# DOTTORATO INDUSTRIALE IN SCIENZE VETERINARIE

**33° CICLO**

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# Effects on development and endocrine system of Glyphosate and Roundup administered at human equivalent doses to Sprague-Dawley rats

## Introduction

Glyphosate [IUPAC chemical name N-(phosphonomethyl)glycine] is the active ingredient of all glyphosate-based herbicides (GBHs), which is the most widely applied pesticide worldwide including the commercial formulation "Roundup" [1]. Since the late 1970s, the volume of GBHs applied has increased around 100-fold [2]. The widespread exposure of human population to GBHs has raised public health concerns, including potential effects on the endocrine system, for example by inhibiting aromatase enzyme activity and/or by activating estrogen receptors (ERs). Both in vitro and in vivo published studies to date, present conflicting findings. Glyphosate alone or GBHs exposures combined may related to adverse developmental or reproductive effects, albeit many studies used very high doses of exposure. Furthermore, relatively few human health studies have been conducted and the epidemiological evidence of GBH effects on reproductive and developmental health outcomes is too limited to draw conclusions.

## Aim

This study examines whether low-dose exposure to Glyphosate and/or its commercial formulation Roundup at the dose of Glyphosate considered to be "safe" (the US Acceptable Daily Intake - ADI - of 1.75 mg/kg bw/day), affect the development and endocrine system across different life stages in Sprague-Dawley rats.

## Methods

Route of administration: test substances were administered ad libitum to Sprague-Dawley (SD) rats , via drinking water.

Compound tested: Glyphosate and it's formulation Roundup.

The study design and the schedule of the treatment are summarized in Table 1 and Figure 1.

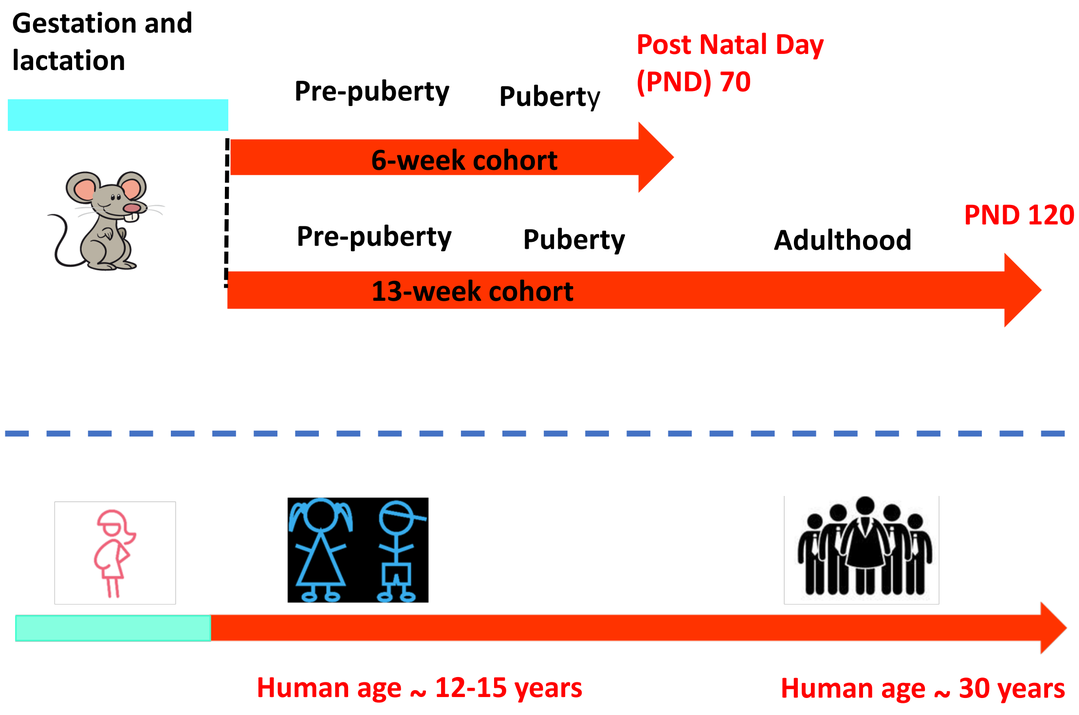
Effects of glyphosate or Roundup exposure were assessed on developmental landmarks and sexual characteristics of pups.

Hormone profiling was determined in all the experimental animals.

Table 1. Glyphosate pilot study: study design.

| GRUPPO | COMPOSTO | DOSE |
|---|---|---|
| I | - | CONTROLLO |
| II | **Glifosato** | USA ADI (1.75 mg/kg/day) |
| III | **Roundup** | USA ADI (1.75 mg/kg/day) |

Figure 1. Glyphosate pilot study: schedule of treatment in the rat study and comparison with human age.




## Results

In pups, anogenital distance (AGD) at PND 4 was statistically significantly increased both in Roundup-treated males and females and in glyphosate-treated males (Fig. 2). Age at first estrous (FE) was significantly delayed in the Roundup exposed group (Fig. 3) and serum testosterone levels significantly increased in Roundup-treated female offspring from the 13-week cohort compared to control animals. A statistically significant increase in plasma thyroid-stimulating hormone (TSH) level was observed in glyphosate-treated males compared with control animals as well as a statistically significant decrease in dihydrotestosterone (DHT) and increase in BDNF (brain-derived neurotrophic factor) in Roundup-treated males. Hormonal status imbalances was more pronounced in Roundup-treated rats with a prolonged exposure.

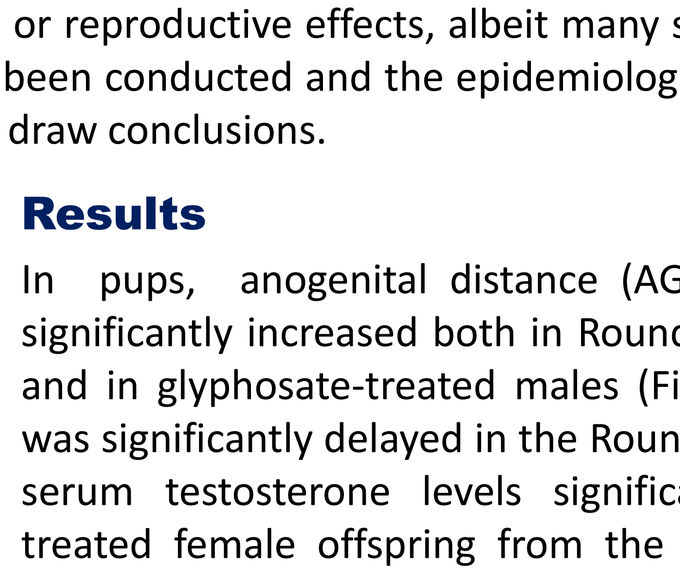



Figure 2. Glyphosate pilot study: anogenital distance (mm) at PND 4

**Analysis performed considering the body weight at evaluation of AGD**

****: Statistically significant (p<0.01) with multilevel linear regression**

**°° :Statistically significant (p<0.01) with multilevel linear regression with litter as random effect**

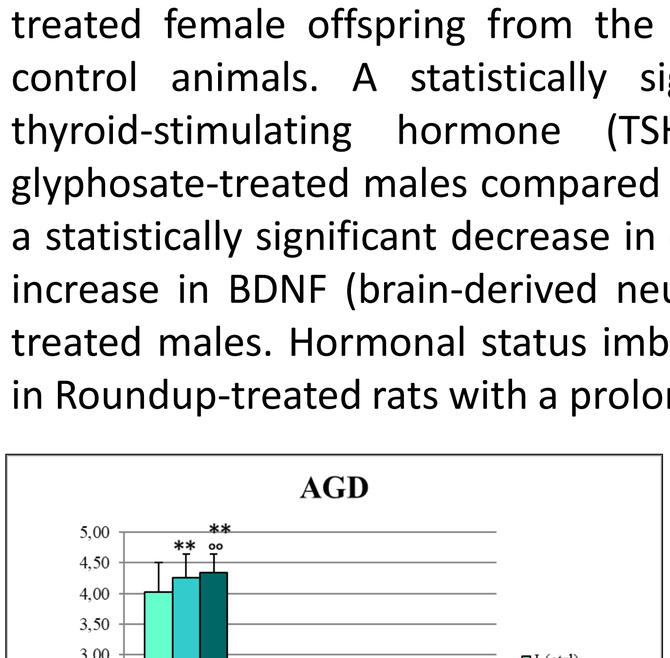



Figure 3. Glyphosate pilot study: age (days) at vaginal opening (VO) and at first estrous (FE).

*: statistically significant with p< 0.05

## Conclusions

The present study demonstrate that Roundup Bioflow exposure, from prenatal period to adulthood, induced endocrine effects and altered reproductive developmental parameters in male and female SD rats. In particular, it was associated with androgen-like effects, including a statistically significant increase of AGDs in both males and females, delay of FE and increased testosterone in female.

## References

1. Benbrook CM. 2016. Trends in glyphosate herbicide use in the united states and globally. Environmental Sciences Europe 28:3.
2. Myers JP, Antoniou MN, Blumberg B, Carroll L, Colborn T, Everett LG, et al. 2016. Concerns over use of glyphosate-based herbicides and risks associated with exposures: A consensus statement. Environmental health : a global access science source 15:19.