In vivo comparison between two nephrotoxic agents, sodium fluoride and uranyl nitrate: phenotypic aspects and molecular mechanisms involved

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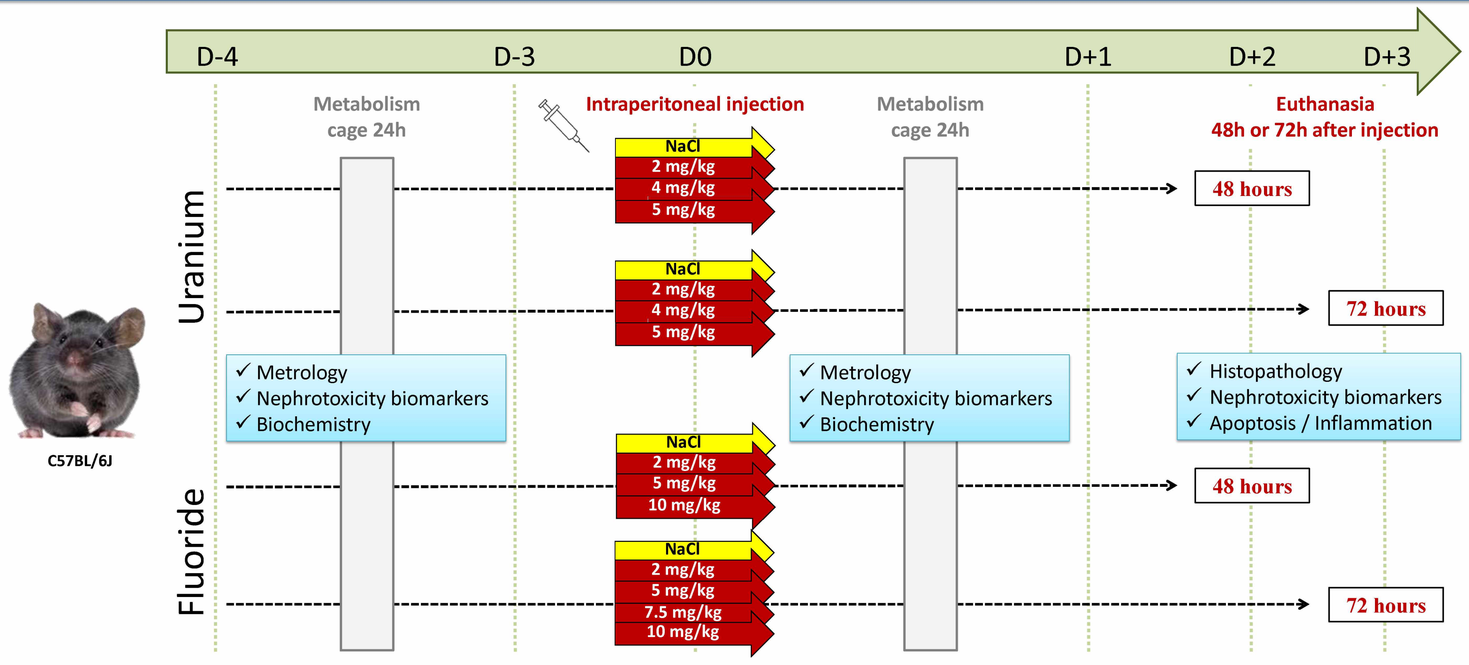
Aim

Fluoride (F) and uranium (U):

- Anthropogenic and natural presence in the environment
- Kidney is a target organ of F and U
- Lack of knowledge of their mechanisms of nephrotoxicity

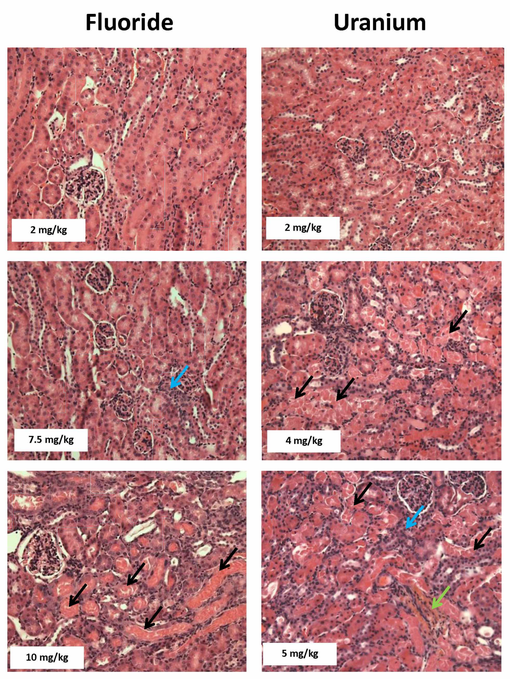
Aim :
To identify the molecular pathways of nephrotoxicity of fluoride and uranium

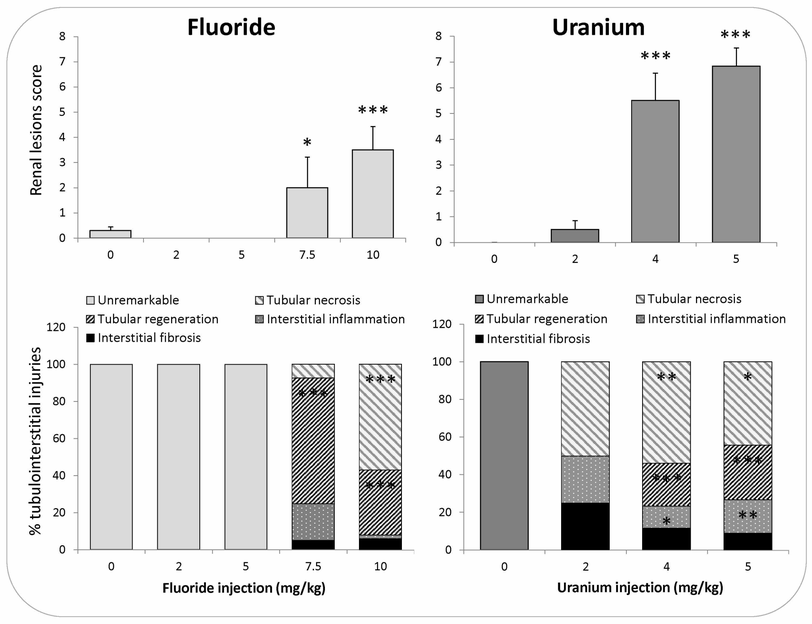
Experimental protocol



Results and Conclusion

I. Both fluoride and uranium induce structural lesions in the kidney

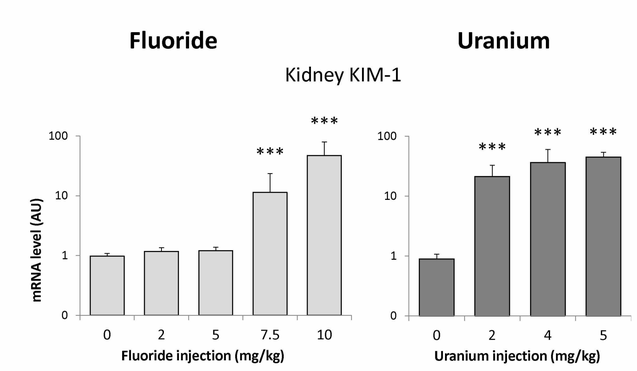


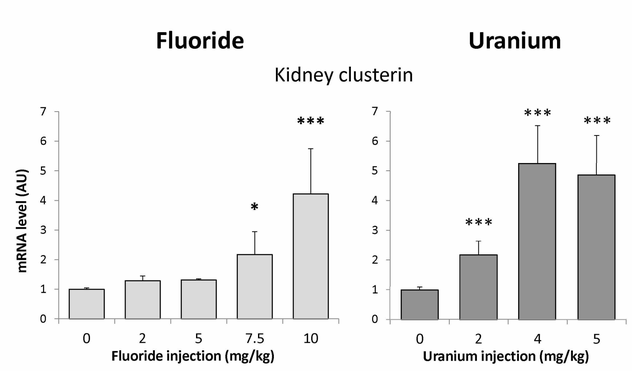


→Tubular epithelium necrosis ; →tubular regneration ; →interstitial fibrosis and inflammation

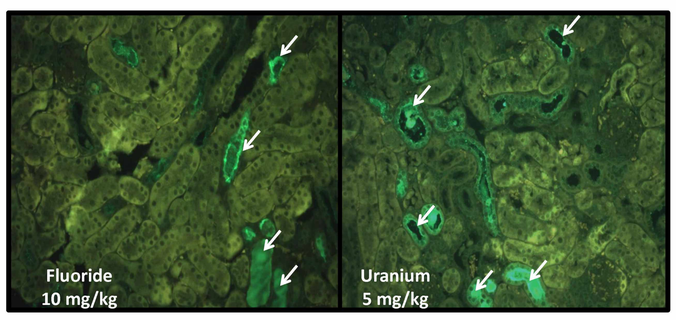
- ✓ Signs of tubular nephrotoxicity starting from 7.5 mg/kg for F and 4 mg/kg for U
- ✓ F induces tubular regeneration at 7.5 mg/kg, and both tubular necrosis at 10 mg/kg of F
- ✓ U triggers tubular regeneration, necrosis, and inflammation starting from 4 mg/kg

II. Sensitive biomarkers of nephrotoxicity increase after fluoride or uranium injection

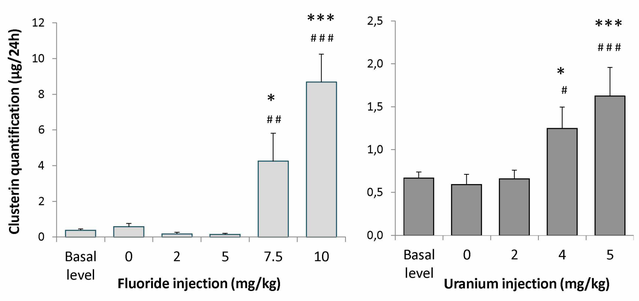




Kidney *in situ* KIM-1

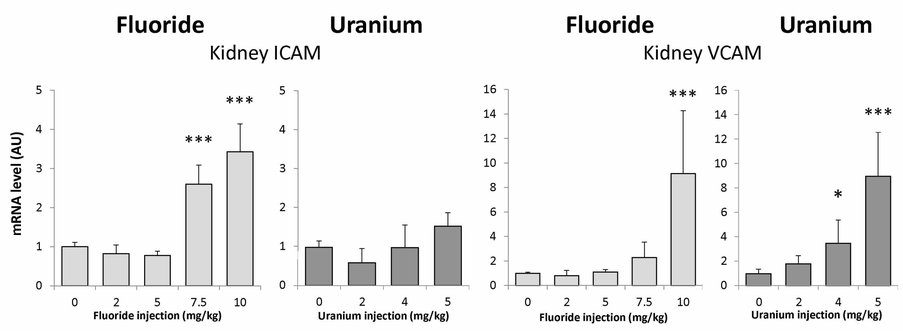


Urine clusterin

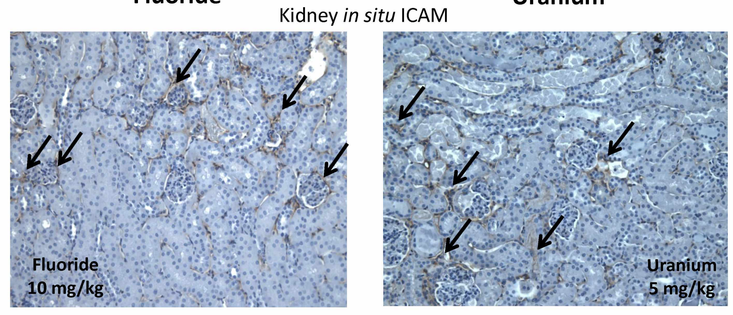


- ✓ Overexpression of KIM-1 and clusterin mRNA beginning at 7.5 mg/kg of F and 2 mg/kg of U
- ✓ Clusterin excretion only induced starting from 4 mg/kg of U (relevant with histopathology)
- ✓ *In situ* expression of KIM-1 in proximal tubules after F or U treatment

III. Fluoride and uranium induce markers of inflammation

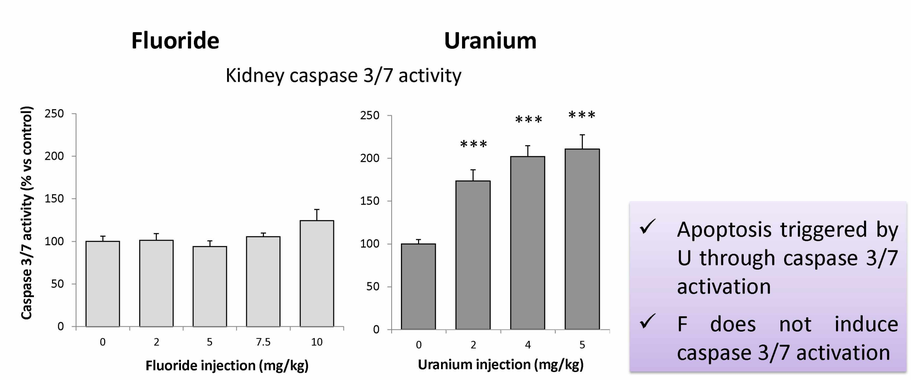


Kidney *in situ* ICAM



- ✓ ICAM and VCAM mRNA expressions are induced after F treatment, whereas only VCAM mRNA is induced by U, starting from 4 mg/kg
- ✓ Increase of ICAM *in situ* expression after F and U treatment : inflammation

IV. Uranium induces caspase 3/7 activation



- ✓ Apoptosis triggered by U through caspase 3/7 activation
- ✓ F does not induce caspase 3/7 activation

V. Conclusion

Fluoride	Uranium
Increased nephrotoxicity 72h after intraperitoneal injection	
Nephrotoxicity threshold at 7.5 mg/kg	Nephrotoxicity threshold at 4 mg/kg
Mechanisms involved in acute nephrotoxicity: Inflammation	Inflammation, Apoptosis

All data shown at 72h after intraperitoneal injection. All graphs are represented as mean ± SEM. Holm-Sidak test: *p<0.05, **p<0.005, ***p<0.001 between treated and control groups ; #p<0.05, ##p<0.005, ###p<0.001 between treated and pre-injected mice