

## EXPERIMENTAL STUDIES OF URANIUM RENAL TOXICOLOGY IN LOW DOSE EXPOSURES

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Exposure of uranium compounds can occur in several situations including nuclear fuel processing, military activities, and natural exposure. Uranium is a radio element with known radiological ( $\alpha$ -emitting radionuclide) and chemical (as a heavy metal) toxicities, which accumulates preferentially in the kidneys and more specifically in proximal convoluted tubules. However significant gaps remain in the evaluation of the risk of renal cancerous or non-cancerous disease in the case of chronic or repeated low-dose exposure to uranium.

The goal of our research projects aim to decipher the biological and pathological responses to uranium low-dose exposure by using experimental models including in vitro 2D or 3D (organoid) cell culture or genetically-engineered mouse (GEM) models. The dose-response relationship of kidney impairment due to uranium induced nephrotoxicity, in an exposure model representative of occupational or military exposure to uranium via inhalation, has been recently published [1]. Nephrotoxicity biomarkers, KIM-1, clusterin and osteopontin, are induced by uranium exposure and associated with changes in renal function (arterial fluxes) measured using non-invasive functional imaging (Doppler-ultrasonography) and confirmed by renal histopathological analysis. To analyze the possible link between uranium exposure and the development of renal cancer at low-dose, GEM model predisposed to its development are used in the UKCAN (Uranium Kidney Cancerous effect) project. Renal carcinogenesis is studied through clinical biochemistry, molecular biology, and imaging tool. The biological mechanisms and pathways impacted by uranium exposure can be formulated into an adverse outcome pathway (<https://aopwiki.org/aops/447>) [2] that allowed us to identify the different steps and gaps between an initiating event to the kidney disease. Kidney organoid model and animals are used in a second project to fill these gaps and study more precisely the uranium low dose effects from subcellular to systemic effects. Molecular pathways triggered by uranium low-dose exposure with particular emphasis on the role of autophagy and inflammatory responses are addressed in this collaborative project in addition to speciation, interaction, and spatial distribution of uranium in our experimental models.

### Bibliography

[1] L. De Castro, A. Manoury, O. Claude, B. Simoneau, V. Monceau, D. Suhard, C. Elie, V. Magneron, L. Roy, C. Bouvier-Capely, C. Ibanez, E. Davesne, Y. Gueguen, Renal toxicity and biokinetics models after repeated uranium instillation, Scientific reports, 13 (2023) 4111.

[2] Y. Gueguen, M. Frerejacques, Review of Knowledge of Uranium-Induced Kidney Toxicity for the Development of an Adverse Outcome Pathway to Renal Impairment, *International journal of molecular sciences*, 23 (2022).