HEAL Webinar – June 28th 2021

Health impact of glyphosate and glyphosate-based herbicides

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY STUDY USING SPRAGUE-DAWLEY RATS EXPOSED UNDER VARIOUS CALENDARS TO THE WEED-KILLER GLYPHOSATE AND A COMMERCIAL FORMULATION GLYPHOSATE-BASED

FIORELLA BELPOGGI, SCIENTIFIC DIRECTOR
RAMAZZINI INSTITUTE, BOLOGNA –ITALY
The Global Glyphosate study

Questions

1. “Have glyphosate and GBHs been tested at currently acceptable daily intake and real-world levels of exposure?”

2. “Does glyphosate and its formulations have different effects?”

3. “What are the possible adverse effects of GBHs other than cancer?”

Answer: The Global Glyphosate Study, an integrated GLP in vivo study

➔ In 2016 the Ramazzini Institute started the Pilot Phase (STAGE I) of the Global Glyphosate Study (STAGE II), involving multiple independent Institutions and Universities in Europe and the U.S.
Partners

➢ University of Bologna (Dpt. of Agriculture; Dpt. Veterinary Medicine; Dpt. of Economics, Management and Statistics), Italy

➢ King’s College London, Gene Expression and Therapy Group, Dept. of Medical and Molecular Genetics, London, UK

➢ Istituto Superiore Sanità, Dept. of Food Safety and Veterinary Public Health Rome, Italy

➢ Environmental Carcinogenesis Unit, Ospedale Policlinico San Martino, Genova, Italy

➢ Mount Sinai School of Medicine, New York, NY, USA

➢ George Washington University, Washington, DC, USA
STAGE I

THE RAMAZZINI INSTITUTE 13-WEEK STUDY ON GLYPHOSATE-BASED HERBICIDES
AT HUMAN EQUIVALENT EXPOSURE LEVELS IN SPRAGUE-DAWLEY RATS

AIMS:
➢ To assess the methodology for conducting a GLP long-term integrated and comprehensive study (ongoing)

➢ To investigate whether exposure to Glyphosate or Roundup affects the development and endocrine system across different life stages of treated Sprague-Dawley rats at human equivalent US Acceptable Daily Intake (1.75mg/Kg bw)
### STAGE I: experimental plan

<table>
<thead>
<tr>
<th>GROUP</th>
<th>TREATMENT</th>
<th>DOSE</th>
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<tbody>
<tr>
<td>I</td>
<td>Drinking water (DW)</td>
<td>-</td>
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<tr>
<td>II</td>
<td>DW + Glyphosate</td>
<td>USA ADI (1.75 mg/Kg bw/day)</td>
</tr>
<tr>
<td>III</td>
<td>DW + Roundup</td>
<td>USA ADI (1.75 mg/Kg bw/day) Glyphosate equivalent</td>
</tr>
</tbody>
</table>

- **Route of Administration:** *ad libitum* in drinking water
- **Test Substances:** Glyphosate (purity > 99.5%) Roundup Bioflow (MON 52276)
**STAGE I: experimental design**

**Glyphosate or Roundup (MON 52276)**
(1.75 mg/Kg/bw = cRfD USA)

Gestation and lactation
(8 dams/group)

<table>
<thead>
<tr>
<th>Pre-puberty</th>
<th>Puberty</th>
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<tbody>
<tr>
<td><strong>6-week cohort</strong> (8/sex/group)</td>
<td><strong>PND 70</strong></td>
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<tr>
<td><strong>13-week cohort</strong> (10/sex/group)</td>
<td><strong>Adulthood</strong></td>
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<td><strong>PND 120</strong></td>
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</table>

**STAGE I: experimental design**

Dr. Fiorella Belpoggi - Health Impact of Glyphosate and GBHS 2021
GBHs: Key characteristics of endocrine disruptors

Evidences in *in vivo* model

### STAGE I: endpoints evaluated

#### Endocrine sensitive endpoints

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight</th>
<th>Water and feed cons.</th>
<th>Urinanalysis</th>
<th>Clinical chemistry</th>
<th>Haematological tests</th>
<th>Organ weight</th>
<th>Histopathology</th>
<th>Micronuclei</th>
<th>Transcriptome</th>
<th>Microbiome</th>
<th>Litter size</th>
<th>Live birth index</th>
<th>Sex ratio</th>
<th>Intra/extraterine death</th>
<th>Anogenital distance</th>
<th>Balano-preputial sep.</th>
<th>Vaginal opening</th>
<th>First estrous</th>
<th>Estrous cyclicity</th>
<th>Hormone analyses</th>
<th>Sperm analyses</th>
<th>Sperm aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (control)</td>
<td>F0</td>
<td>✓</td>
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<td>II (Glyphosate)</td>
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<td>III (Roundup)</td>
<td>F0</td>
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STAGE I: in life endocrine - sensitive endpoints

- **Start of treatment**
- **Weaning**
  - **GD 6**
  - **Maternal reproductive outcome of dams**
    - **Anogenital distance (PND 4)**
    - **Litter data** (sex ratio, size, survival index, ...)
  - **AGD**
  - **Vaginal opening**
  - **First estrus**
  - **6-week cohort**
    - **PND 28**
    - **PND 35**
    - **Balano-preputial separation**
  - **13-week cohort**
    - **PND 95**
    - **Estrous cycle**

DR. FIORELLA BELPOGGI - HEALTH IMPACT OF GLYPHOSATE AND GBHS 2021
STAGE I: end of life endpoints

Start of treatment → Weaning

- GD 6
- PND 28

6-week cohort

13-week cohort

Hormone and haematological analysis; clinical chemistry
Sperm analysis
Histopathology/Transcriptome
STAGE I: results

- In pups, **anogenital distance (AGD)** at PND 4 was significantly **increased** both in Roundup-treated males and females and in glyphosate-treated males

- **Age at first estrus (FE)** was significantly **delayed** in the Roundup exposed group

Analysis performed considering the body weight at evaluation of AGD

**: p<0.01 with multilevel linear regression

***: p<0.01 with multilevel linear regression with litter as random effect

*: p< 0.05
## STAGE I: results: _hormones in females_

<table>
<thead>
<tr>
<th>Serum Hormones</th>
<th>6-week cohort</th>
<th>13-week cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyphosate</td>
</tr>
<tr>
<td>No. of females examined</td>
<td>8 (8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td><strong>TT (ng/ml)</strong></td>
<td>0.66 ± 0.064</td>
<td>0.75 ± 0.12</td>
</tr>
<tr>
<td><strong>fT (pg/ml)</strong></td>
<td>6.49 ± 1.00&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6.74 ± 1.89&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>DHT (pg/ml)</strong></td>
<td>294.28 ± 50.40</td>
<td>328.34 ± 51.93&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>SHBG (ng/ml)</strong></td>
<td>864.82 ± 30.24</td>
<td>952.75 ± 54.98</td>
</tr>
<tr>
<td><strong>E2 (pg/ml)</strong></td>
<td>14.95 ± 7.24</td>
<td>32.24 ± 8.77</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Plasma Hormones</th>
<th>6-week cohort</th>
<th>13-week cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyphosate</td>
</tr>
<tr>
<td>No. of females examined</td>
<td>7 (8)</td>
<td>7 (8)</td>
</tr>
<tr>
<td><strong>FSH (ng/ml)</strong></td>
<td>3.95 ± 2.50</td>
<td>2.67 ± 1.22</td>
</tr>
<tr>
<td><strong>LH (ng/ml)</strong></td>
<td>5.75 ± 3.04</td>
<td>4.86 ± 1.93</td>
</tr>
<tr>
<td><strong>PRL (ng/ml)</strong></td>
<td>102.34 ± 164.71&lt;sup&gt;c&lt;/sup&gt;</td>
<td>27.49 ± 30.23</td>
</tr>
<tr>
<td><strong>GH (ng/ml)</strong></td>
<td>12.61 ± 13.30</td>
<td>3.85 ± 0.97&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>TSH (ng/ml)</strong></td>
<td>2.70 ± 1.13</td>
<td>3.02 ± 2.00</td>
</tr>
<tr>
<td><strong>ACTH (pg/ml)</strong></td>
<td>331.60 ± 89.59</td>
<td>314.09 ± 170.60</td>
</tr>
<tr>
<td><strong>BDNF (pg/ml)</strong></td>
<td>245.03 ± 155.68</td>
<td>483.62 ± 301.02</td>
</tr>
</tbody>
</table>

<sup>a</sup>: 7 out 8; <sup>b</sup>: 9 out 10; <sup>c</sup>: 6 out 8; <sup>d</sup>: 5 out 8; <sup>e</sup>: 4 out 10; <sup>f</sup>: 2 out 10

<sup>g</sup>: Not statistically evaluated due to insufficient sample size after clustering on the basis of the estrous cycle

* p < 0.05 with Kruskal-Wallis’ tests  ** p < 0.01 with Kruskal-Wallis’ tests  note: data reported as Mean ± standard deviation
### STAGE I: results_hormones in males

#### Serum Hormones

<table>
<thead>
<tr>
<th>Serum Hormones</th>
<th>6-week cohort</th>
<th>13-week cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyphosate</td>
</tr>
<tr>
<td>No. of males examined</td>
<td>8 (8)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>TT (ng/ml)</td>
<td>1.12 ± 0.12</td>
<td>1.02 ± 0.28</td>
</tr>
<tr>
<td>fT (pg/ml)</td>
<td>14.53 ± 2.37</td>
<td>7.45 ± 2.23&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>DHT (pg/ml)</td>
<td>761.11 ± 136.21</td>
<td>575.28 ± 238.24</td>
</tr>
<tr>
<td>SHBG (ng/ml)</td>
<td>861.20 ± 30.24</td>
<td>833.24 ± 21.15</td>
</tr>
<tr>
<td>E2 (pg/ml)</td>
<td>1.04 ± 0.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.29 ± 1.85</td>
</tr>
</tbody>
</table>

#### Plasma Hormones

<table>
<thead>
<tr>
<th>Plasma Hormones</th>
<th>6-week cohort</th>
<th>13-week cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Glyphosate</td>
</tr>
<tr>
<td>No. of males examined</td>
<td>7 (8)</td>
<td>6 (8)</td>
</tr>
<tr>
<td>FSH (ng/ml)</td>
<td>7.00 ± 1.38</td>
<td>6.43 ± 1.16</td>
</tr>
<tr>
<td>LH (ng/ml)</td>
<td>3.76 ± 0.79</td>
<td>2.87 ± 0.63</td>
</tr>
<tr>
<td>PRL (ng/ml)</td>
<td>3.83 ± 0.64</td>
<td>3.00 ± 0.64</td>
</tr>
<tr>
<td>GH (ng/ml)</td>
<td>6.03 ± 4.32&lt;sup&gt;g&lt;/sup&gt;</td>
<td>23.19 ± 21.17&lt;sup&gt;h&lt;/sup&gt;</td>
</tr>
<tr>
<td>TSH (ng/ml)</td>
<td>4.23 ± 0.76</td>
<td>8.17 ± 1.58&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>ACTH (pg/ml)</td>
<td>346.67 ± 35.52</td>
<td>255.18 ± 43.29</td>
</tr>
<tr>
<td>BDNF (pg/ml)</td>
<td>99.49 ± 25.32&lt;sup&gt;b&lt;/sup&gt;</td>
<td>148.85 ± 37.53</td>
</tr>
</tbody>
</table>

<sup>a</sup>: 7 out 8; <sup>b</sup>: 6 out 8; <sup>c</sup>: 9 out 10; <sup>d</sup>: 8 out 10; <sup>e</sup>: 6 out 10; <sup>f</sup>: 7 out 10; <sup>g</sup>: 5 out 8; <sup>h</sup>: 3 out 8; <sup>i</sup>: 4 out 8

* p < 0.05 with Kruskal-Wallis’ tests  ** p < 0.01 with Kruskal-Wallis’ tests  note: data reported as Mean ± standard deviation
STAGE I: other important results

Glyphosate or Roundup (MON 52276) 
(1.75 mg/Kg/bw = cRfD USA)

X8 per group from GD6 up to PND70 or PND 120

- Inorganic Phosphate
- Creatinine (only female)
- Total protein (only male)
- Lymphocyte Count (only Roundup at PND 120)

- Renal tubular degeneration (only dams-A)
- Focal minimal inflammation (only dams-B) (only Roundup)

- MN-PCE % (only Roundup at PND 70)

- Bacteriodetes (Prevotella)
- Firmicutes (Lactobacillus) (both Glyphosate and Roundup at PND 31)
STAGE I: publications

The Ramazzini Institute 13-week study on glyphosate-based herbicides at human-equivalent dose in Sprague Dawley rats: study design and first in-life endpoints evaluation

Simona Panzacchi,1, Daniele Mandrioli,2, Fabiana Manservisi,1,3, Luciano Bui,1, Laura Falcioni,1, Marcella Spinaci,1, Giovanna Galeati,1, Giovanni Dinelli,2, Rossella Miglio,2, Alberto Mantovani,2, Stefano Lorenzetti,1, Jianzhong Hu,1, Jia Chen,2, Melissa J. Perry,3, Philip J. Landrigan,3 and Fiorella Belpoggi,1

The Ramazzini Institute 13-week pilot study glyphosate-based herbicides administered at human-equivalent dose to Sprague Dawley rats: effects on development and endocrine system

Fabiana Manservisi,2,3, Corina Lesueur,3, Simon Panzacchi,1, Daniele Mandrioli,1,4, Laura Falcioni,1, Luciano Bui,1, Marco Manservisi,1, Marcella Spinaci,1, Giovanna Galeati,1, Alberto Mantovani,2, Stefano Lorenzetti,1, Rossella Miglio,2, Anderson Martin Andrade,2, David Malbjer Kristensen,2, Melissa J. Perry,3, Shanna H. Swan,3, Jia Chen,2 and Fiorella Belpoggi,1

The Ramazzini Institute 13-week pilot study on glyphosate and Roundup administered at human-equivalent dose to Sprague Dawley rats: effects on the microbiome

Qing Mao,1,2, Fabiana Manservisi,2, Simon Panzacchi,1, Daniele Mandrioli,2, Iara Mengheri,3, Andrea Vomol,1, Luciano Bui,1, Laura Falcioni,1, Corina Lesueur,3, Jia Chen,2, Fiorella Belpoggi,1 and Jianzhong Hu,1
STAGE I: publications

Dr Michael Antoniou and his staff; joint publications with the Ramazzini Institute

Use of Shotgun Metagenomics and Metabolomics to Evaluate the Impact of Glyphosate or Roundup MON 52276 on the Gut Microbiota and Serum Metabolome of Sprague-Dawley Rats

Robin Mesnage,1 Maxime Teixeira,2 Daniele Mandrioli,3 Laura Falciomi,1 Quentin Raymond Duceron,4 Romy Danielle Zwittink,5 Francesca Mazzacurva,5 Anna Caldwell,2 John Halket,6 Caroline Amiel,2 Jean-Michel Panoff,2 Fiorella Belpoggi,1 and Michael Nicolas Antoniou1

1Gene Expression and Therapy Group, Department of Medical and Molecular Genetics, King's College London, Faculty of Life Sciences & Medicine, Guy's Hospital, London, UK
2Unité de Recherche Aliments Bioproduits Toxicologie Environnement, University of Caen Normandy, Caen, France
3Ramazzini Institute, Bologna, Italy
4Centre for Microbiome Analysis and Translomics, Leiden University Medical Center, Leiden, Netherlands
5Mass Spectrometry Facility, King's College London, London, UK

Environ Health Perspect. 129: 17005, 2021


In-depth comparative toxicogenomics of glyphosate and Roundup herbicides: histopathology, transcriptome and epigenome signatures, and DNA damage

Robin Mesnage1, Mariam Ibragim1, Daniele Mandrioli2, Laura Falciomi3, Fiorella Belpoggi2, Inger Brundin1, Emma Bourne4, Emanuel Savage5, Charles A Mein6, Michael N Antoniou7

1 Gene Expression and Therapy Group, King's College London, Faculty of Life Sciences & Medicine, Department of Medical and Molecular Genetics, Guy's Hospital, London, SE1 9RT, UK
2 Cesare Maloni Cancer Research Center, Ramazzini Institute (RI), Via Saliceto, 3, 40010 Bentivoglio, Bologna, Italy
3 Toxyx, Robert Bolyeweg 4, 2333 OG, Leiden, The Netherlands
4 Genome Centre, Barts and the London School of Medicine and Dentistry, Bizard Institute, London E1 2AT, United Kingdom
STAGE I: publications
Dr. Jia Chen and her staff

Environmental Pollution 280 (2021) 117002

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

Maternal urinary levels of glyphosate during pregnancy and anogenital distance in newborns in a US multicenter pregnancy cohort

Corina Lesseur a, Patrick Pirrotte b, Khubatben V. Pathak b, Fabiana Manservisi c, d, Daniele Mandrioli c, Fiorella Belpoggi c, Simona Panzacchi c, Qian Li a, Emily S. Barrett e, Ruby H.N. Nguyen f, Sheela Sathyanarayana g, Shanna H. Swan a, Jia Chen a, *

a Department of Environmental Medicine and Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA
b Collaborative Center for Translational Mass Spectrometry, Translational Genomics Research Institute, Phoenix, AZ, USA
c Cesare Maltoni Cancer Research Center (CMCRC), Ramazzini Institute (RI), Via Saliceto, 3, 40010, Bentivoglio, Bologna, Italy
d Department of Veterinary Medical Sciences, University of Bologna, Italy
e Department of Biostatistics & Epidemiology, Rutgers School of Public Health, Piscataway, NJ, USA
f Department of Epidemiology & Community Health, University of Minnesota, Minneapolis, MN, USA
g Department of Pediatrics, University of Washington and Seattle Children’s Research Institute, Seattle, WA, USA

* Corresponding author.
STAGE II

INTEGRATED EXPERIMENTAL STUDY ON SUB-CHRONIC TOXICITY, CARCINOGENICITY, REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

AIMS:

➢ To go deeper into studying the most important parameters emerged from the pilot study;
➢ assess multiple toxicological parameters in a single protocol
➢ test human-equivalent doses;
➢ explore windows of biological susceptibility, in particular for endocrine disruptive end-points
**STAGE II: experimental plan**

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<th>GROUP</th>
<th>TREATMENT</th>
<th>DOSES</th>
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<tr>
<td>I</td>
<td>Drinking water (DW)</td>
<td>-</td>
</tr>
<tr>
<td>II-IV</td>
<td>DW + Glyphosate</td>
<td>0 - 0.5 (ADI EU) – 5 – 50 (NOAEL EU) mg/Kg bw/day</td>
</tr>
<tr>
<td>V-VII</td>
<td>DW + Roundup Bioflow</td>
<td>0 -0.5 (ADI EU) – 5 – 50 (NOAEL EU) mg/Kg bw/day Glyphosate equivalent</td>
</tr>
</tbody>
</table>

- **Route of Administration:** *ad libitum* in drinking water
- **Test Substances:** Glyphosate (purity > 99.5%); Roundup Bioflow.
STAGE II: experimental design (OECD guidelines, GLP standard operating procedures)

Breeders (F0)

51F+51M /control group
29F+29M /treated group
TOT= 312 dams

GD 0
GD 6
Delivery
GD 23
Pup’s weaning
PND 28

Offspring (F1)

Carcinogenicity
Sub-chronic toxicity

Offspring (F1)

WOS prenatal
WOS adult
WOS pubertal

ARM A

ARM B

Treatment
No treatment
Start of treatment
Sacrifice

PND 21
PND 120
PND 28
PND 63
PND 180
PND 84

Sub-chronic toxicity
Carcinogenicity

DR. FIORELLA BELPOGGI - HEALTH IMPACT OF GLYPHOSATE AND GBHS 2021
Global Glyphosate study: why we need to publish the data before the end of 2021?

- No further robust data with GLP methods were produced since last approval in 2017.
- Glyphosate could be renewed as indicated by the Assessment Group on Glyphosate conclusions.
- We must publish our results before the end of 2021.
- Data from the Ramazzini Institute ARM B study on both Glyphosate and GBHs include:
  - multi-generational effects
  - neurotoxic effects
  - endocrine disrupting effects
  - prenatal developmental toxicity effects
  - Effects on the microbiome
Global Glyphosate study

What we need in term of costs (human and material resources) in order to publish the data on the endocrine disruptive effects and other important toxicological end points?

The whole amount for concluding and publishing the study is about

1 million of Euros
Global Glyphosate study: why we need to publish the data before the end of 2021?

The Global Glyphosate Study will supply valuable data of unprecedented power to enable regulators, governments and the general public of every Country to answer the questions:

- could glyphosate be re-authorized in 2022?
- Is it really safe when we consider end-points other than cancer?
Global Glyphosate study: conclusions

Whatever the outcome of the Ramazzini Institute study, the findings will provide regulatory agencies and policy-makers with **solid independent results obtained by a shared research project** on which they can confidently base their risk assessments and their evaluations, including the upcoming **decision for the reauthorization for glyphosate use in Europe in 2022**.
Thank you!