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► To cite this version:

Audrey Legendre, Christelle Elie, Camille Ramambason, Line Manens, Maâmar Souidi, et al.. Effects of uranium on reproductive function in rats exposed from fetal life to adulthood. Journées du GdR 3606 Repro, Apr 2017, Tours, France. 2017, 2èmes Journées Scientifiques du GdR Repro. hal-01605331

HAL Id: hal-01605331

<https://hal.science/hal-01605331>

Submitted on 1 Aug 2023

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Effects of uranium on reproductive function in rats exposed from fetal life to adulthood.

Audrey Legendre¹, Christelle Elie¹, Camille Ramambason¹, Line Manens¹, Maamar Souidi¹, Pascal Froment², and Karine Tack¹

1: Laboratoire de RadioToxicologie Expérimentale, Service de Radiobiologie et d'Epidémiologie, Institut de Radioprotection et Sûreté Nucléaire, B.P.17, 92262 Fontenay aux Roses Cedex, France
2: UMR- PRC INRA, Centre INRA de Val de Loire, 37380 NOUZILLY, France

INTRODUCTION

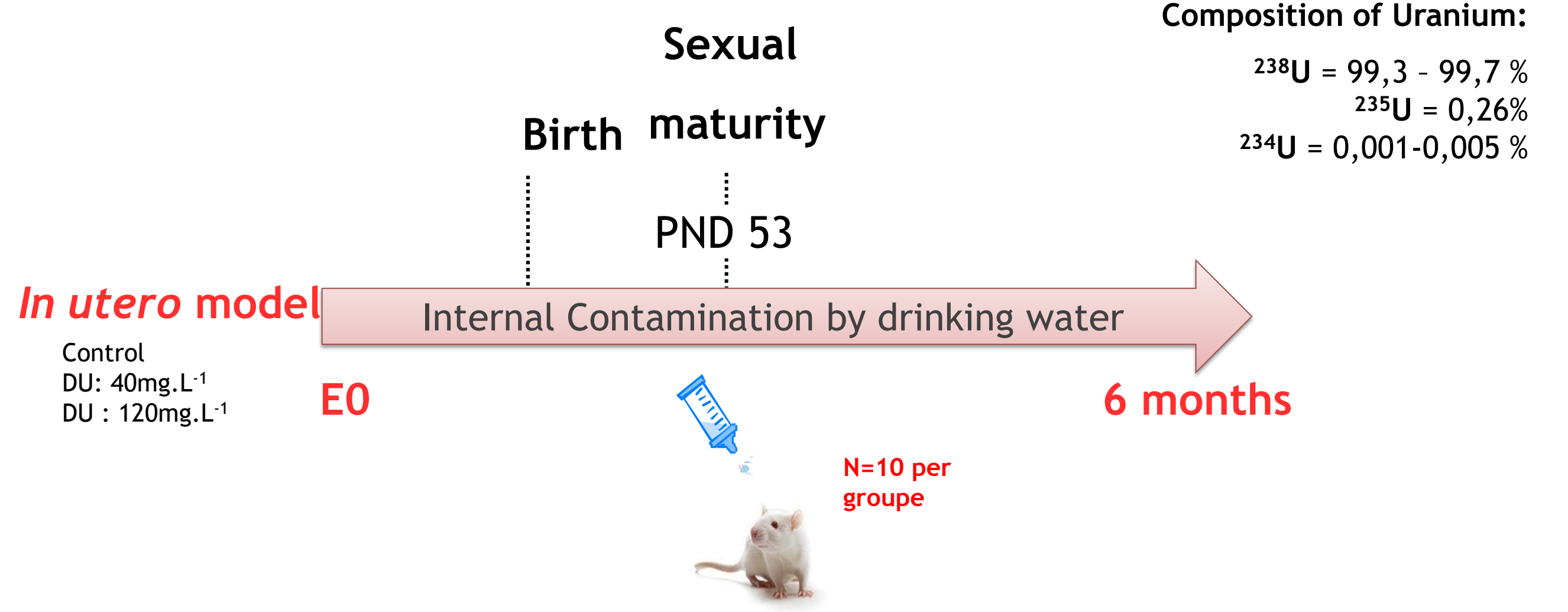
Some environmental contaminants interact with hormones and may exert adverse effects which could explain the increased risk of fertility problems and reproductive dysfunctions observed since several years. Uranium is a heavy metal naturally found in the environment. Its many uses in civil or military technologies give cause of concern about human health risks.

Recently, some studies have suggested that uranium is an endocrine-disrupting chemical, causing estrogen receptor-dependent responses in female mice. In regards to increased risk of fertility problems and reproductive dysfunctions, populations exposed to environmental uranium should be followed for their reproductive function.

The objective of our project is to identify and evaluate endocrine activity of uranium on male reproductive parameters after lifelong exposure. Rats are chronically exposed by ingestion of drinking water with Depleted Uranium (DU)(40mg.L⁻¹ and 120mg.L⁻¹, supra-environmental and non toxic concentration).

This project should improve the scientific research about biological effects of internal contamination induced by chemical properties of uranium on male reproductive function.

PROTOCOL

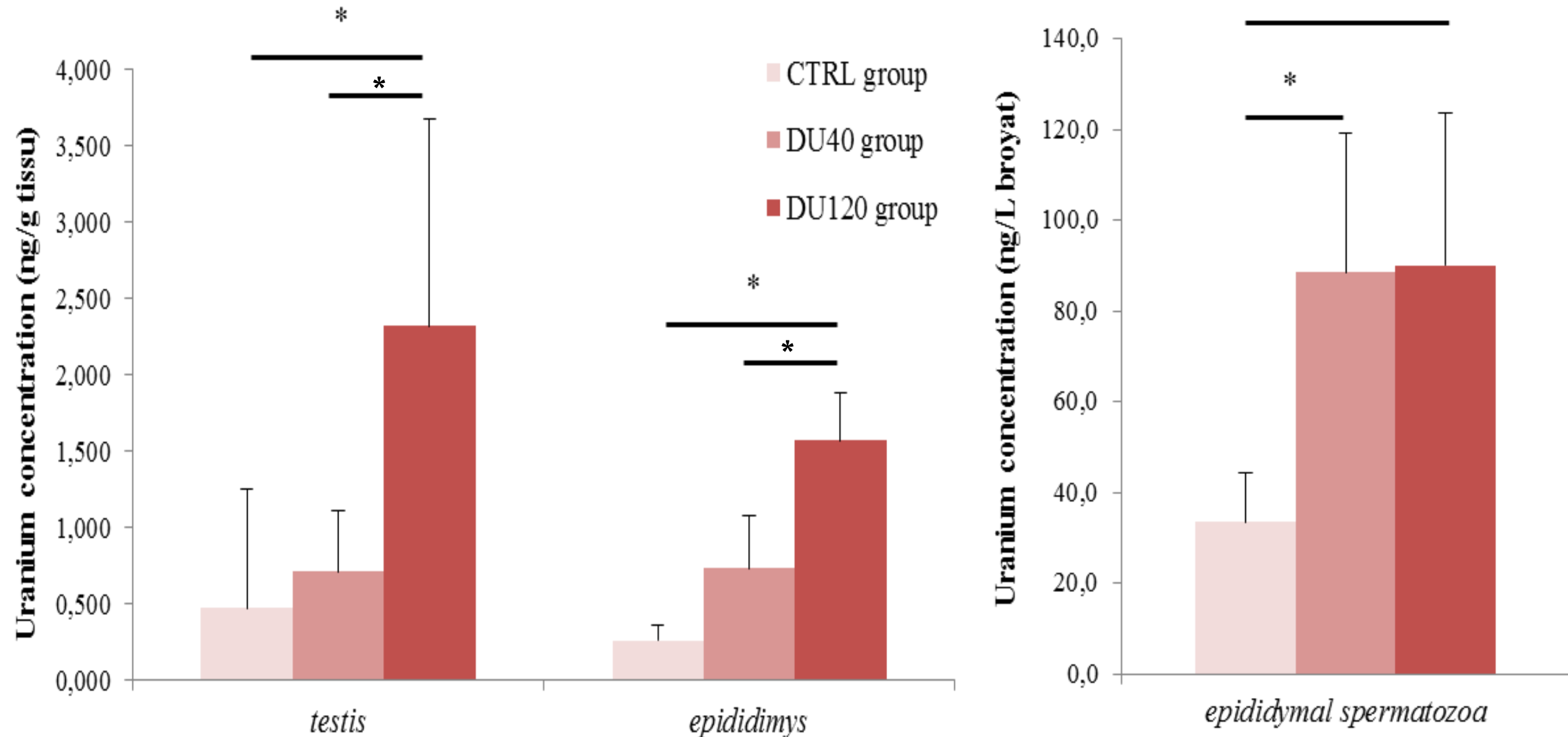


- Uranium content : ICP MS
- Intratesticular and plasma hormones : ELISA, RIA
- RT- qPCR : targets related to sexual steroidogenesis, and spermatogenesis

RESULTS

A / Uranium content

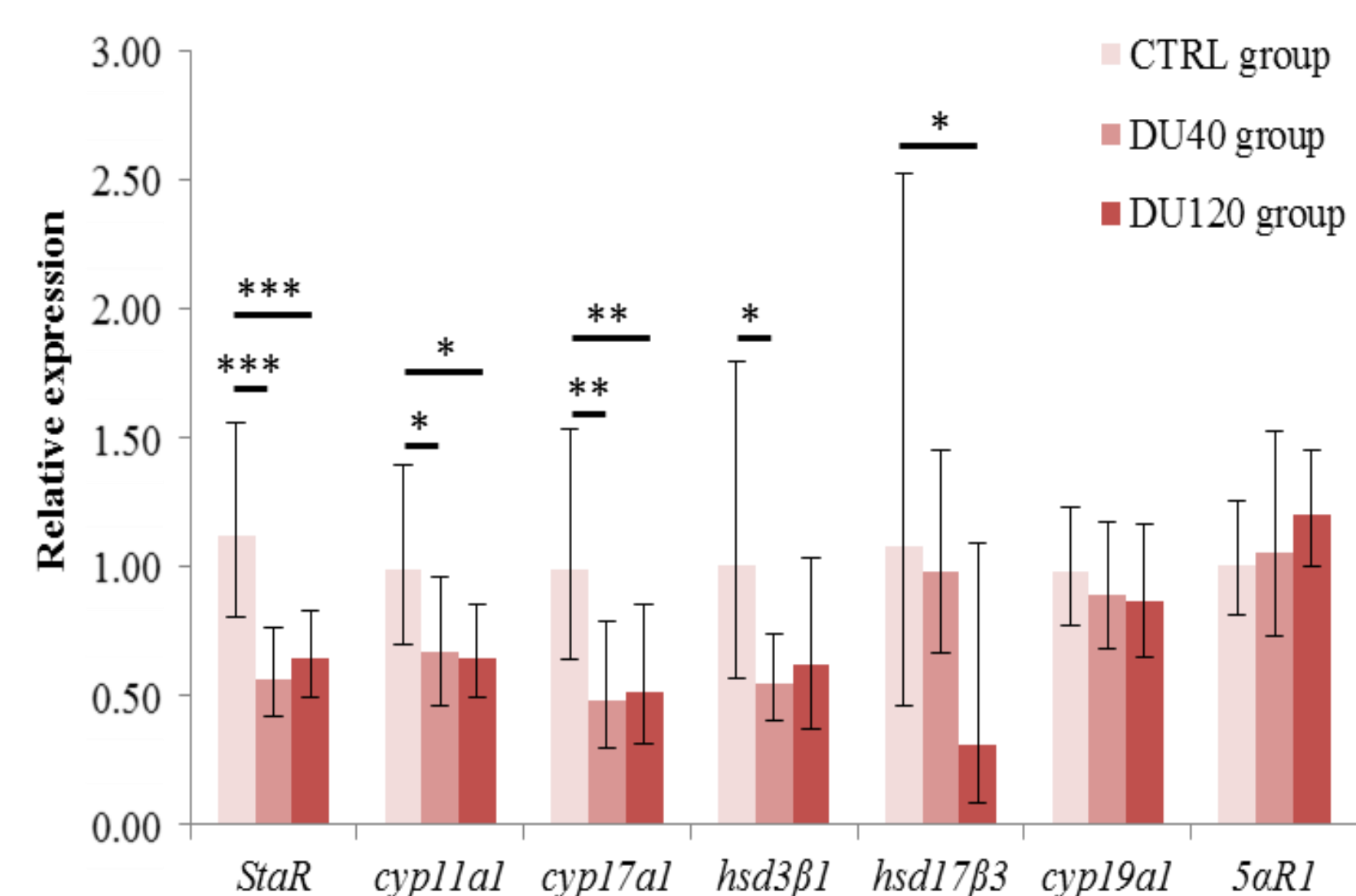
N= 10 per group^b



Uranium content is detected in testis and epididymis in DU120 group and in epididymal spermatozoa in both groups.

C / mRNA expression

N= 5-10 per group^a



Gene expression of the earliest actors of steroidogenesis were inhibited after DU exposure.

B / Intratesticular and plasma Hormones

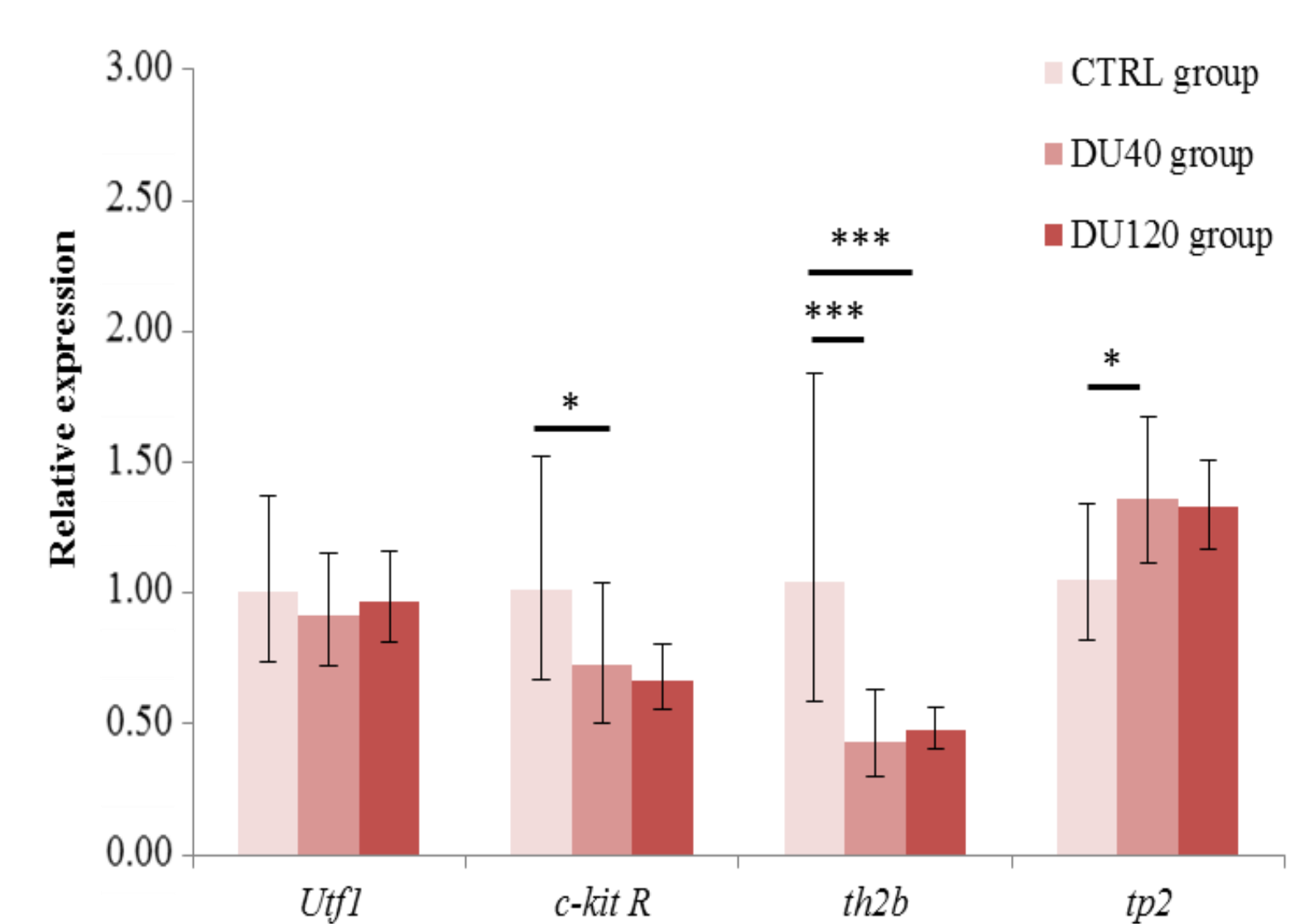
N= 10 per group	CTRL	DU40	DU120
Testosterone (T)			
Plasma level (ng.mL ⁻¹)	2.60 ± 1.37	1.93 ± 0.84 ^{b*}	2.74 ± 1.61 ^{b#}
Intratesticular level (ng.mL ⁻¹)	1.70 ± 1.91	0.71 ± 0.26 ^{b*}	1.05 ± 0.57 ^{b#}
Estradiol (E)			
Plasma level (pg.mL ⁻¹)	57.85 ± 17.89	50.477 ± 9.77 ^a	45.79 ± 15.51 ^a
Intratesticular level (pg.mL ⁻¹)	15.53 ± 1.67	13.91 ± 1.11 ^{b*}	13.62 ± 0.41 ^{b*}
LH (pg.mL ⁻¹)	2.28 ± 0.54	2.47 ± 0.92 ^a	3.39 ± 0.98 ^{a**}
FSH (pg.mL ⁻¹)	29.02 ± 14.39	27.41 ± 15.38 ^a	52.60 ± 13.32 ^{a***###}

Plasma levels of pituitary hormones (LH, FSH) were induced only in DU120 group.

Plasma and intratesticular testosterone were reduced in DU40 group.

Intratesticular estradiol level increased in both DU groups.

N= 8-10 per group^a



Gene expression of spermatogonia, spermatocytes were inhibited after DU exposure.

Results are expressed as mean value ± S.D.

^{*}p<0.05, ^{**}p<0.005 and ^{***}p<0.001 versus control. [#]p<0.05, [#]p<0.005 and ^{###}p<0.001 versus DU40
^a One-way ANOVA and the Holm-Sidak test. ^b Kruskal-Wallis test and Dunn's test.

CONCLUSION & PERSPECTIVES

Our study show that :

- fetal life is a critical window for chronic uranium exposure
- the endocrine activities of low-dose uranium could disrupt steroidogenesis through the hypothalamic-pituitary-testicular axis, particularly in 120 mg.L⁻¹ group. (figure D)

Regarding the real challenge of risk assessment (REACH, ECETOC), identify endocrine activity and disrupting properties of uranium is necessary, particularly thanks to **multigenerational studies**. In this way, recent experimental studies have been performed to identify the effects of uranium on reproductive function and epigenetic profile on the next generations.

D / Hypothesis for the Male Reproductive Effects of lifelong DU exposure

