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D9.50 – Creation of statistical model

Lead Author: DH-PHE

With contributions from: All project partners (HMGU, ENEA, DU, OBU) and Advisory Board members

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Abstract

The lens of the eye is known to be more radiosensitive than previously thought but, despite a substantial reduction in occupational dose limits based on recent epidemiological information and reanalyses, the mechanisms of low dose radiation cataract induction are still unclear. This is an important current public health issue, for instance for medical radiation workers, many of whom will need to amend their working practices despite a clear understanding of the effects of chronic, low dose, ionising radiation exposure.

The LDLensRad project aims to bring together experts from across Europe to answer a number of key research questions on this topic, including: how does low dose radiation cause cataracts; is there a dose rate effect, and how does genetic background influence cataract development after radiation exposure. CONCERT Deliverable 9.50 describes progress to date in the statistical modelling of the LDLensRad individual endpoints and combined data towards development of further mechanistic hypotheses.

Progress summary

The aim of WP4 of the LDLensRad project, Statistical modelling, was to ensure sufficient statistical analysis was carried out for all the endpoints, and then to attempt to combine the data to build statistical models to contribute to hypothesis generation.

At the LDLensRad Final Meeting in Rome in December 2019, the statistical analysis of data under WP4 was discussed. The original plans as defined at the previous meetings were for individual tasks, that each lab/individual was responsible for the provision of high quality uncertainty estimates on each and every measurement made – to ensure the analysis methods are driven by the data. This has been carried out highly successfully (deliverable D9.54). Analysis would nominally be with variance-based approaches for multiple experimental factors – 'ANOVA' or non-parametric equivalents where necessary, together with multivariate approaches where appropriate. In practice, although individual endpoint analysis is almost complete, as we are only now at the stage where the data are being finally collated and thus methodological modelling is still underway. However, as an example, MANOVA has been applied to cell density and proliferation data from HMGU and the results demonstrate a borderline statistical link between the endpoints in terms of mutation status (wildtype (B6C3F1) and heterozygous mutant Ercc2$^{+/S737P}$ mice).

It was then intended to focus on development of methodological models where possible to investigate whether data could be combined with 'systems' style modelling. Finally, whether it is possible to apply pathway-based and network-based analysis methods, for example to propose Adverse Outcome Pathways (AOP) would be investigated.

Adverse outcome pathways can be described as a hypothesized chain of action from the initializing event to the health effect, via a chain of events, in order to promote further understanding of the interplay between a complex set of factors in terms of the action of ionising radiation (Chuahan et al., 2019).

Systems biology is a tool that allows consideration of multiple levels of data in order to attempt to partially or fully explain a causal chain of action (Unger, 2014).

The LDLensRad data are still being collated, however, as is clear from the results presented in deliverable D9.54 (the final year report), although a huge amount of data has been generated, the consortium has by no means solved the question of exactly how ionizing radiation causes or contributes to cataracts at low doses. There are a number of endpoints that need further consideration or were not considered during the project. Going forward, it is thus intended to carry out a focused consideration of the sets of data that can potentially be compared – for example the DNA damage, cell density and proliferation data for all the animal models, the imaging and NGS data for the ENEA mice; the Scheimpflug, OCT, retinal, visual acuity and behavioural data from HMGU – with systems biology/ AOP style approaches to identify statistical links as 'jigsaw' pieces in an ultimate mechanistic model or set of models. It is anticipated that the results of this work will be included in the proposed special issue of Radiation Research due to be published in Spring 2021 (details in deliverable D9.58).