Possible Consequences of Inhomogeneous Suborgan Distribution of Dose and the Linear No-Threshold Dose-Effect Relationship

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Abstract. The current system of radiation protection is based on the assumption that the risk of stochastic effects of radiation exposure is directly proportional to effective dose. Effective dose being the weighted sum of absorbed organ doses is independent of the spatial dose distribution within the organs. However, experiments in radiation biology pointed out on such phenomena, which may play a role in carcinogenesis and other processes leading to stochastic effects, but their extents are non-linear function of absorbed dose. These non-linear phenomena observed even in microscopic scale suggest that the risk of stochastic effects induced by ionizing radiation depends even on the suborgan distribution of absorbed dose. In the present study, an alternative method of calculation of effective dose is introduced, which offer the opportunity for the consideration of suborgan inhomogeneity of exposure. It is also investigated, how microscopic nonlinearities may manifest at macroscopic level in case of homogeneous and inhomogeneous exposures. It was presented that if alternative effective dose is linear function of absorbed dose then it is independent on the suborgan dose distribution. It was shown that inhomogeneous exposures result in lower significance of nonlinearity than homogeneous exposures. If besides the inhomogeneous a smaller homogeneous exposure is also considered, the significance of low dose nonlinearity seems to be even smaller. Based on the present study, it is suggested that nonlinearity in low dose effects may be less significant in case of inhaled radon progeny than in case of radiation sources producing homogeneous exposures. However, in case of inhomogeneous exposures other biological mechanisms may arise in the mostly exposed parts of the organs, which can significantly influence the risk.

Key Words. radon progeny, inhomogeneous exposure, effective dose, LNT assumption

I. Introduction

The current system of radiation protection is based on the assumption that the risk of stochastic effects of radiation exposure is directly proportional to effective dose. Effective dose being the weighted sum of absorbed organ doses is independent of the spatial dose distribution within the organs. However, experiments in radiation biology pointed out on such phenomena, which may play a role in carcinogenesis and other processes leading to stochastic effects, but their extents are non-linear function of absorbed dose. Typical examples for such phenomena are bystander effects (Blyth and Sykes, 2011), adaptive response (Tapio and Jacob, 2007), and genomic instability (Morgan et al., 1996). These non-linear phenomena observed even in microscopic scale suggest that the risk of stochastic effects induced by ionizing radiation depends even on the suborgan distribution of absorbed dose.

Besides experiments, a theoretical consideration also raises the question, whether suborgan dose distribution plays no role in the formation of radiation induced stochastic effects. Namely, if the risk was independent of the microscopic dose distribution, it would mean that 1 J ionizing energy results in the same macroscopic effect if it is absorbed homogeneously in an organ, in its half, in its tenth or ad absurdum in one of its cells. This seems to be improbable. One can say that it is not the purpose of radiation protection to deal with unrealistic exposure scenarios. However, radon progeny, which are responsible for the main part of natural radiation burden of the public, results in very inhomogeneous exposure in the lungs (Balásházy et al., 2009, Madas et al., 2011, Szőke et al., 2009, Farkas et al., 2011). Thus, the question about the role of spatial distribution of absorbed dose is not just theoretical; the answer may have practical implications.

In the present study, an alternative method of calculation of effective dose is introduced, which offer the opportunity for the consideration of suborgan inhomogeneity of exposure. It is also investigated, how microscopic nonlinearities may manifest at macroscopic level in case of homogeneous and

inhomogeneous exposures. All the computations are performed for radon progeny deposited in the lungs. Although, new methods are introduced and investigated, the consistency with the current system of radiation protection is also considered.

II. Methods

For the consideration of suborgan distribution of absorbed dose, the investigated organ must be divided into small parts (we call them tissue units – TUs), where absorbed doses and equivalent doses are computed. To determine effective dose, equivalent doses of TUs are summed up over the TUs with an appropriate weighting. This method of calculation involves the assumption that the biological effects on the different TUs are independent of each other and can be interpreted as the relevant biological targets of ionizing radiation are not the organs and tissues, but the TUs. The absorbed dose distribution in the lungs is approximated by the absorbed dose distribution in a five bifurcation unit of the central airways, because for these parts of the lungs detailed α-hit distribution data are available. Exposure of any other organs is not considered in this study.

The absorbed dose distribution and therefore the estimated local biological effect depend on the size of the TUs. Thus, selecting a mathematically and biologically plausible size would be a delicate task (Farkas et al., 2011). However, the purpose of this study is not to give a quantitative estimation of (alternative) nominal risk or effective dose, rather to highlight on the possible qualitative consequences of inhomogeneous dose distribution. The mean size of TUs in the present study is 250 × 250 μm^2 with a thickness of 57.8 μm characteristic of the large bronchi (Mercer et al., 1991). This size is in accord with recent estimates for the range of bystander effect around an irradiated cell of 0.21 mm (Leonard, 2009) and 0.1 mm (Gaillard et al., 2009).

For the alternative calculation of effective dose, weighting factors of TUs must be introduced. To avoid inconsistency, it is necessary that homogeneous exposures result in the same effective dose and nominal risk independently of the method of calculation and the size of TUs. To fulfil this criterion, the sum of the weighting factors of TUs ($w_{TU,i}$) must be equal to the tissue weighting factor (w_T):

$$\sum_i w_{TU,i} = w_T. \quad (1)$$

There is no information about differences in radiation sensitivity of the different parts of the bronchial epithelium. Therefore, it is supposed that the weighting factors of the TUs are uniform or more precisely proportional to the mass of the TUs ($m_{TU,i}$), if their size is not uniform:

$$w_{TU,i} = \frac{m_{TU,i}}{m_T} \cdot w_T, \quad (2)$$

where m_T is the mass of the tissue. After the definition of "TU weighting factors", alternative effective dose can be determined by the following expression:

$$E = \sum_i w_{TU,i} \cdot \sum_j w_{R,j} \cdot D_{i,j}, \quad (3)$$

where $w_{R,j}$ is the radiation weighting factor, $D_{i,j}$ is the dose absorbed by the i^{th} TU from radiation type j, and so $\sum_j w_{R,j} \cdot D_{i,j}$ is the equivalent dose (H_E) in the i^{th} TU. Here, it is supposed that only the lungs, but not the other organs are exposed.

In microscopic level, such effects of ionizing radiation can be observed which may be involved in carcinogenesis or other processes leading to stochastic effects, but their extent is not proportional to dose. The dose-effect relationships of most of these phenomena are influenced by many other factors than dose and therefore cannot be easily described. In the present study, however, it is not intended to consider quantitatively precise relationships. Rather four basically different functions are investigated, which are non-linear below but linear over a threshold dose, and may roughly describe the dependence of some biological quantities on dose. These functions are summarized in table 1 and plotted in figure 1.

Table 1. The non-linear functions applied for alternative equivalent dose.

Type	Alternative equivalent dose
supralinear	$H_E(D) = w_R \cdot D \cdot \left(1 + \exp(-36 \cdot D)\right)$
sublinear	$H_E(D) = w_R \cdot D \cdot \left(1 - \exp(-36 \cdot D)\right)$
biopositive	$H_E(D) = w_R \cdot D \cdot \left(1 - 10 \cdot \exp(-72 \cdot D)\right)$

threshold	$H_E(D) = \begin{cases} 0, & \text{if } D \leq 96 \text{ mGy} \\ w_R \cdot D \cdot \left(1 - 10 \cdot \exp(-24 \cdot D)\right), & \text{if } D > 96 \text{ mGy} \end{cases}$

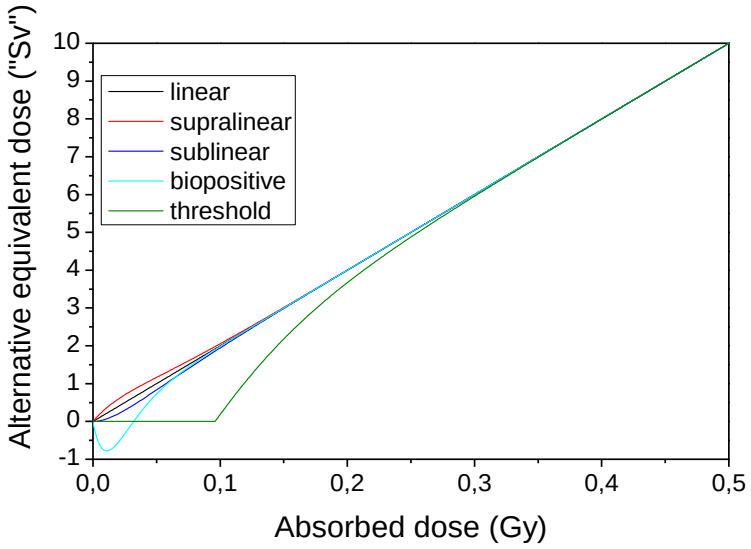

Figure 1. The functions applied in the determination of alternative equivalent and effective dose, if the tissue is exposed only to α-particles.

The computation time needed for the determination of α-track distribution increases by the number of inhaled particles simulated. Existing data obtained from earlier simulations correspond only to 0.0129 WLM and approximately 0.5 mGy mean tissue dose (Madas et al., 2011, Szőke et al., 2009). At this exposure, a significant number of TUs is not hit by α-particles. To investigate the dose-effect relationship in a wider range than 0-0.5 mGy, extrapolation is necessary. For the sake of simplicity, it is estimated that the hit number distribution among TUs does not change with exposure over 0.0129 WLM. This is certainly not true because of the non-hit TUs, and may lead to false conclusions. The effect of non-hit TUs can be investigated by adding a homogeneous dose distribution to the inhomogeneous one. Therefore, a β-radiation exposure supposed to be homogeneous in the lungs is considered in another simulation. The ratio of mean tissue dose due to α- and β-radiation (0.7/0.3) is obtained from the computations performed by Nikezic et al. (2006) and Markovic et al. (2011). The alternative equivalent dose due to this mixed field exposure is computed by summing absorbed doses in the exponent without weighting and summing absorbed doses before the exponent with the radiation weighting factors applied in radiation protection. The functions applied are summarized in table 2.

Table 2. The non-linear functions applied for alternative equivalent dose, if both α- and β-exposure is considered.

Type	**Alternative equivalent dose**
supralinear	$H_E(D_\alpha, D_\beta) = \left(w_{R,\alpha} \cdot D_\alpha + w_{R,\beta} \cdot D_\beta\right) \cdot \left(1 + \exp\left(-36 \cdot \left(D_\alpha + D_\beta\right)\right)\right)$
sublinear	$H_E(D_\alpha, D_\beta) = \left(w_{R,\alpha} \cdot D_\alpha + w_{R,\beta} \cdot D_\beta\right) \cdot \left(1 - \exp\left(-36 \cdot \left(D_\alpha + D_\beta\right)\right)\right)$
biopositive	$H_E(D_\alpha, D_\beta) = \left(w_{R,\alpha} \cdot D_\alpha + w_{R,\beta} \cdot D_\beta\right) \cdot \left(1 - 10 \cdot \exp\left(-72 \cdot \left(D_\alpha + D_\beta\right)\right)\right)$
threshold	$H_E(D_\alpha, D_\beta) = \begin{cases} 0, & \text{if } D_\alpha + D_\beta \leq 96 \text{ mGy} \\ \left(w_{R,\alpha} \cdot D_\alpha + w_{R,\beta} \cdot D_\beta\right) \cdot \left(1 - 10 \cdot \exp\left(-24 \cdot \left(D_\alpha + D_\beta\right)\right)\right), & \text{if } D_\alpha + D_\beta > 96 \text{ mGy} \end{cases}$

III. Results and discussion

Figure 2 shows alternative effective doses as the function of mean tissue dose in the case when only α-exposure is considered. Exposure in WLM computed from effective dose applying a recent estimation of dose conversation coefficient of 15 mSv/WLM (Al-Jundi et al., 2011) and alternative excess nominal risk (corresponding alternative effective dose multiplied by 0.05 mSv^{-1}) are also presented using additional axes. In panel a, absorbed dose is averaged over the whole tissue (over the five bifurcation unit), i.e. the dose distribution over the TUs is not considered. In panel b, alternative effective doses are computed by summing up alternative equivalent doses of TUs, however the hit probability distribution over TUs is uniform. Panel c show the case when the realistic deposition distribution of radon progeny is considered, i.e. the hit distribution is strongly inhomogeneous over the TUs.

The black lines in all the three panels represent that if alternative effective dose is linear function of absorbed dose, then it is independent on the suborgan dose distribution. This result was expected, because this is a mere mathematical identity. This is clear if in equation (3) $w_{TU,i}$ is replaced using equation (2) and $D_{i,j}$ is written as the ratio of locally absorbed energy ($E_{i,j}$) and mass of the TU:

$$E = \sum_i \frac{m_{TU,i}}{m_T} \cdot w_T \cdot \sum_j w_{R,j} \cdot \frac{E_{i,j}}{m_{TU,i}}. \quad (4)$$

Changing the order of summations, the following form is obtained:

$$E = w_T \cdot \sum_j w_{R,j} \cdot \frac{\sum_i E_{i,j}}{m_T}, \quad (5)$$

where the fraction is equal to tissue dose received from the exposure type *j*, i.e. the effective dose is obtained as it is currently used in radiation protection. In this deduction, we do not consider the absorbed dose of other organs. However, if the weighting factors are introduced with equation (2), and alternative equivalent dose is linear function of the absorbed dose, then alternative effective dose is independent on the TU size where absorbed dose is calculated even in the case of a whole body exposure.

Comparing panels a and b, it can be observed that the threshold where green line starts to increase is smoother in panel b than in panel a. Since the variance of dose absorbed by individual TUs is not zero, absorbed dose in some TUs reach the threshold of 96 mGy at lower exposure than the average over all the TUs. In case of the other curves no significant differences can be observed. This means that at the applied TU size, microdosimetric approach is not necessary if the dose distribution is homogeneous.

Comparing panels a and c, it can be observed that all the non-linear functions are much smoother in panel c than in panel a. If the exposure is inhomogeneous, the range where a difference between the linear and non-linear functions can be seen is wider, but the maximal difference is much less. This suggests that possible nonlinearity in the low dose range is less significant in case of inhomogeneous exposures than in case of homogeneous ones.

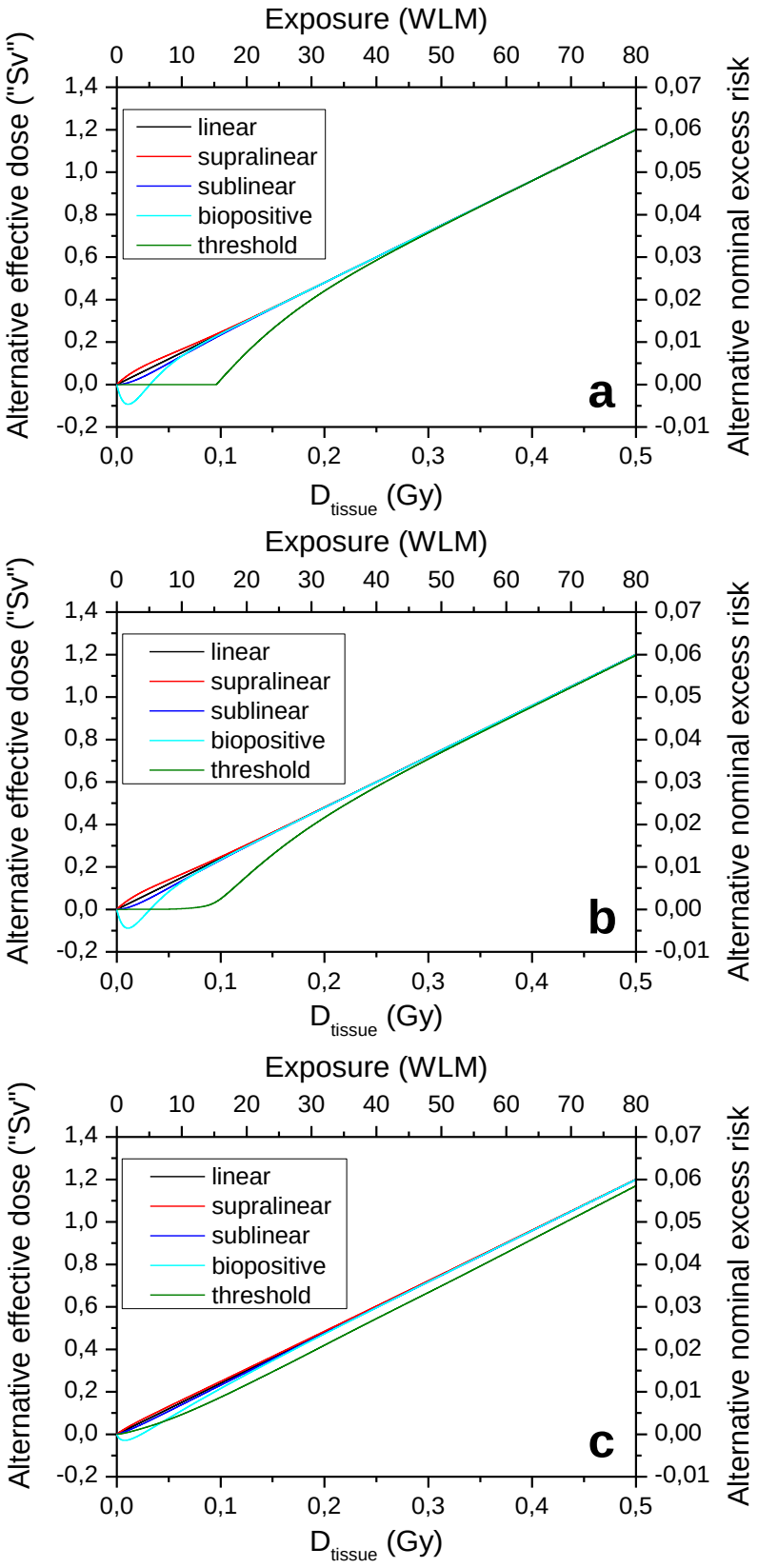

Figure 2. Alternative effective dose as the function of mean tissue dose computed from the mean tissue dose (panel a), considering the dose distribution in TUs supposing homogeneous exposure (panel b), and considering the dose distribution in TUs taking into account the realistic inhomogeneous exposure (panel c). The figure does not give account on the β-radiation dose.

Figure 3 shows the case when besides α-radiation a homogeneous β-exposure is also considered. Panel a represents the simulations when TUs are not taken into account, i.e. alternative effective dose and nominal excess risk are calculated from absorbed dose averaged for the whole tissue. In panel b, absorbed doses are computed for the TUs, however α-hit distribution is supposed to be homogeneous over the TUs. In panel c, the realistic inhomogeneous deposition distribution of radon progeny is considered resulting in inhomogeneous α-exposure, but β-exposure is supposed to be homogeneous. It is important to note that the slope of the curves over the low dose range is less in figure 3 than in figure 2, because the same absorbed dose from a mixed α- and β-exposure results in lower equivalent (and effective) dose than that from a pure α-exposure.

Similarly to figure 2, only one difference between panel a and b can be observed in figure 3. In case of the green line, the threshold dose is less sharp if absorbed dose is not averaged over the whole tissue (panel b). The non-linear curves in panel c are much smoother than the corresponding ones in panel a and b, which can be interpreted that nonlinearity in low dose effects are less significant if the exposure is inhomogeneous than if it is homogeneous.

Panel c of figure 3 can be compared to panel c of figure 2. It can be observed, that the range where difference between the linear and non-linear curves is larger than a given value is less wide if a homogeneous exposure is added to the inhomogeneous one. Furthermore, the maximal differences between the non-linear and linear functions are also smaller if the homogeneous β-exposure is taken into account. These results suggest that the significance of any non-linearity in the low dose range may be even lower if there is a homogeneous exposure besides the inhomogeneous one. However, it is worth to mention that in case of inhomogeneity parts of the tissue may receive high doses, where other biological mechanisms may be activated resulting high-dose nonlinearity which may significantly change the related risk (Madas and Balásházy, 2011).

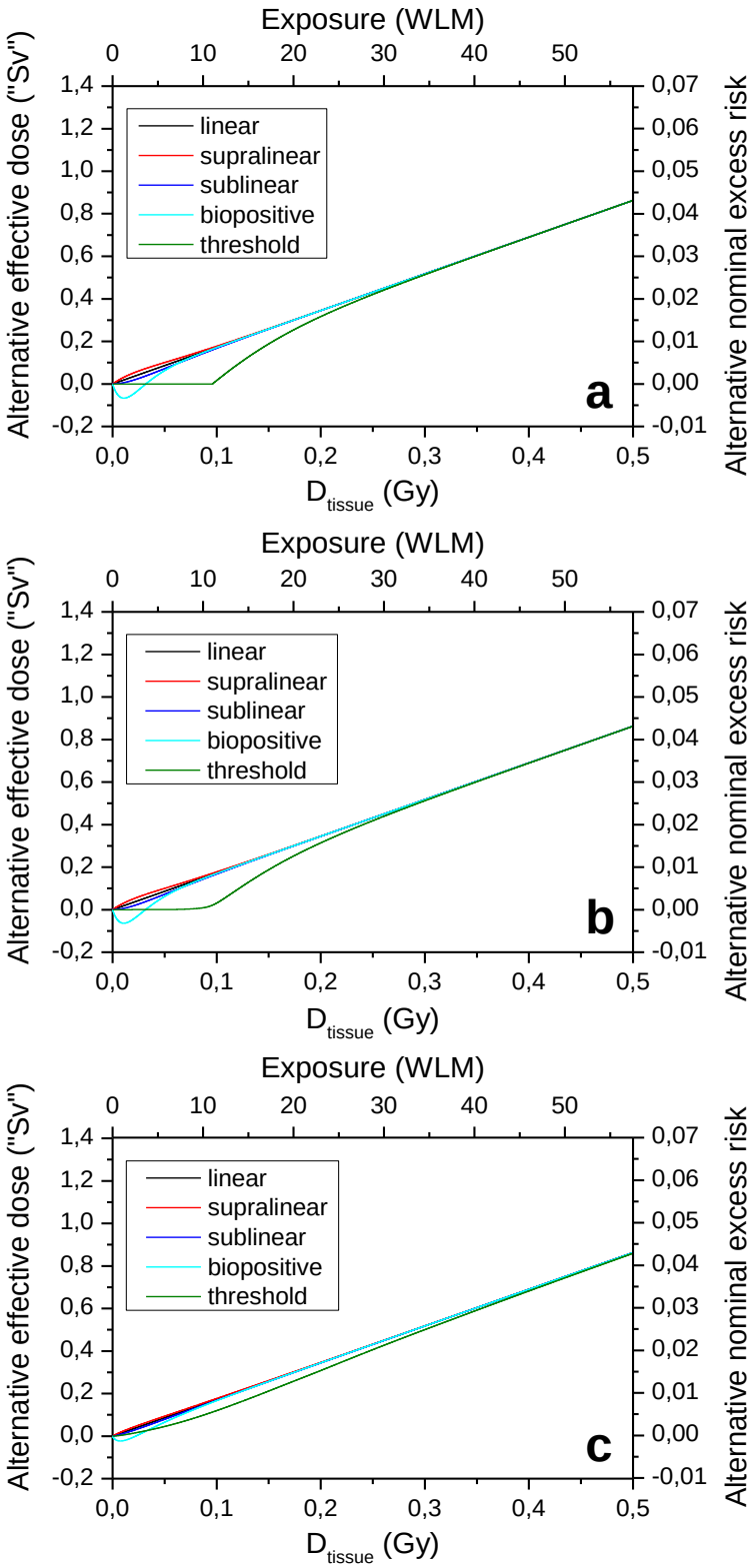

Figure 3. Alternative effective dose as the function of mean tissue dose computed from the mean tissue dose (panel a), considering the dose distribution in TUs supposing homogeneous exposure (panel b), and considering the dose distribution in TUs taking into account the real, inhomogeneous exposure (panel c). In this figure both the inhomogeneous α- and the homogeneous β-radiation dose is considered.

IV. Conclusions

The current system of radiation protection does not distinguish between the expositions distributed homogeneously and inhomogeneously within the organs. With the example of radon progeny, it was shown that inhomogeneity cannot be and need not be considered if the relationship between absorbed dose, equivalent dose, effective dose and nominal risk are linear. Since microscopic investigations suggest that non-linear relationships may exist between absorbed dose and cell biological quantities potentially related to stochastic effects of radiation, the possible consequences of nonlinearity and inhomogeneous exposure were also studied. It was shown that inhomogeneous exposures result in lower significance of nonlinearity than homogeneous exposures. If besides the inhomogeneous a smaller homogeneous exposure is also considered, the significance of low dose nonlinearity seems to be even smaller. Based on the present study, it is suggested that nonlinearity in low dose effects may be less significant in case of inhaled radon progeny than in case of radiation sources producing homogeneous exposures. However, in case of inhomogeneous exposures other biological mechanisms may arise in the mostly exposed parts of the organs, which can significantly influence the risk.

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