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Abstracts

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Dose estimation with uncertainty quantification from the gamma-H2AX assay

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Introduction
Over recent years, the suitability of the gamma-H2AX foci assay as a biomarker for ionizing radiation has been clearly established in principle. However, dose estimation and uncertainty quantification from this assay requires special care due to intra-individual, inter-individual and inter-laboratory variation. This contribution discusses adequate statistical methodology and presents a web applet.

Methods
We distinguish two steps in this process: Firstly, the construction of an adequate dose-response curve from in vitro laboratory data, and secondly, the estimation of radiation dose, using the calibration curve, for a new sample of foci counts, from, say, a potentially exposed individual. Due to the count data character of the response, standard least squares regression is not adequate, and instead a quasi-Poisson modelling approach is taken. Dose estimation is carried out through inverse regression, where uncertainties can be decomposed into different sources via the delta method.

Results
While there is a physical argument for the calibration curves to be linear, in practice the curves show a quadratic shape with significant negative quadratic coefficient due to a saturation effect. With the help of a reference sample [1] to account for inter-laboratory variation if required, doses can be estimated generally with reasonable accuracy. For instance, from mean foci yields obtained from 50 sample cells 1h after exposure, standard errors normally do not exceed 0.5Gy. The uncertainty contributed by the sampling error will generally overwhelm other sources of uncertainty (especially the one related to the calibration curve). For estimation 24h after exposure, the resulting standard errors can become much higher, and reach 2Gy or more.

Conclusion
For the gamma-H2AX assay, the uncertainty of (`whole body') dose estimates has been assessed by decomposing this uncertainty into its individual sources. For foci counts obtained after 1h, the uncertainties are relatively small and allow for precise dose estimates. After 24h, uncertainties can be large which however does not render the dose estimates useless as they may still be usable for triage purposes, or in conjunction with other measurements/biomarkers. Accompanying this work, an (R Shiny) web applet has been produced, which will be made freely available.

References
[1] Ainsbury EA, Higueras M, Puig P, Einbeck J, Samaga D et. al. (2017). Uncertainty of fast biological radiation dose assessment for emergency response scenarios. International Journal of Radiation Biology 93(1):127-135.