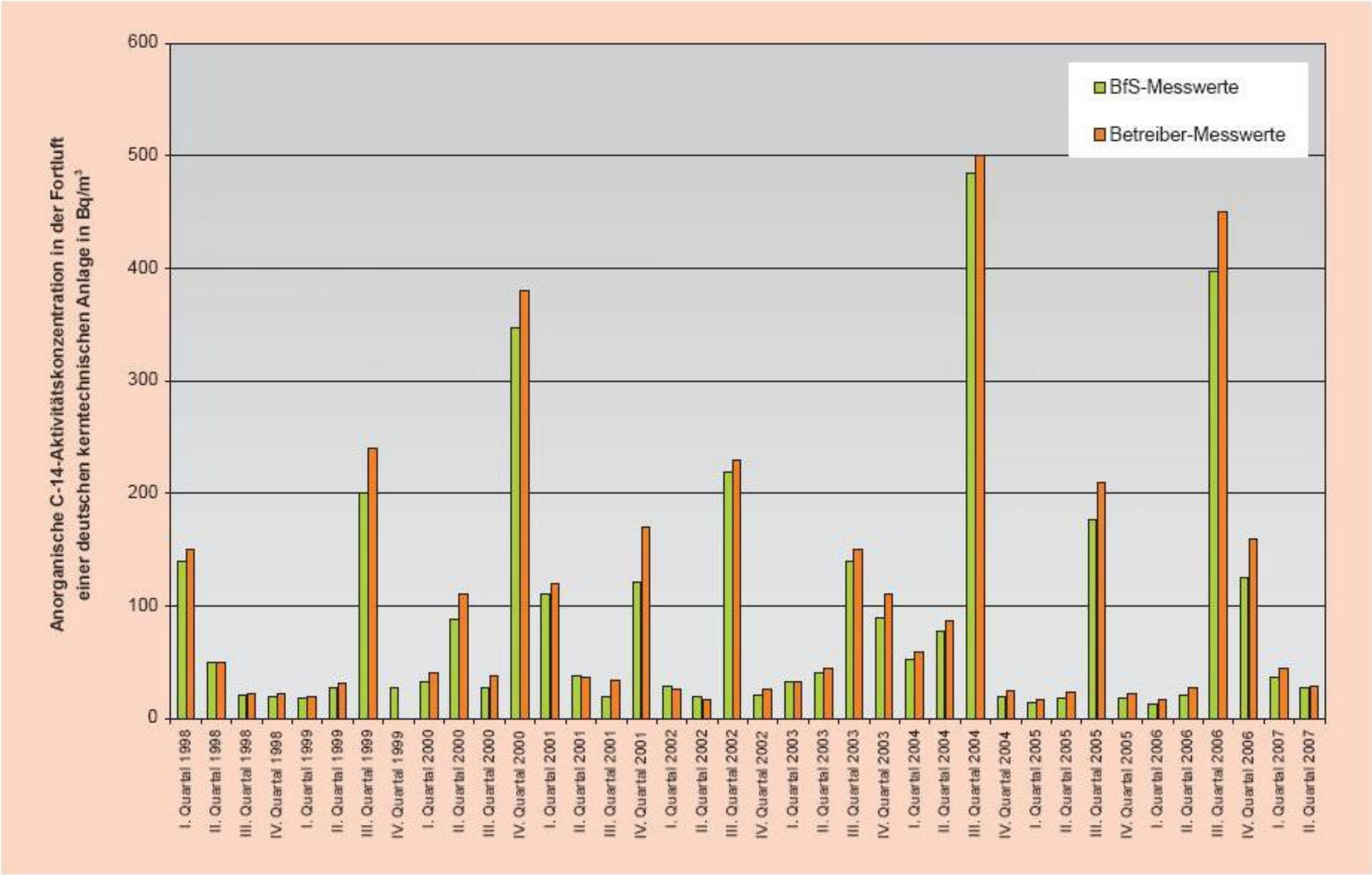
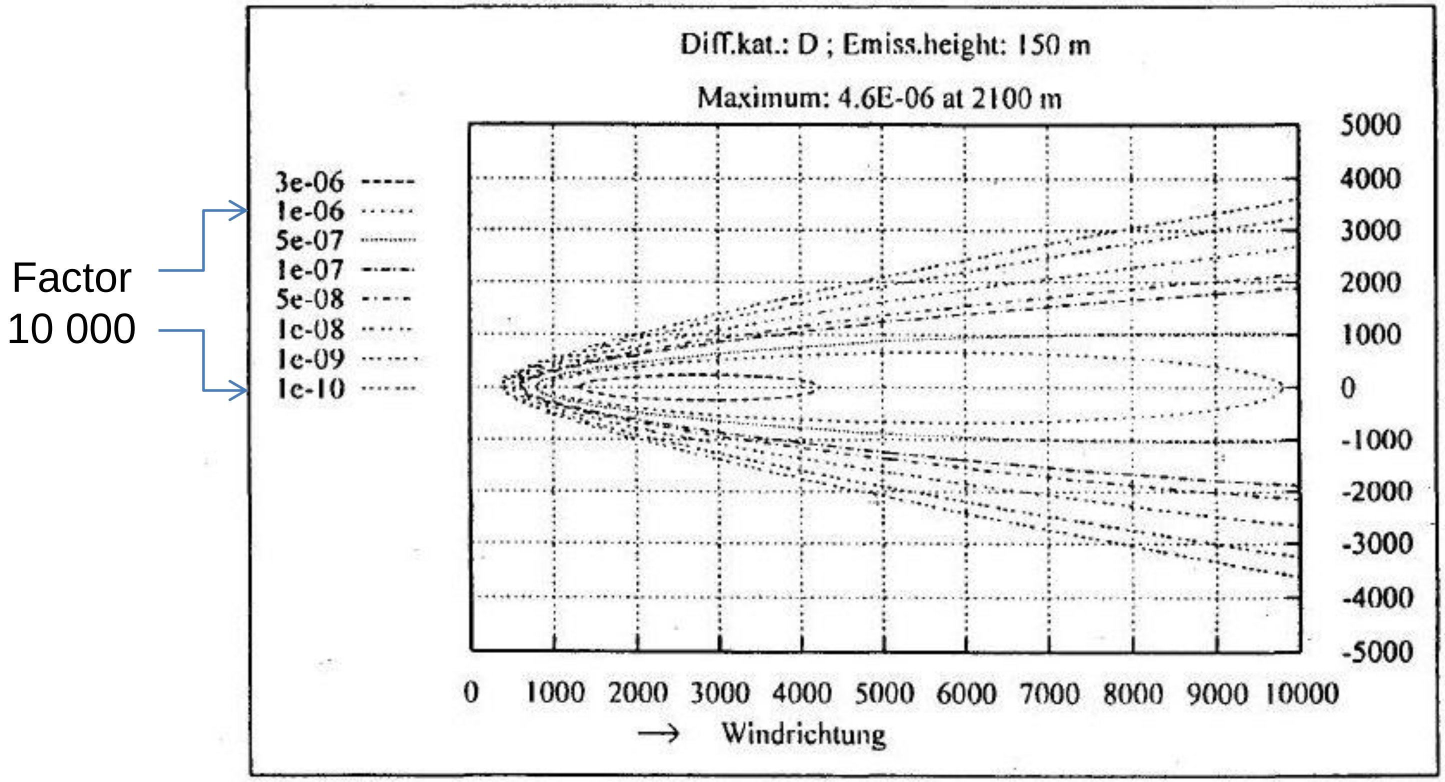


Vergleich der vom Betreiber und dem BfS ermittelten Kohlenstoff-14-Aktivitätskonzentrationen in der Fortluft am Beispiel eines süddeutschen Druckwasserreaktors (KKW Neckarwestheim 2)

Quarterly C-14 air concentrations near the German Neckarwestheim NPP. The columns are measurements by BfS (green) and by the utility (orange)
from: http://www.bfs.de/de/bfs/druck/uus/jb06_Gesamtbericht.pdf

Fig. 2: Isolines of the fallout disperison coefficient for a height of 150 m



Calculated isolines of the fallout dispersion coefficient for diffusion category D and stack height 150 meters. The calculated maximum fallout occurs at a distance of 2100 m from the NPP

From: Otfried Schuhmacher, Portsmouth conference 1996

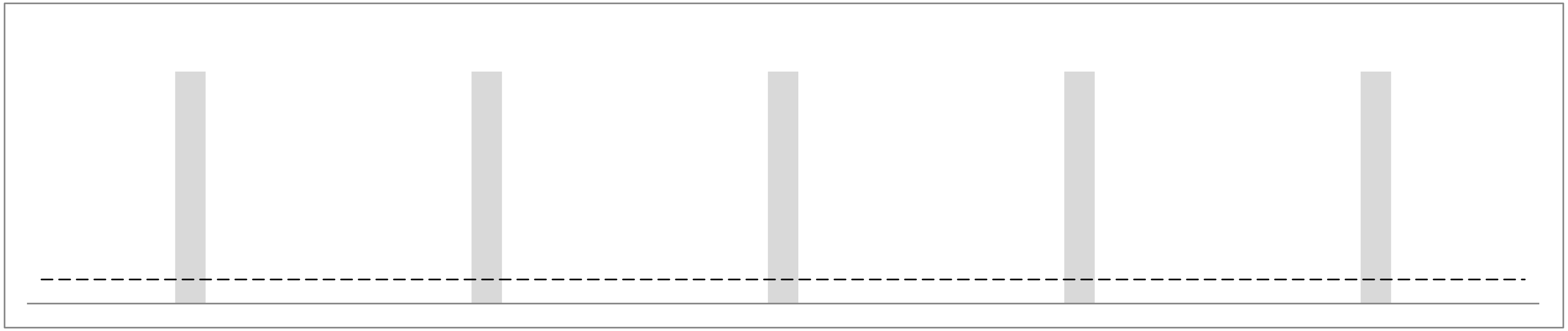
http://strahlentelex.de/PORTS_Schumacher.pdf

Combined effect of discontinuous emissions and curvilinear dose-response

Model calculation:

Natural background radiation: 1 mSv/y
Annual dose from muclear power plant: 0.1 mSv/y
Discontinuous emissions: 100% dose delivered in 1/10 of a year
Curvilinear dose-response with power of dose 3.5: risk ~ dose^3.5
Average risk: 0.1*(1+1)^3.5 + 0.9*(1+0)^3.5 = 2.03

Result: 10% increase in average dose -> 103% increase in risk!



Curvilinear dose-response relationship:

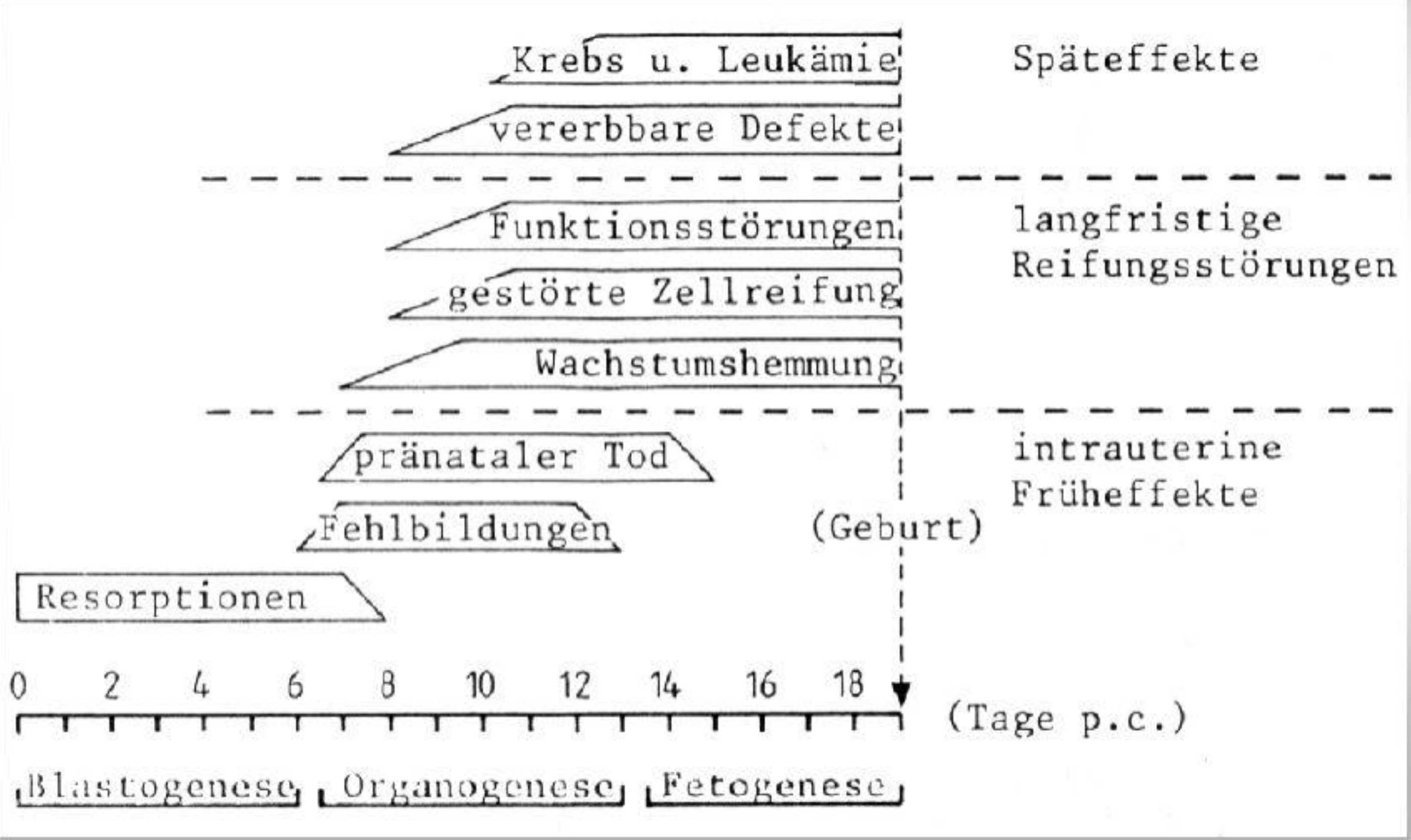
Results of model calculations for the dependency of relative risk on dose

excess relative dose from NPP			0,01			enhancement factor		
factor / power	10	20	30		factor / power	10	20	30
3	1,03	1,04	1,04		3	3,3	3,6	4,0
4	1,05	1,05	1,06		4	4,6	5,4	6,2
5	1,06	1,07	1,09		5	6,1	7,4	9,0
excess relative dose from NPP			0,03					
factor / power	10	20	30		factor / power	10	20	30
3	1,12	1,15	1,20		3	4,0	5,2	6,5
4	1,19	1,28	1,40		4	6,2	9,3	13,4
5	1,27	1,47	1,79		5	9,0	15,8	26,4
excess relative dose from NPP			0,10					
factor / power	10	20	30		factor / power	10	20	30
3	1,70	2,30	3,10		3	7,0	13,0	21,0
4	2,50	5,00	9,50		4	15,0	40,0	85,0
5	4,10	13,10	35,10		5	31,0	121,0	341,0

power = power of dose
factor = 365 days / exposure period [days]
RR = (1+avdose*factor)^power/factor + (factor-1)/factor
enhancement factor = (RR-1) / excess relative dose

STRAHLENBIOLOGIE – Teratogenes Risiko

Pränatale Induktionsphasen für Strahlenwirkungen bei der Maus



from: http://radioonkologie.uniklinikum-leipzig.de

Strahlenwirkung

http://gd1.med.uni-giessen.de/ugm_2/deu/ugi_nuk/PDF/Rad_V2_Strahlentherapie.pdf

Assumptions

1. Annual background dose (excluding radon) ~ 1 mSv/a
2. Average additional dose from NPP: ~ 0.1 mSv per year (ie ~ 10-100 times larger than official estimates)
3. Discontinuous emissions from NPPs
4. Random distribution of both doses and radiosensitivities in a population

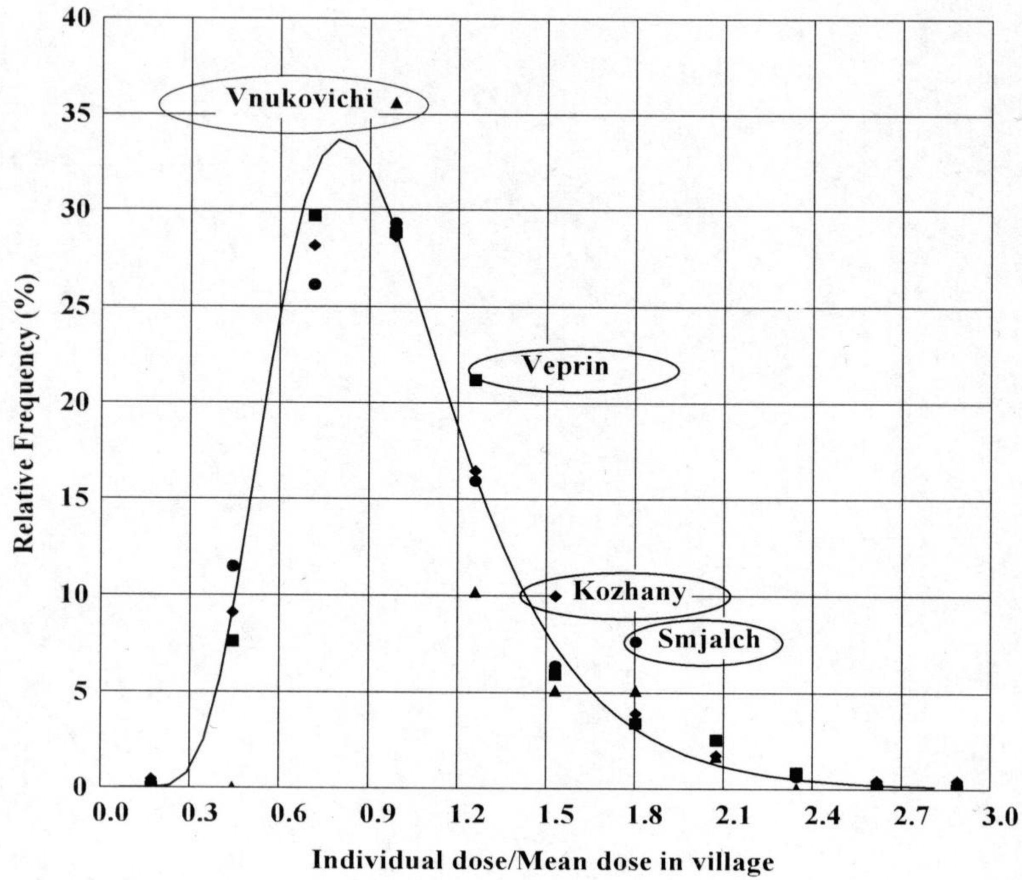


FIG. 4.11. Frequency distributions of monthly effective external doses of individual persons as measured in summer 1993 with TL dosimeters in four villages of the Bryansk Oblast (points) and calculated by the stochastic model (curve). Doses are normalized to the arithmetic mean of the individual doses determined for each of the villages. From Golikov et al. (2002).

Shape of the dose-response curve

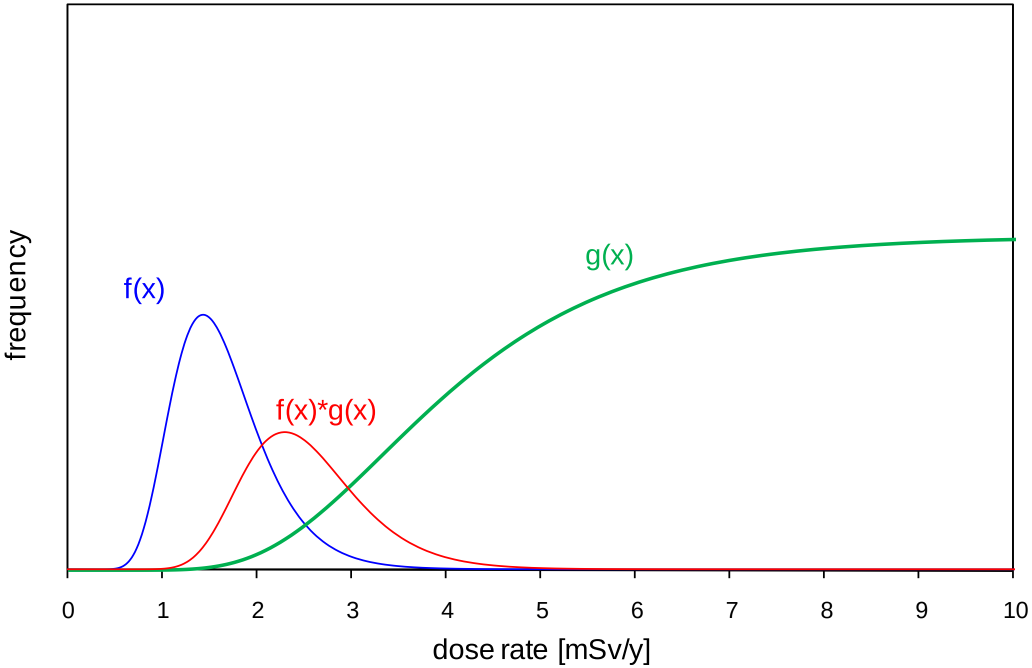
Mathematical derivation

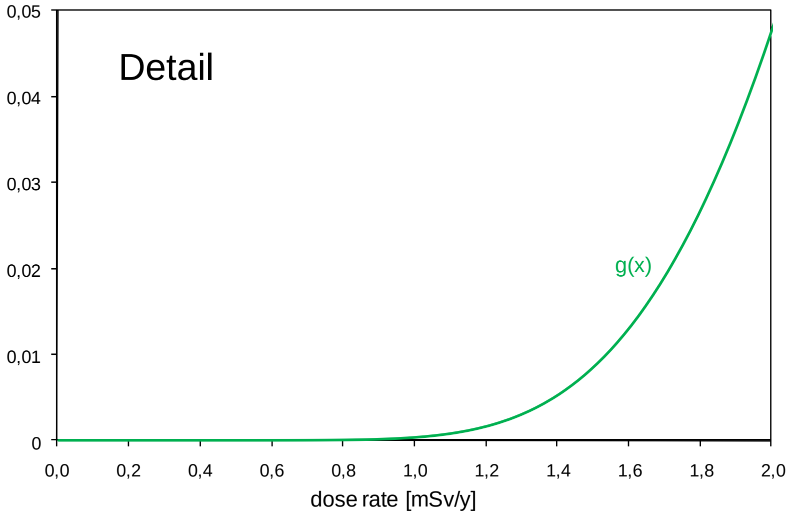
Assumptions:

A Random distribution of doses in a cohort:
lognormal distribution with median dose $x=\mu_1$ and standard deviation σ_1:
density function $f(x) = 1/(x*\sigma_1*(2\pi)^{1/2})*\exp(-(\ln(x)-\mu_1)^2/2\sigma_1^2)$

B Random distribution of radiosensitivity:
cumulative lognormal distribution function $g(x, \mu_2, \sigma_2)$

C Effect in a small dose interval (x, x+dx) is ~ $f(x)*g(x)*dx$
Sum effect = $\int f(x)*g(x)*dx$.

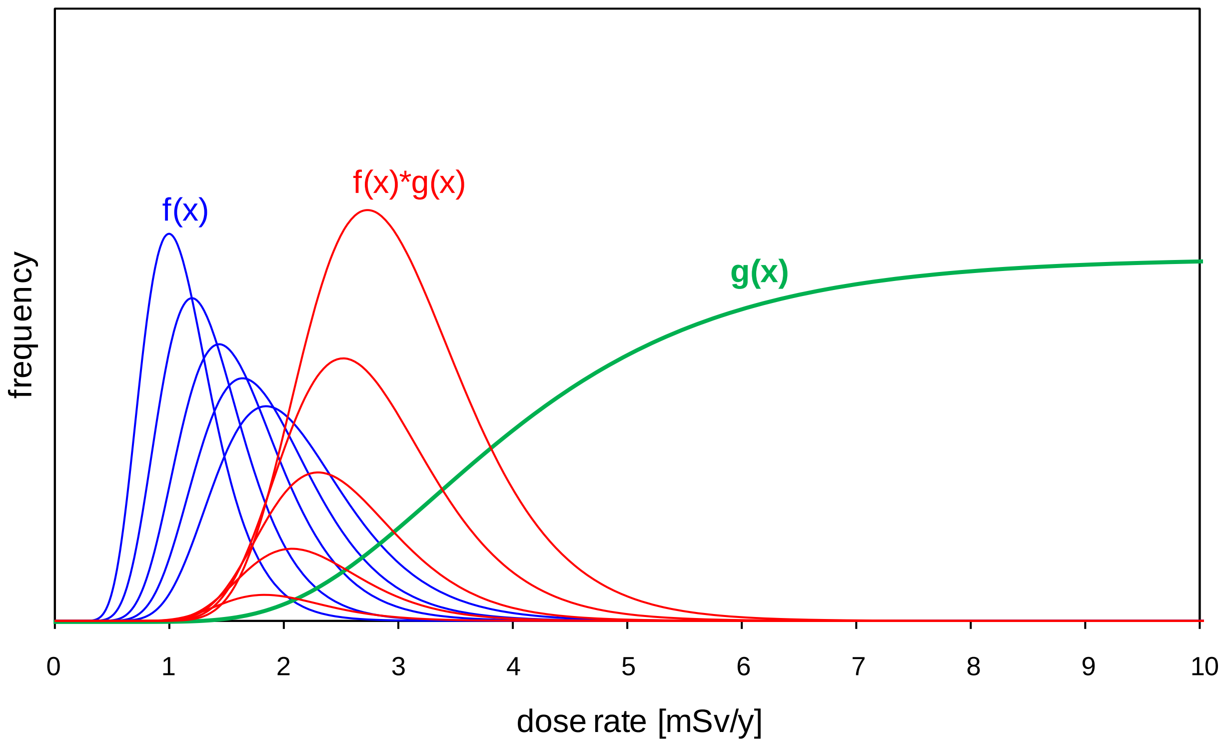




Example

Dose distribution with μ_1= 1.4 mSv; σ1=0.3
Probability of detriment at dose x: g(x) =lognormal(x; μ_2=4mSv; σ_2=0.4)
Overall detriment = $\int(f(x)*g(x))dx$

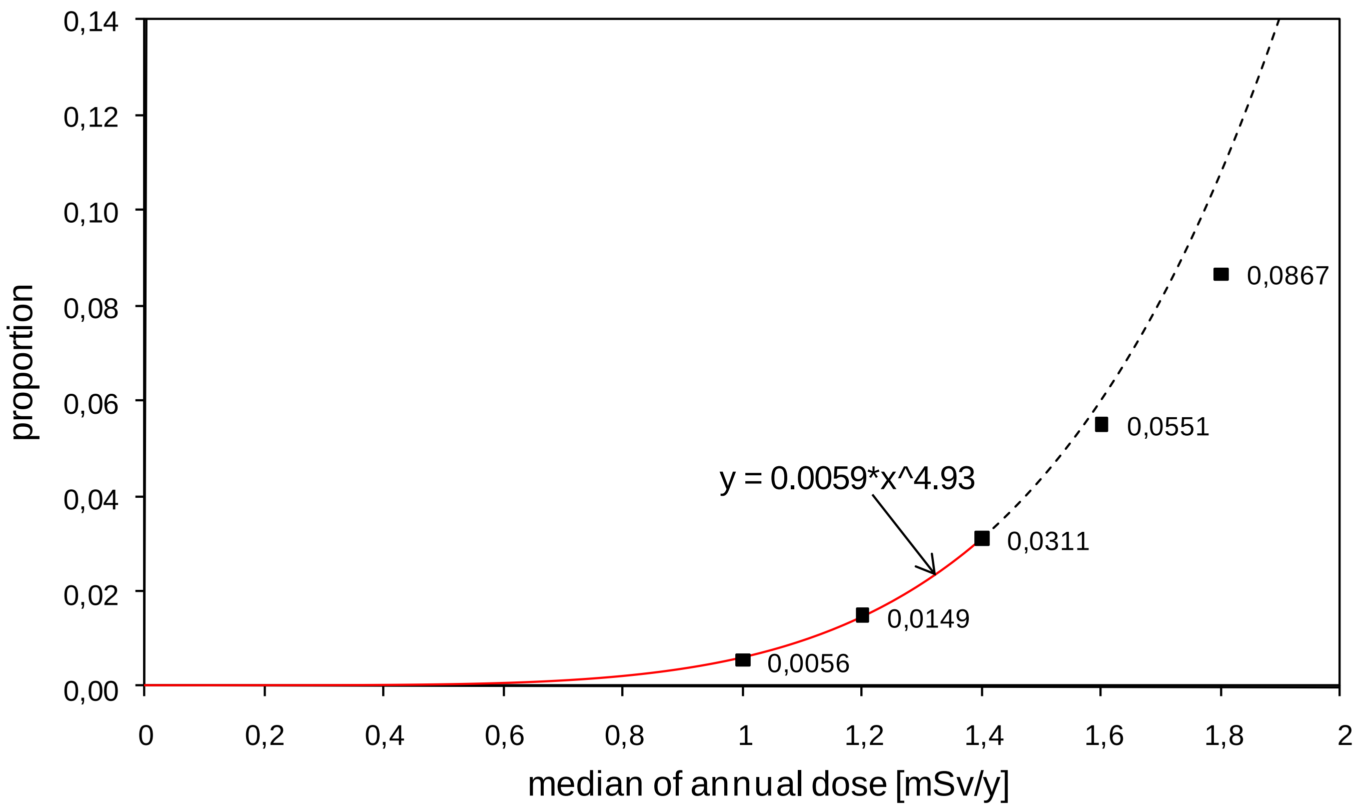
Effect grows disproportionately with median dose



median annual doses: μ_1 = 1.0, 1.2, 1.4, 1.6, 1.8 mSv; σ_1= 0.3

Shape of the dose response curve

Regression with model y=x^n yields power of dose n=4.9

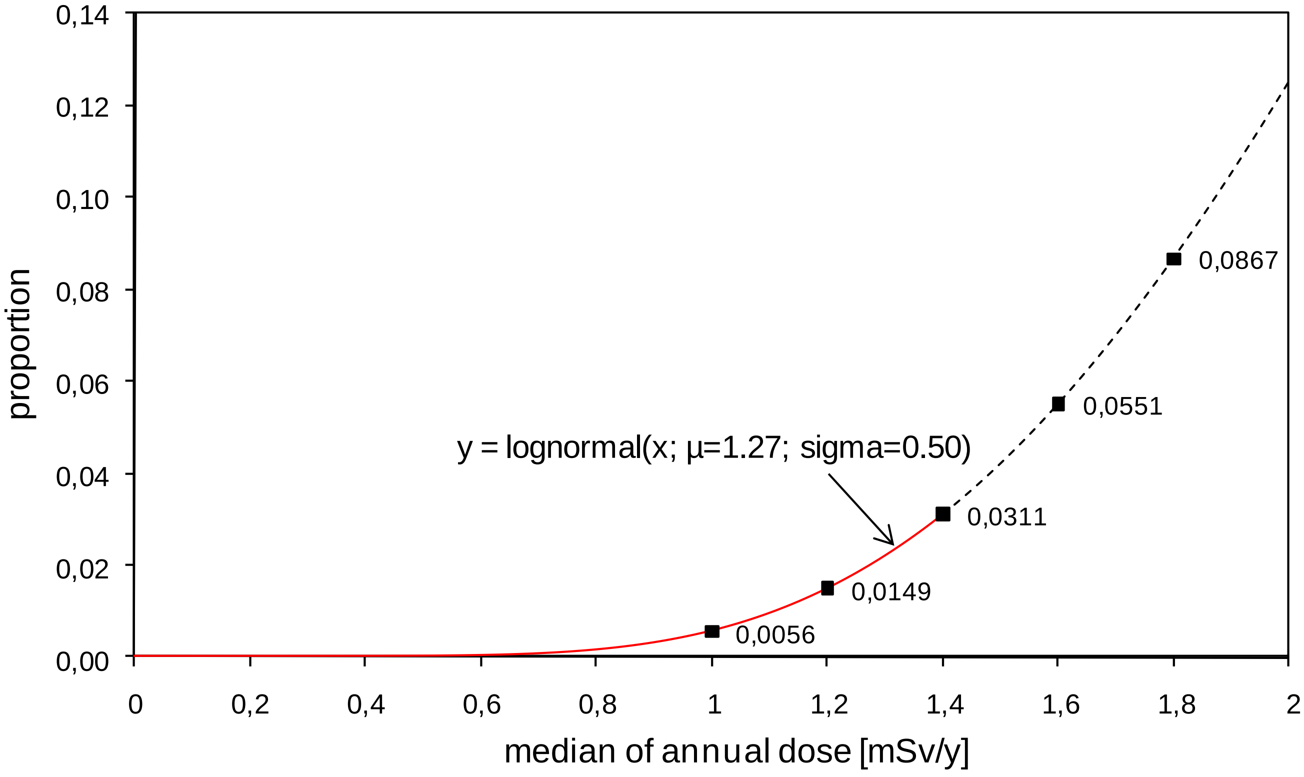


Shape of the dose response curve

Regression with lognormal distribution function

$(\sigma^2 = \sigma_1^2 + \sigma_2^2)$

Increase of dose	Increase of risk
20%	170%
40%	460%
60%	880%
80%	1450%



Epidemiological evidence for curvilinear dose response: Chernobyl consequences

- Significant association of perinatal mortality with the caesium burden of pregnant women in Germany. The dose response is curvilinear with a best estimate of 3.5 for the power of dose (95% CI: 1.5-7.5)
  (Körblein and Küchenhoff, Rad Environ Biophys, 1997)

- Significant association of monthly infant mortality with the caesium burden of pregnant women in Poland. Curvilinear dose response with a power of dose of 3.8.

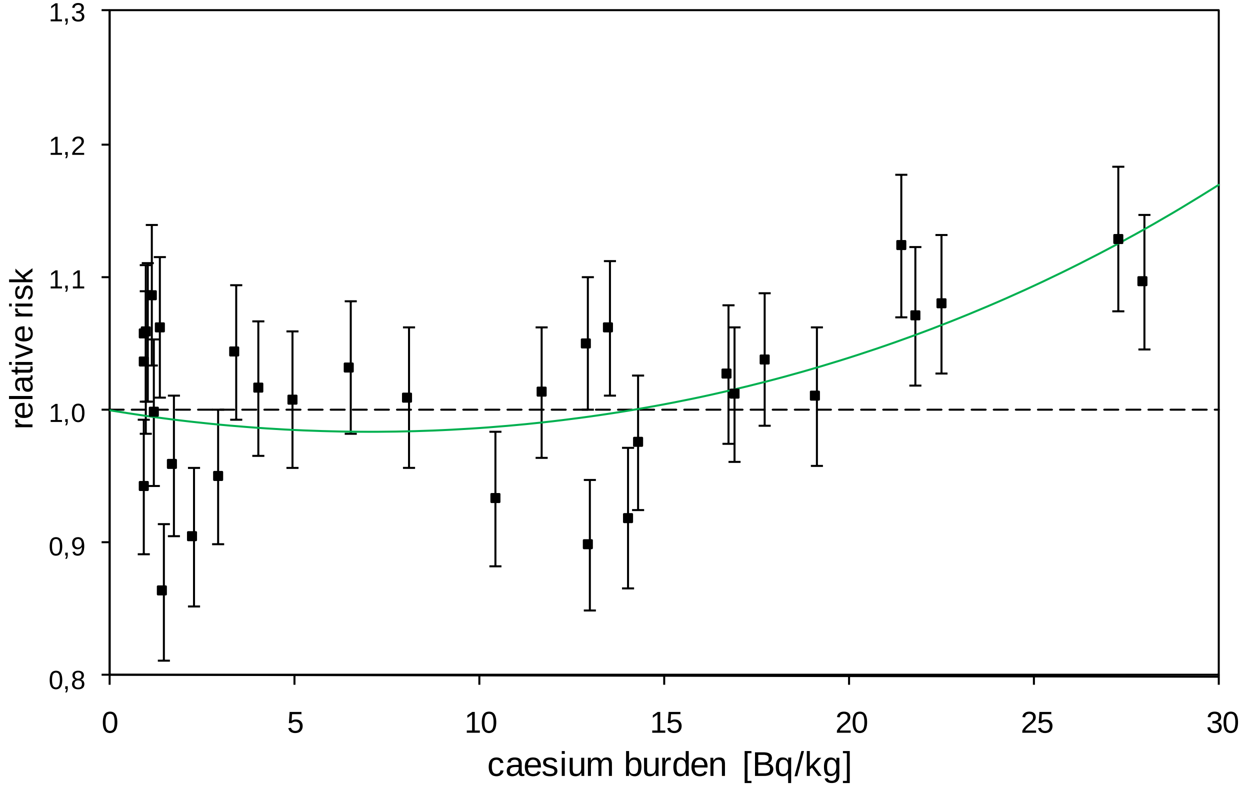
- Significant association of congenital malformations with caesium ground deposition in Bavaria. Curvilinear dose response.

Example 1: Perinatal mortality in West Germany

linear-quadratic regression model for caesium effect

caesium effect is significant: p=0.0005 (chisquare test, df=2)

quadratic term is significant: p=0.0057 (chisquare test, df=1)

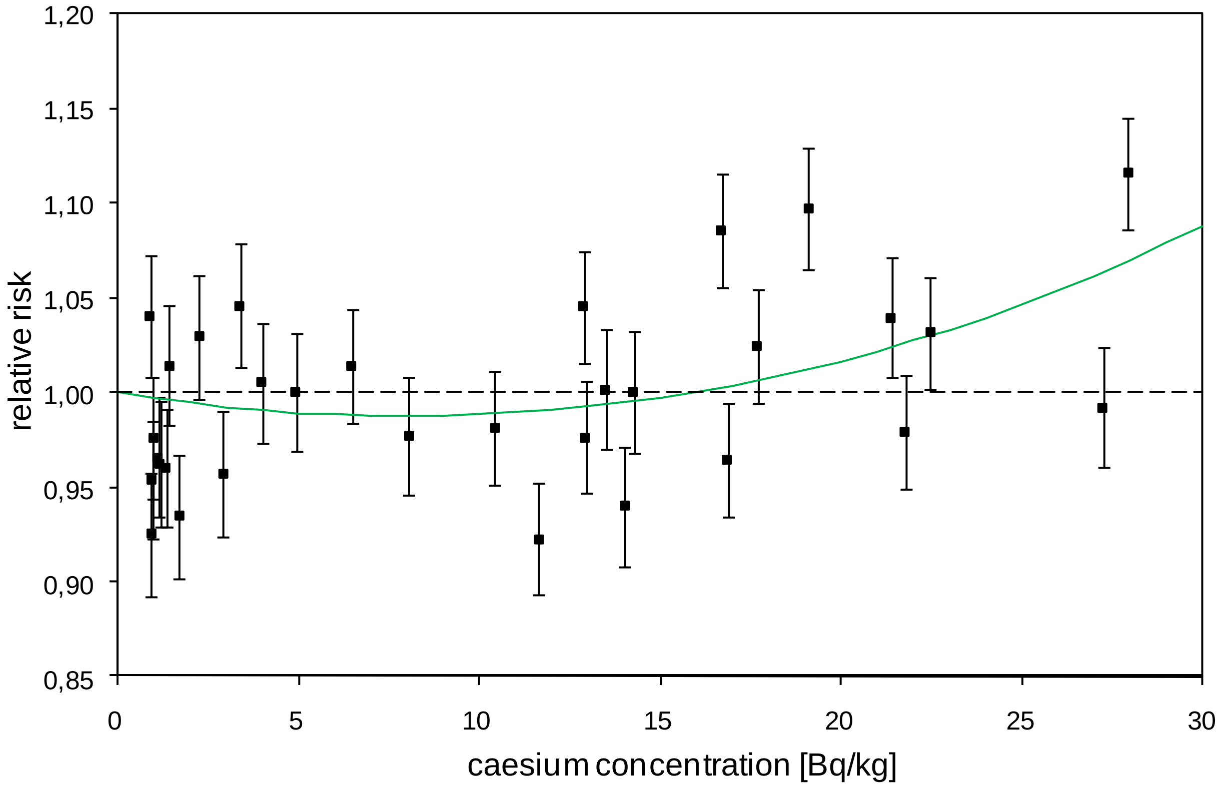


Example 2: Infant mortality in Poland

linear-quadratic regression model for caesium effect

caesium effect is significant: p=0.0032 (chisquare test, df=2)

quadratic term is significant: p=0.0066 (chisquare test, df=1)

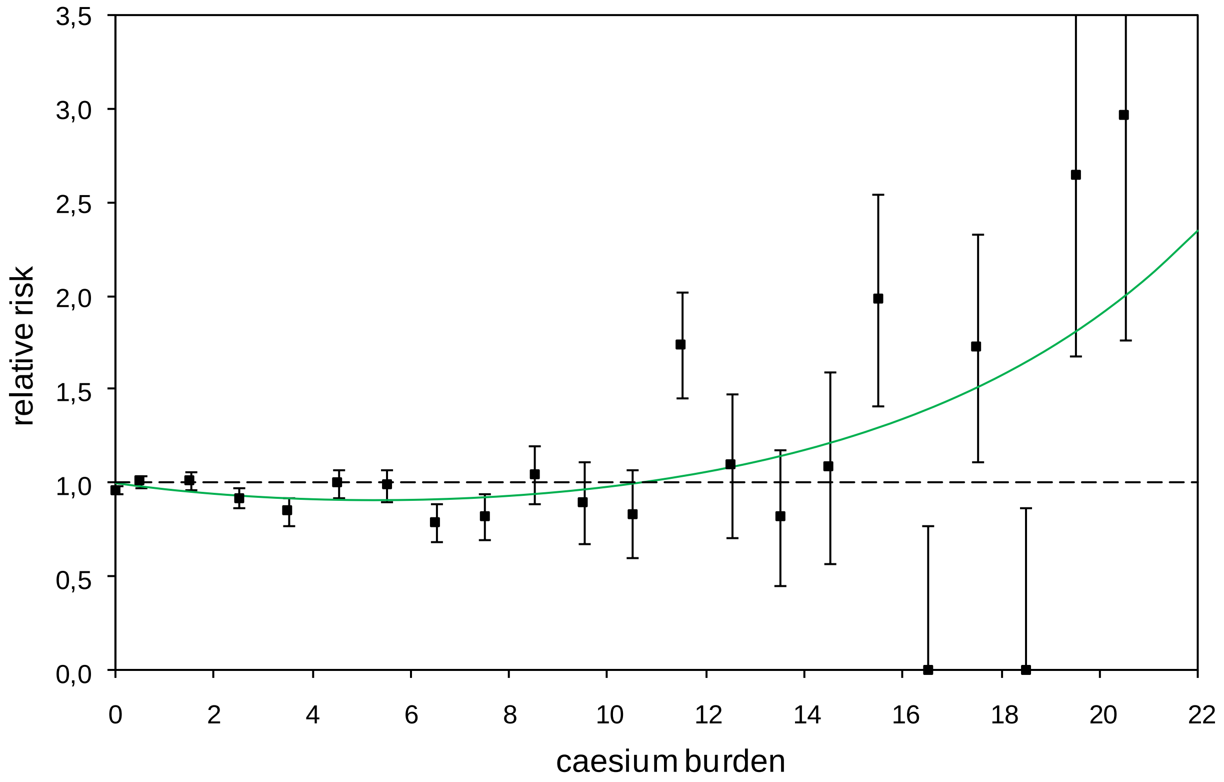


Example 3: Congenital malformations in Bavaria

linear-quadratic regression model for caesium effect

caesium effect is significant: p=0.0064 (chisquare test, df=2)

quadratic term is significant: p=0.0032 (chisquare test, df=1)



Summary

- The mathematical form of the dose-response relationship is a cumulative lognormal distribution function.
- The only assumption for the calculation is that both the doses and the radiosensitivities are randomly distributed in a population.
- The present model, together with revised dose estimates, has the potential to explain the size of the increased childhood leukaemia rates observed near German NPPs.

email from A. Körblein to Prof. Müller (SSK), from 11 July 2008:

Sehr geehrter Herr Müller,
anbei leite ich Ihnen meine Überlegungen zur Form der DWB weiter bei Effekten, bei denen die Existenz einer Schwellendosis vermutet wird.
Freundliche Grüße,
Alfred Körblein

Reply from Prof. Müller, the same day:

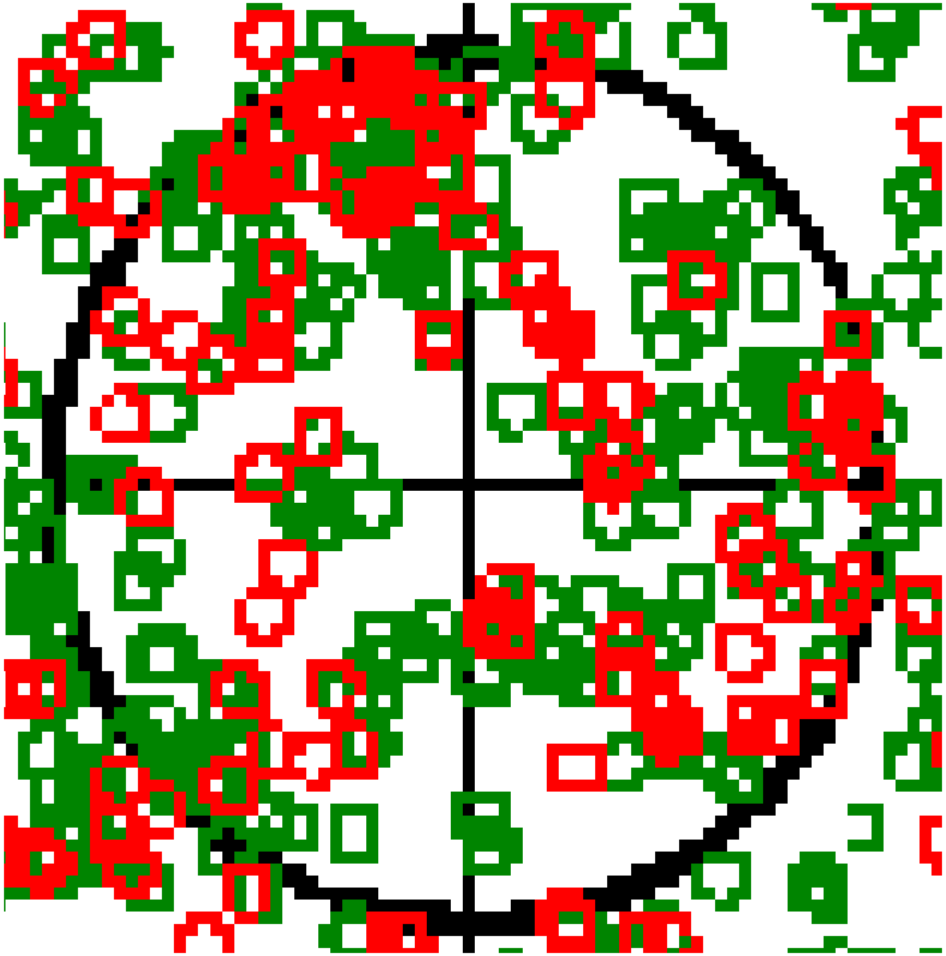
Sehr geehrter Herr Körblein,
haben Sie vielen Dank für die Übersendung der Information.
Ich finde solche Überlegungen auch immer wieder faszinierend, habe aber nach wie vor die Überzeugung, dass wir mit solchen Modellen der Komplexität der biologischen Systeme nicht gerecht werden. Intellektuell aber auf jeden Fall reizvoll.
Beste Grüße, ein schönes Wochenende,
Wolfgang-U. Müller

Prof. Dr. Wolfgang-Ulrich Müller
Institut für Medizinische Strahlenbiologie
Universitätsklinikum Essen

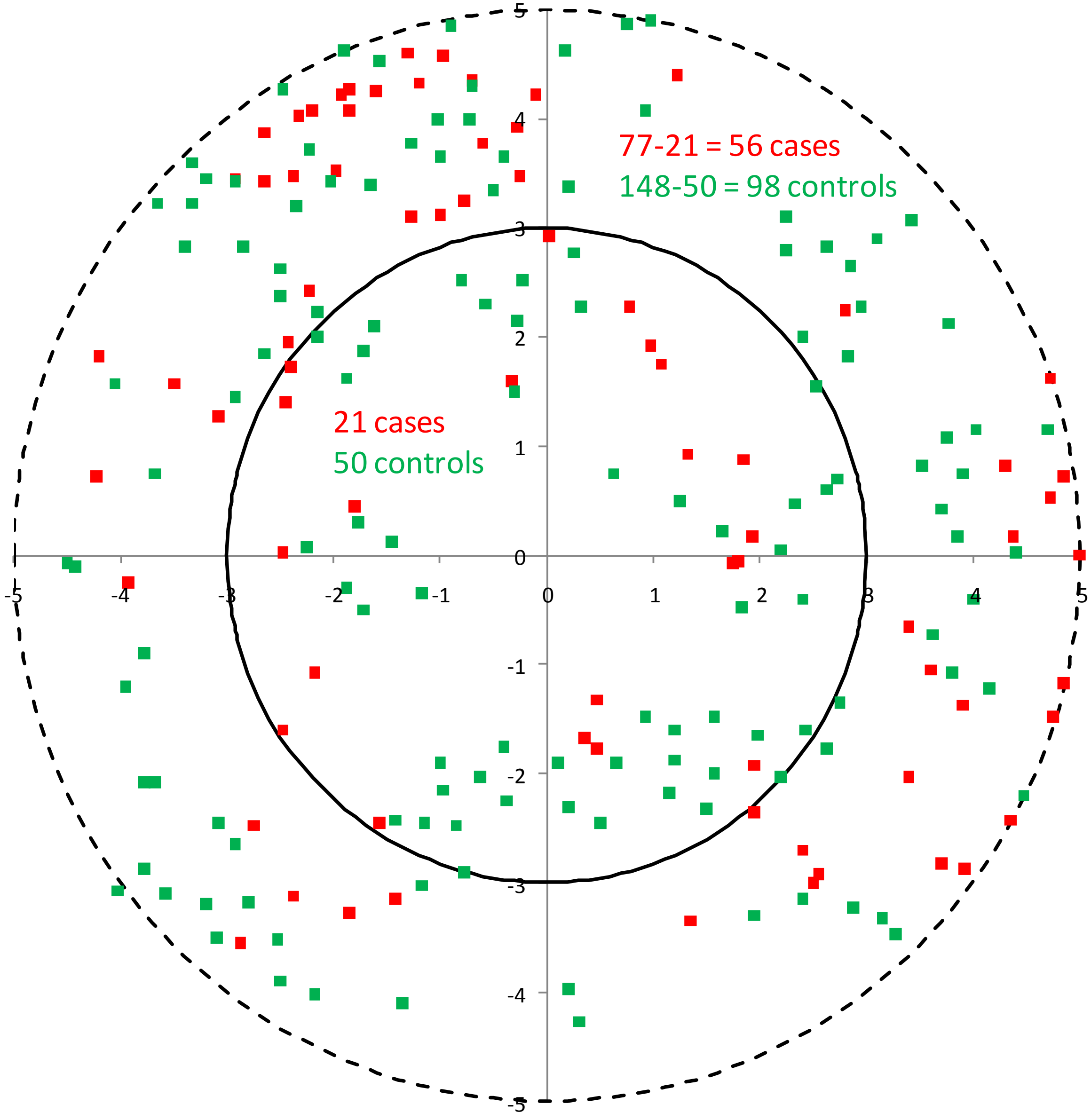
Thank you for your ~~attention~~ patience!

Distance dependency of relative risk

cases and controls within 5 km of German NPPs

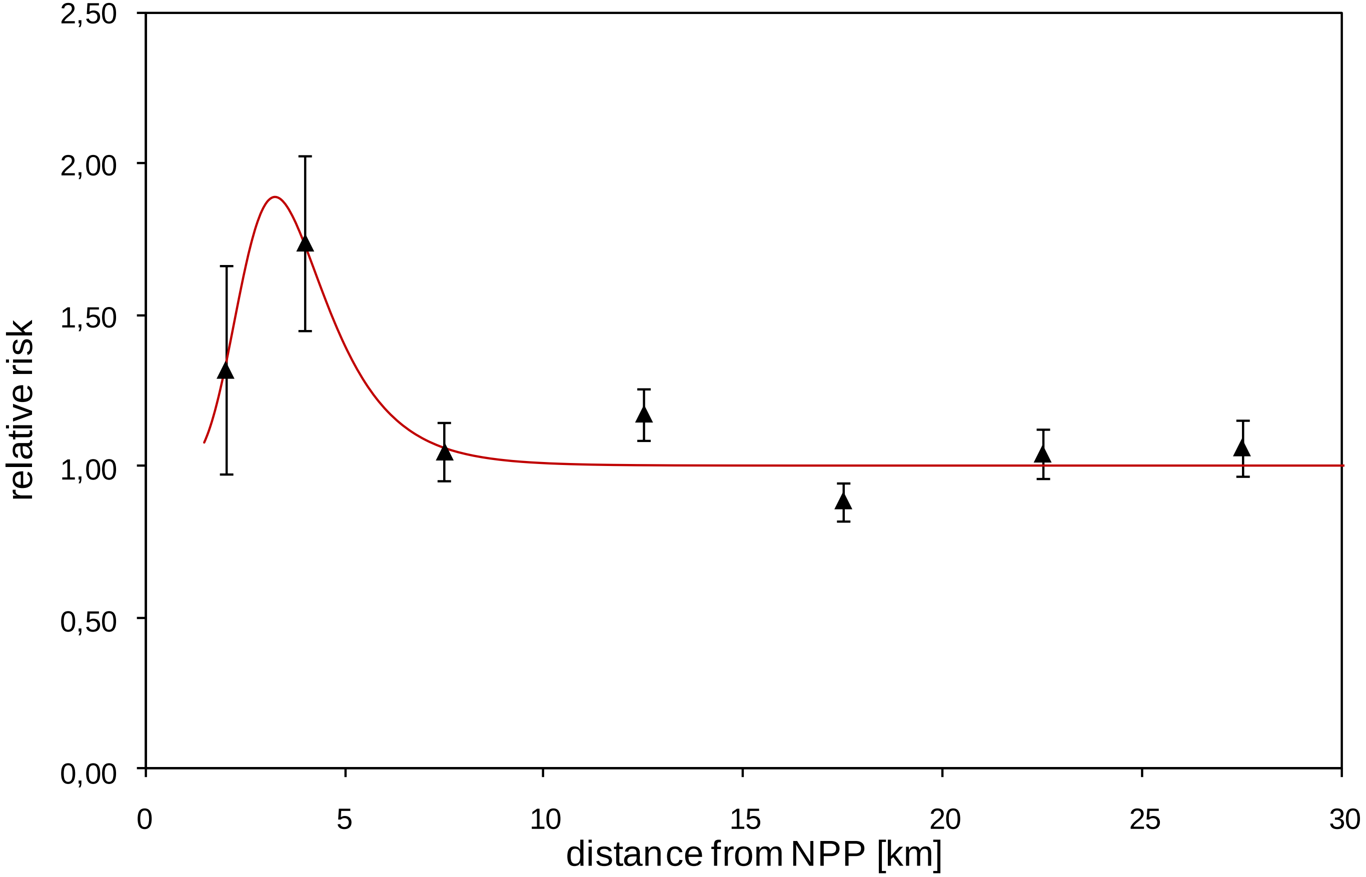


From Figure 3.5 of KiKK technical report

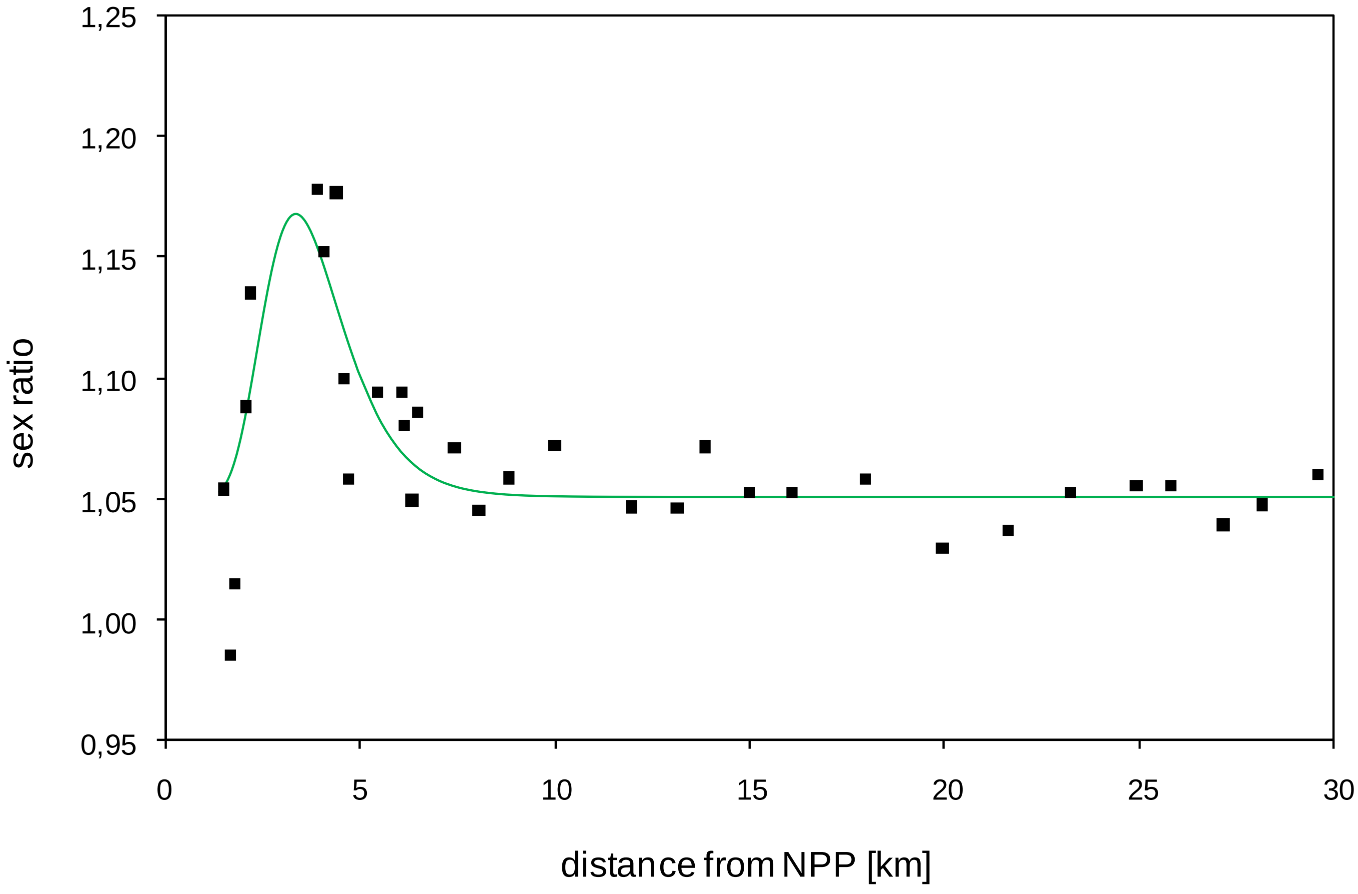


Thanks to Ralf Kusmierz who provided the graphical software to determine the midpoints

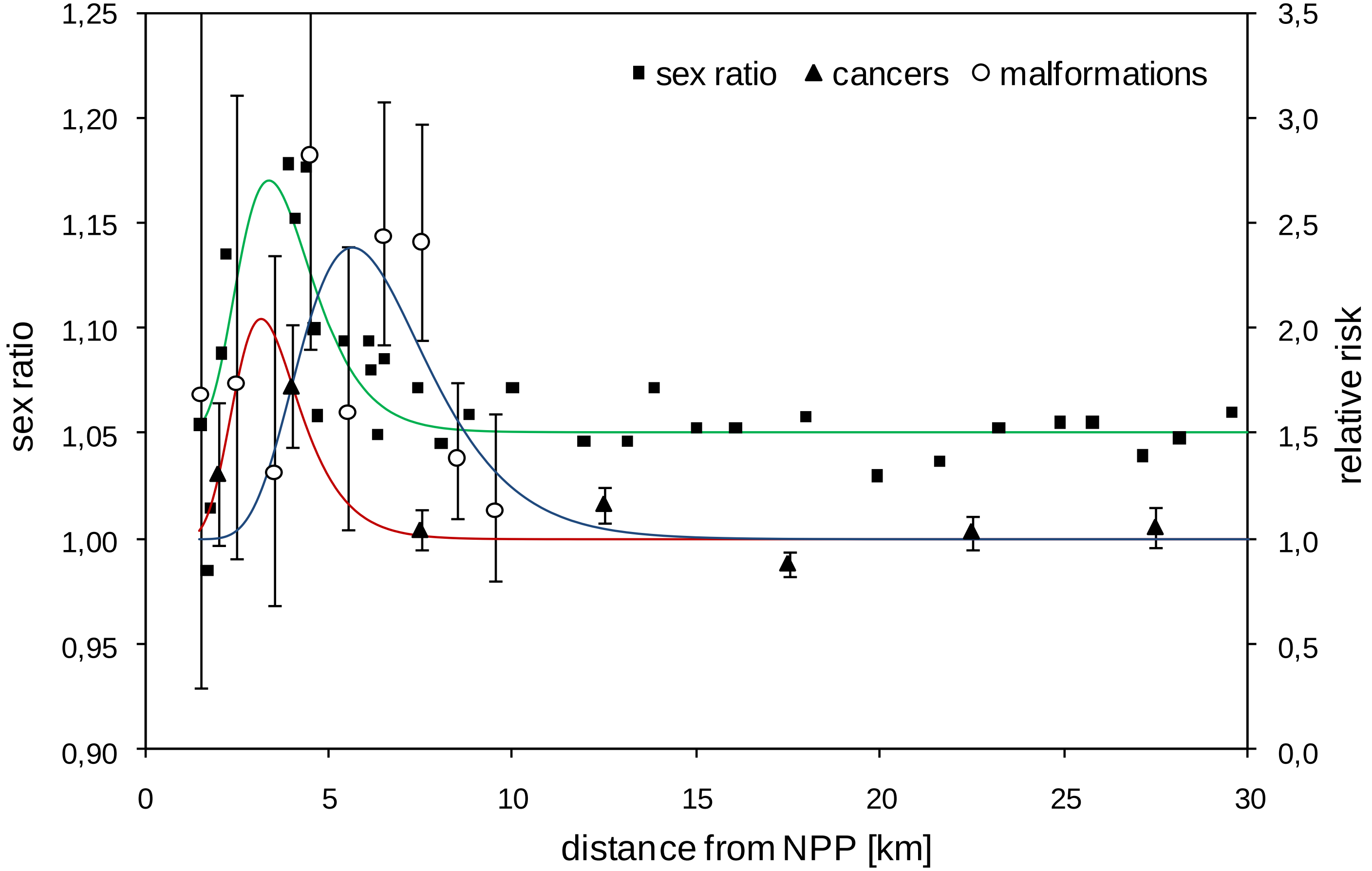
All cancers in children < 5 y near German NPPs



Sex ratio at birth (ratio of male to female births) near Bavarian NPPs



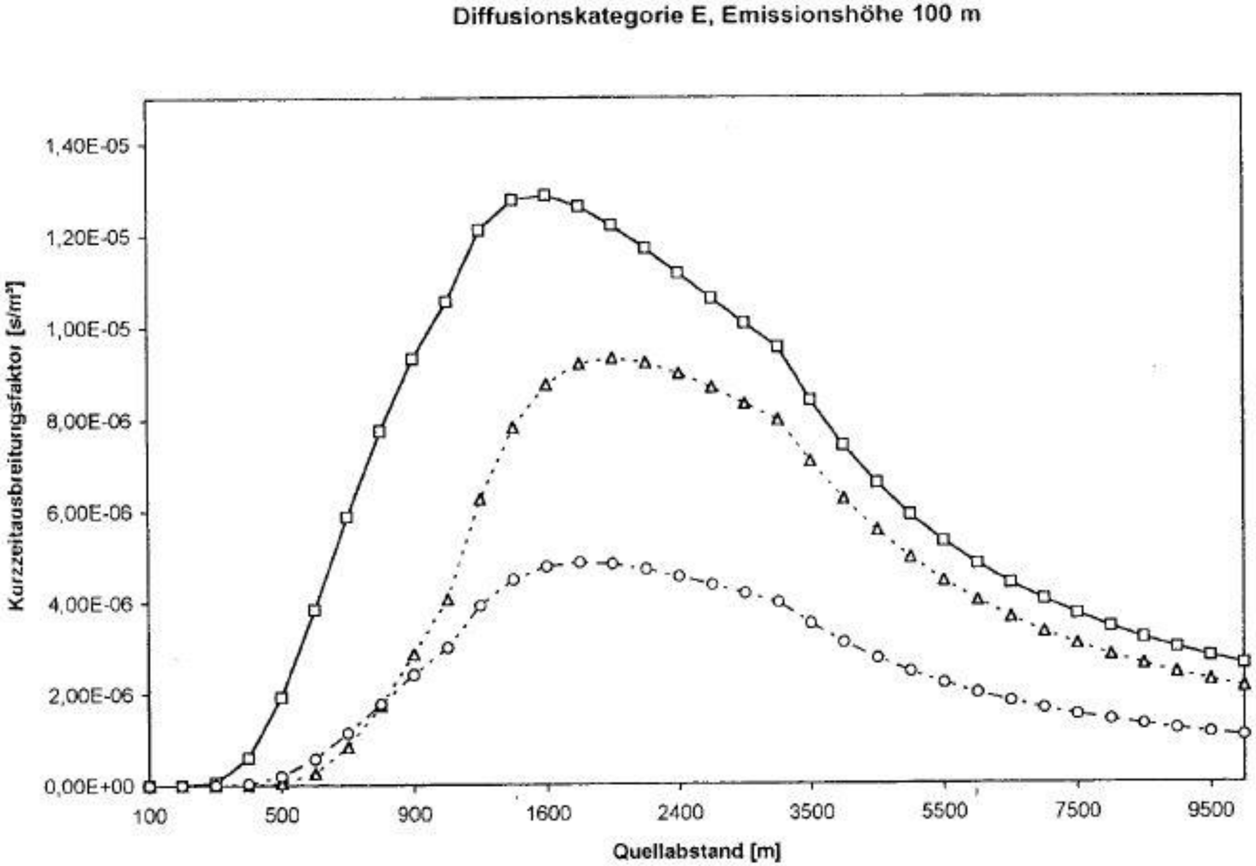
Early childhood cancer - congenital malformations - sex ratio near NPPs
(error bars: 1 standard deviation)



Results of a combined regression
(lognormal distributions with common sigma)

parameter	data	estimate	SD	t value	p value
intercept	cancer	0,2469	0,0053	46,47	0,0000
ampl	cancer	0,1545	0,0740	2,088	0,0378
median	cancer	3,1641	0,4766	6,638	0,0000
intercept	sexratio	0,5124	0,0008	669,1	0,0000
ampl	sexratio	0,0268	0,0126	2,135	0,0337
median	sexratio	3,3614	0,3517	9,557	0,0000
intercept	malf	0,0247	0,0108	2,290	0,0228
ampl	malf	0,0323	0,0149	2,165	0,0313
median	malf	5,6499	0,6231	9,068	0,0000
sigma		0,1908	0,0920	2,074	0,0390

$p = 0.0009$ (chisquare test with df=7)



short-term propagation factor

distance from source [metres]

From: Strahlenbiologisches Gutachten, Appendix C1: O. Schumacher: Zuverlaessigkeit der AVV