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Can Adaptive Response Be Considered in Radiation Risk Assessment?

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The linear no-threshold (LNT) model serves as the foundation of radiation protection standards worldwide. However, numerous studies indicate that it may not be valid in the low-dose radiation exposure range, where several nonlinear phenomena have been observed. This issue has been the subject of scientific debate for years.

One proposed modification of the LNT model is the inclusion of the possibility of radiation adaptive response. This phenomenon involves, among other mechanisms, the enhancement of cellular repair processes, regulation of apoptosis, and modulation of protein production in response to low-dose or low-dose-rate ionizing radiation exposure. It appears that these effects could be effectively incorporated into radiation risk assessment, a concept introduced more than 20 years ago by Prof. Ludwig Feinendegen.[1] He defined the resultant cancer risk (R) as a probability function of radiation risk for an individual exposed to ionizing radiation dose (D): $R = P_{ind}D - p_{AR}(D,t) \cdot (R_{spo} + P_{ind}D) \approx P_{ind}D - p_{AR}\,R_{spo}$, where $P_{ind}\ D$ represents the LNT component, p_{AR} is the probability function of adaptive response dependent on dose and time, and R_{spo} denotes the spontaneous lifetime cancer risk of an exposed individual.[1]

However, Feinendegen's model did not gain widespread acceptance, as the occurrence of radiation-induced adaptive response is not universal and is associated with substantial uncertainty. It is estimated that radioadaptation is observed in approximately 50-78% of cases under suitable conditions.[2] This naturally raises the question of whether incorporating this phenomenon into general risk calculations is justified.

Building upon certain assumptions of Feinendegen's model, the radiation-induced adaptive response phenomenon has recently been described in detail from a theoretical perspective using a new three-parametric mechanistic biophysical model, known as the "Warsaw Model".[3] This model accounts for the dose- and time-dependent probability distribution of adaptive response occurrence, $p_{AR}(D,t)$, thus inherently assuming only a certain likelihood of its manifestation. The shape of this function may of course vary depending on the experimental findings, initial assumptions or biophysical foundations, but assuming the humpback curve proposed by Feinendegen, we obtain[3] $p_{AR}(D,t) = \alpha_0 D^2 t^2 \exp(-\alpha_1 D - \alpha_2 t)$, where D represents a single absorbed dose received t time ago, and $\{\alpha\}$ are free parameters calculated in experimental way. In the special case of the long time irradiation, with constant dose-rate ($\dot{D} = const$), one get simpler version of the adaptive response probability distribution as $p_{AR}(\dot{D}) = \alpha_3 \dot{D}^2 \exp(-\alpha_1' \dot{D})$ which is time independent.[3] Of course mixture of both approaches are also possible.

The proposed model has been successfully applied and validated based on various radiobiological and epidemiological datasets, including radioadaptation resulting from a priming dose effect (so-called Raper-Yonezawa Effect, where adaptive response parameters were calculated as $\alpha_0 = 22.9^{+0.5}_{-4.0}$ $\mathrm{Gy^{-2}h^{-3}}$, $\alpha_1 = 79.4^{+5.5}_{-11.2}$ $\mathrm{Gy^{-1}}$ and $\alpha_2 = 0.0832^{+0.0093}_{-0.0082}$ $\mathrm{h^{-1}}$ for human lymphocytes in vitro)[4] and population-based data from High Background Radiation Areas, where $\alpha_1' = 0.201 \pm 0.054$ (year·mGy) and $\alpha_3 = 0.019 \pm 0.013$ ($\mathrm{year^2 \cdot mGy^{-2}}$).[5] This suggests that the presented biophysical formalism could be extended to multiple other applications, including radiation risk assessment for narrowed, adaptive-response-prone populations.

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For instance, in the case of a single dose D received t time ago, radiation risk in the Warsaw Model can be expressed as: $R = (1 + aD)\exp[-\alpha_0 D^2 t^2 \exp(-\alpha_1 D - \alpha_2 t)]$, where the first term is associated with the linear dose-effect relationship according to the LNT model, and the second part is related to the occurrence of the adaptive response, which introduces a shift from the straight line for small doses. Similarly, for continuous exposure at a dose-rate $\dot{D}$ over a period T, radiation risk in the Warsaw Model is given by: $R = \left(1 + a\dot{D}T\right)\exp\left[-\alpha_3 \dot{D}^2 \exp\left(-\alpha_1' \dot{D}\right)\right]$, where a is a typical LNT coefficient. In some cases, the $\dot{D}T$ term can be replaced by the total dose. The above equations are purely theoretical and are based on the mathematical formalism of the validated adaptive response model. All parameters were precisely calculated using purely radiobiological and epidemiological data.[4,5] Importantly, both equations assume that adaptive response has indeed occurred, which, as discussed earlier, is not always the case.[2]

We hope that these conceptual considerations will contribute to a better understanding of the role of adaptive response in radiation risk assessment, particularly in shaping the dose-effect relationship for radiation-induced cancer risk.

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