The explanation of B.L. Cohen's radon data and the low-LET ARIP-data with the Random Coincidence Model

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Abstract The Random Coincidence Model (RCM) describes the formation of cancer if caused by a multistep series of point mutations in the critical regions of tumor associated genes such as proto-oncogenes or tumor-suppressor genes. It is the central thesis of the model that a point mutation mainly occurs through the random coincidence of two base lesions or two single strand breaks of complementary DNA bases (strands) during the repair time of the first base lesion or SSB.

Introduction The effect of radiation hormesis can be observed in an increasing number of epidemiological studies investigating the cancer rate at different levels of background radiation. At this low level dose rate the mortality rate for several types of cancers decreases with an increasing dose rate while others do not. In his epidemiological investigations, B.L. Cohen (1) measured the average radon level in homes in 1730 counties of the USA and correlated these data with lung cancer mortality. He found a clear tendency of decreasing lung cancer mortality with an increasing radon dose. Years ago N.A. Frigerio (2) got the same results for background radiation (terrestrial- and cosmic γ-radiation, K-40).

The RCM proposes the randomly coincident destruction of the complementary DNA base (nucleotide) before or during the repair of the first damaged base (nucleotide). Random coincidence means that after the first base (nucleotide) lesion the second damage on the complimentary base (nucleotide) occurs randomly before the repair of the first base (nucleotide) lesion is finished and coincidently within the repair time. This approach implies that the rate of damage fixation depends on the repair time of the first base lesion or SSB. The repair time is a function of the repair enzyme concentration as indicated by the Michaelis-Menten relation. To explain radiation hormesis we have to assume that the repair enzyme concentration and the concentration of scavengers, radical detoxification systems, is direct proportional to the dose rate.
Wallace has recently reviewed the nature of the DNA lesions caused by active oxidizing species produced both naturally and by low-LET radiation (3). Oxidizing radicals and especially OH radicals resulting from either cause produce similar types of DNA lesions (3-5). The enzymes involved in their repair are similar no matter whether the DNA damage is produced spontaneously or by radiation (6).
We therefore explain radiation hormesis as a result of the reduction of the spontaneous (chemical) damage probability by a small dose rate of ionizing radiation causing an additional genetic expression of repair enzymes and scavengers.

The Model $C\alpha$ is the chemical damage probability per second and nucleotide, caused by the natural cell metabolism and by chemical carcinogens. $\dot{D}\beta$ is the radiological damage probability per second and nucleotide. $\dot{D}\beta$ includes the possibility that radiation directly interacts with the nucleotide or indirectly by radicals.
The probability per second that the complementary base (nucleotide) is also damaged before or during the repair of the first base (nucleotide) is described by the equation:

$$S_{fixed}=(C\alpha + \dot{D}\beta)^2 \tau \qquad (1)$$

This is the fixation rate of point mutations caused by a randomly coincident destruction of both complementary bases or a randomly coincident caused double strand break. The coincidence takes place during the repair time.
v is proportional to the enzyme concentration and it is indirectly proportional to the repair time τ:

$$\tau = \frac{\tau_0}{1+\delta\dot{D}} \qquad (2)$$

with $\delta \cdot \dot{D}$ describing the additional genetical expression of repair enzymes.
Besides the three terms in equation (3), describing a randomly coincident fixation of base lesions or a randomly coincidently caused double strand break, we also have to take into account that both nucleotides may be damaged immediately one after the other by the same particle or by the same cloud of radicals originating from one particle. In this case no repair of the complementary base (nucleotide) is possible and therefore there is no τ in

the corresponding term, which is $\vartheta\dot{D}$. $\kappa(\dot{D})$ represents the probability that cells are killed by radiation in high dose regions. κ is the cell killing probability. Killed cells cannot become tumorigenic.

$$S_4=\left(C^2\alpha^2+2C\alpha\dot{D}\beta+\dot{D}^2\beta^2\right)\tau+\vartheta\dot{D}-\kappa(\dot{D}) \tag{3}$$

The following differential equation describes the time dependent behaviour of the arising of the first step in the successive process of damage.

$$\frac{dM_1(t,C,\dot{D})}{dt}=(B_0M_0-B_1M_1)\left(\left(C\alpha+\dot{D}\beta\right)^2\tau+\frac{1}{f_{nuc}}\bar{z}_F\beta^2\dot{D}-\kappa(\dot{D})\right) \tag{4}$$

M_1 (t, C, $\dot{D}$) is the number of cells per individuum at time t which are in the first transformation step, i.e.: which have one point mutation on a critical, tumor relevant gene locus caused by a chemical carcinogen with concentration C or by a dose rate $\dot{D}$. M_0 is the number of all human cells which are not yet transformed. Equation (4) describes the first step necessary for a complete carcinogenesis. The number of steps necessary for the induction of cancer defines a system of coupled differential equations. Each transformation is represented by one differential equation. B_0 is the number of critical DNA bases (nucleotides) in critical codons of all tumor associated genes per cell. B_1 is the number of critical DNA bases (nucleotides) in critical codons of all tumor associated genes per cell after the first transformation.

The first sink on the right side of equation (4) ($-B_1M_1$ ...) is due to the fact that cells which have reached the first step of damage are a source term for the second step. M_1 is several orders of magnitude smaller than M_0. Therefore this sink can be neglected. In the case of constant chemical and radiological influences (C=const., $\dot{D}$=const.), the coefficients of the differential equation (4) are time independent and the equation can be directly integrated:

$$M_1(t)=B_0M_0\left(\left(C\alpha+\dot{D}\beta\right)^2\tau+\frac{1}{f_{nuc}}\bar{z}_F\beta^2\dot{D}-\kappa(\dot{D})\right)t \tag{5}$$

For M_n (t) we get with $A_1:=B_0B_1B_2\ldots B_{n-1}M_0\frac{1}{n!}$

$$M_n(t)=A_1\left(\frac{C^2\alpha^2\tau_0}{\left(1+\delta_S\dot{D}\right)^2\left(1+\delta\dot{D}\right)}+\frac{2C\alpha\dot{D}\beta\tau_0}{\left(1+\delta_S\dot{D}\right)\left(1+\delta\dot{D}\right)}+\frac{\dot{D}^2\beta^2\tau_0}{1+\delta\dot{D}}+\frac{1}{f_{nuc}}\bar{z}_F\beta^2\dot{D}-\kappa(\dot{D})\right)^n t^n \tag{6}$$

where δ_s describes the extent of the production of additional scavengers caused by radiation. The term $\kappa(\dot{D})$ is approximately zero because cell killing is not a relevant effect in the low dose regions refered to in the data which are used for regression analysis. For an anambiguous data fit this equation has to be slightly transformed and we can only determine $\frac{\beta}{C\alpha}$ and $\delta=\delta_s$. For τ_0 we take 40 minutes /7/. $\frac{1}{f_{nuc}}$ can be derived as approximately 3.3 /8/. For a critical volume with a radius of 4.66 µm, the average radius of a bronchial epithelial cell nucleus, D.R. Fisher, V.P. Bond et al. /9/ received $\bar{z}_F$=0.5 Gy. Data fits are done with all 1601 data points using the Levenberg-Marquardt algorithm and the Nelder-Mead simplex search method. For n, the number of transformations, we take 4, which was received by a data fit of age dependent ARIP data for I.C.D. 140-205 (all cancers).

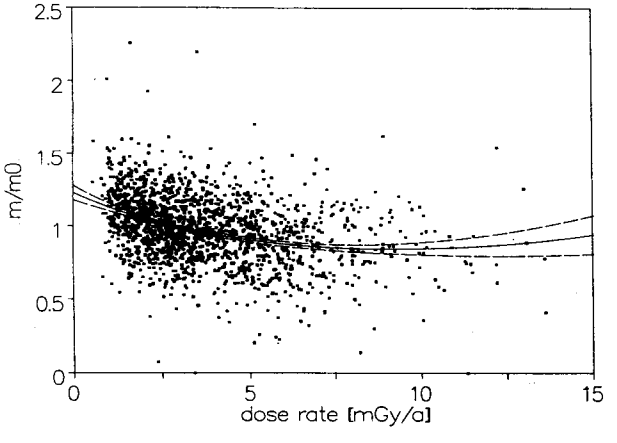

Fig. 1 Data fit of the smoking corrected, age adjusted lung cancer mortality rates (I.C.D. 163-164) for males; the 95 % confidence band is shown.

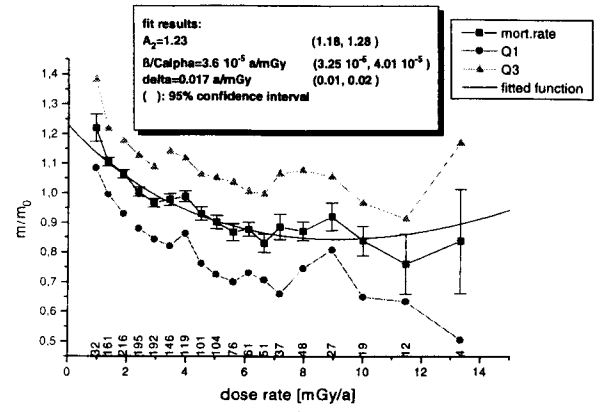

Fig. 2 Data fit of the smoking corrected, age adjusted lung cancer mortality rates (I.C.D. 163-164) for males, grouped into intervals of dose rate. The number of counties in each group is shown on the base line. We plot the mean value of m/m_0 for each group, its standard deviation, the first and third quartiles of the distribution and the fitted function.

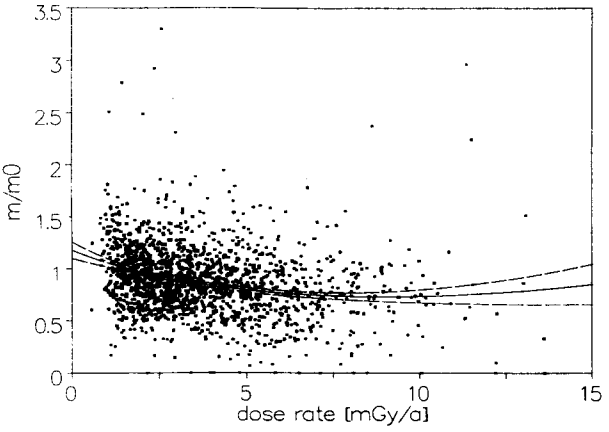

Fig. 3 Data fit of the smoking corrected, age adjusted lung cancer mortality rates (I.C.D. 163-164) for females; the 95 % confidence band is shown.

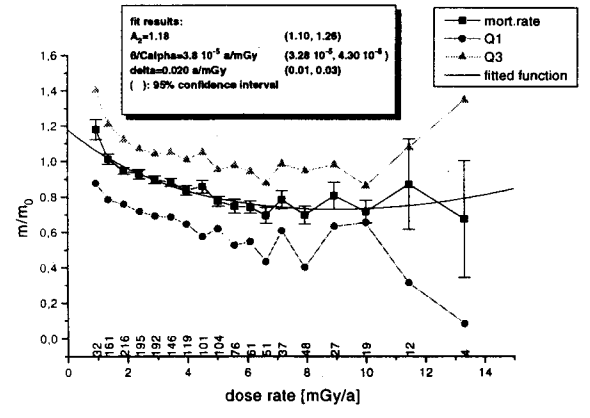

Fig. 4 Data fit of the smoking corrected, age adjusted lung cancer mortality rates (I.C.D. 163-164) for females, grouped into intervals of dose rate.

1. B. L. Cohen, Test of the linear- no threshold theory of radiation carcinogenesis for inhaled radon decay products, *Health Physics* **68**(2): 157-174 (1995)
2. N. A. Frigerio, K. F. Eckerman, R. S. Stowe, *The ARGONNE RADIOLOGICAL IMPACT PROGRAM (ARIP)*, Part I. Carcinogenic Hazard from low-level, low-rate radiation (September 1973)
3. S. S. Wallace, AP-endonucleases and DNA-glycosylases that recognize oxidative DNA damage. *Environ. Mol. Mutagen.* **12**, 431-477 (1988)
4. F. Hutchinson, Chemical changes induced in DNA by ionizing radiation. *Prog. Nucleic Acid Res. Mol. Biol.* **32**, 115-154 (1985)
5. H. Joenje, Genetic toxicology of oxygen. *Mutat. Res.* **219**, 193-208 (1989)
6. D. Billen, Spontaneous DNA damage and its significance for the 'negligible dose' controversy in radiation protection, *Rad. Res.* **124**, 242-245 (1990)
7. Dr. P. Eckl, Institute of Genetics and General Biology, University of Salzburg, personal communications
8. A. Sinabel, thesis, TU Wien, 1995
9. D.E. Fisher, T.E. Hui, V.P. Bond, A.C. James, Microdosimetry of radon progeny: application to risk assessment, Hanford Life Sciences Symposium, 1991