

1.08.10 Multiomics Dose-Response Modeling Identifies Low-Dose Hazards of Ionizing Radiation to *Daphnia* and Supports an Adverse Outcome Pathway Network

Y. Song, Norwegian Institute for Water Research (NIVA) / Ecotoxicology and Risk Assessment; K. Zheng, D.A. Brede, B. Salbu, Norwegian University of Life Sciences (NMBU) / Centre for Environmental Radioactivity (CERAD); K. Tollefsen, NIVA - Norwegian Institute for Water Research / Section of Ecotoxicology and Risk Assessment. Elevated levels of ionizing radiation from radionuclides released due to nuclear accidents, authorized releases and from naturally occurring radioactive materials may pose hazards to aquatic organisms. While adverse biological effects of acute high-dose ionizing radiation have been extensively investigated, knowledge on low-dose chronic effects is scarce. The aims of the present study were to: 1) Identify low-dose hazards of ionizing radiation to *Daphnia magna* using multiomics dose-response modeling; 2) demonstrate the use of omics data to support an adverse outcome pathway (AOP) network developed for ionizing radiation. Neonatal *D. magna* were exposed to gamma radiation for 8 days. Transcriptomic analysis (RNA-seq) was performed after 4 days and 8 days of exposure, whereas metabolomics (UHPLC-HRMS/MS) and assays for functional endpoints, such as reactive oxygen species (ROS) formation, mitochondrial membrane potential (MMP) and whole-organism ATP content, were conducted after 8 days of exposure. Dose-response modeling and functional integration of the multiomics data were performed using the R package DRomics and MetaboAnalyst, respectively. Benchmark doses (BMDs, 5%) as points of departure (PODs) were estimated for both dose-responsive genes/metabolites and the enriched KEGG pathways. The PODs of relevant pathways and functional endpoints were then overlaid with a previously published AOP network. The results showed that several KEGG pathways were highly relevant to the known modes of action of gamma radiation, including oxidative stress, DNA damage, mitochondrial dysfunction, protein degradation and apoptosis. The functional assays showed increased ROS production, and decreased MMP and ATP. Ranking of PODs at the pathway and functional levels showed that oxidative damage related functions had relatively low PODs, followed by DNA damage, energy metabolism and apoptosis. These were in agreement with the proposed AOP network for ionizing radiation. The present study employed multiomics dose-response modeling to identify low-dose hazards of ionizing radiation to *Daphnia*. This approach yielded promising results and can potentially provide additional empirical evidence to support AOPs. **Acknowledgement** - This project was funded by the Research Council of Norway through the Centre of Excellence project 223268 (www.niva.no/en/projectweb/cerad), and supported by the NIVA Computational Toxicology Program (www.niva.no/nctp).