

1 THE NEED FOR INDEPENDENT RESEARCH ON THE HEALTH EFFECTS OF
2 GLYPHOSATE-BASED HERBICIDES

3 **Authors:** PHILIP J. LANDRIGAN (1) and FIORELLA BELPOGGI (2)

4

5 **Institutions:**

6 1. Dean for Global Health

7 Professor of Environmental Medicine and Pediatrics Arnhold Institute for Global

8 Health Icahn School of Medicine at Mount Sinai

9 One Gustave L. Levy Place, Box 1057

10 New York, NY 10029

11 USA

12 e-mail: philip.landrigan@mssm.edu

13

14 2. Director Research Department Cesare Maltoni Cancer Research Center

15 Ramazzini Institute

16 Via Saliceto, 3

17 40010 Bentivoglio (Bologna)

18 Italy

19 e-mail: belpoggif@ramazzini.it

20

21 **Address correspondence to:**

22 Dr. Fiorella Belpoggi, Director, Research Area, Ramazzini Institute

23 Via Saliceto, 3, 40010 Bentivoglio, Bologna, Italy

24 Tel. +39 051 6640460 - Fax +39 051 6640223

25 e-mail: belpoggif@ramazzini.it - www.ramazzini.org

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35 **ABSTRACT**

36 **Background.** Glyphosate, formulated as Roundup, is the world's most widely used
37 herbicide. Glyphosate is used extensively on genetically modified (GM) food crops
38 designed to tolerate the herbicide, and global use is increasing rapidly. Two recent
39 reviews of glyphosate's health hazards report conflicting results. An independent
40 review by the International Agency for Research on Cancer (IARC) found that
41 glyphosate is a "probable human carcinogen". A review by the European Food Safety
42 Agency (EFSA) found no evidence of carcinogenic hazard. These differing findings
43 have produced regulatory uncertainty.

44 **Regulatory actions.** Reflecting this regulatory uncertainty, the European Commission
45 on November 27 2017, extended authorization for glyphosate for another 5 years,
46 while the European Parliament opposed this decision and issued a call that pesticide
47 approvals be based on peer-reviewed studies by independent scientists rather than on
48 the current system that relies on proprietary industry studies.

49 **Ramazzini Institute response.** The Ramazzini Institute has initiated a pilot study of
50 glyphosate's health hazards that will be followed by an integrated experimental
51 research project. This evaluation will be independent of industry support and entirely
52 sponsored by worldwide crowdfunding. The aim of the Ramazzini Institute project is
53 to explore comprehensively the effects of exposures to glyphosate-based herbicides at
54 current real-world levels on several toxicological endpoints, including
55 carcinogenicity, long-term toxicity, neurotoxicity, endocrine disrupting effects,
56 prenatal developmental toxicity, the microbiome and multi-generational effects.

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58 **KEY WORDS:**

59 Glyphosate, Roundup, Glyphosate Based Herbicides, GBH, carcinogenicity,

60 crowdfunding

61 **BACKGROUND**

62 **History and use**

63 Glyphosate is the world's most widely used herbicide [1]. Glyphosate Based
64 Herbicides (GBHs) were first authorised for agricultural use in the US in 1974 by the
65 Environmental Protection Agency. In Europe, glyphosate was authorised by the
66 European Commission in 2002. In the US, glyphosate use has increased by more than
67 250-fold in the past 4 decades — from 0.4 million kg in 1974 to 113 million kg in
68 2014. Global glyphosate use has also increased from 3,200 tons/year in 1974 to
69 825,000 tons/year in 2014, and glyphosate is now used in over 140 countries [1]. In
70 future years, glyphosate use is projected to continue to increase and by 2020 is
71 estimated to reach one million tons per year.

72

73 Glyphosate, formulated as Roundup, is used on corn and soybeans that have been
74 genetically engineered to be resistant to glyphosate. These “Roundup- Ready” crops
75 were first introduced in the mid-1990s and now account for more than 90% of the
76 corn and soybeans planted in the United States [2]. Today glyphosate is contained in
77 over 750 commercial herbicide products designed for intensive crop-growing, market
78 gardening and gardens in general. This massive use of glyphosate in the most varied
79 sectors of agriculture has led to widespread environmental dissemination. Trace
80 levels of glyphosate can now be found widely in soil, foodstuffs, air and water as well
81 as human urine [3; 4; 5].

82

83 **Regulatory actions**

84 On November 27 2017, the European Commission extended the authorization for

85 glyphosate for another 5 years. The European Parliament, however, opposed this
86 decision and issued a call for pesticide approvals to be based on published peer-
87 reviewed studies by independent scientists instead of the current system, which is
88 largely based on unpublished proprietary studies. Regulatory uncertainty and debate
89 are extensive [6; 7]. Key milestones in the risk assessment process that has led to the
90 current regulatory debate about the safety of glyphosate may be summarized as
91 follows:

- 92 - March 2015: the World Health Organization's International Agency for Research
93 on Cancer (IARC) conducted an extensive review of the published peer-
94 reviewed epidemiologic, toxicologic and genetic literature on glyphosate,
95 independent of influence by the pesticide manufacturing industry, and
96 concluded that glyphosate is "probably carcinogenic to man" (Category 2A
97 [8]).
- 98 - November 2015: the EFSA deemed glyphosate "unlikely to pose a cancer risk for
99 man". That conclusion was based on a glyphosate renewal assessment report
100 (RAR) presented in January 2014 by the Federal German Institute for Risk
101 Assessment (Bundesinstitut für Risikobewertung, BfR) [9]. The EFSA and
102 RAR review groups included scientists that did not disclose their names and
103 financial interests and also relied on unpublished, non-peer-reviewed reports
104 generated by industry [10].
- 105 - March 2017: following a heated argument over the safety of glyphosate, and
106 numerous deferments of the European ballot, the European Union (EU)
107 appointed the European Chemicals Agency (ECHA) to look into the issue of
108 glyphosate toxicity. The ECHA's Risk Assessment Committee analysed an
109 enormous amount of scientific data and concluded that "the scientific evidence

110 so far available does not satisfy the criteria for classifying glyphosate as
111 carcinogenic, mutagenic or toxic for reproduction.” [11]. According to the
112 ECHA, glyphosate may cause grave damage to the eyes and be toxic to
113 aquatic organisms with long-term effects.

114 - November 2017: The EU voted to extend glyphosate authorization for an
115 abbreviated period of five years; the Acceptable Daily Intake (ADI) was
116 increased from 0.3 to 0.5 mg/kg bw/day [12]. The deliberation frustrated
117 parties on all sides. Agrochemical companies criticized the review process as
118 driven more by politics than science after it became clear that the weed killer’s
119 use would not be re-authorized for the 15 years typical for such chemicals.
120 Environmental advocates said that the agrochemical industry had tainted
121 scientific reviews in Europe by interfering in them.

122

123 **MAIN TEXT**

124 **The Ramazzini Institute Research Project**

125 **Pilot study.** A ‘pilot’ experimental study of the toxicity of GBHs was carried out at
126 the Ramazzini Institute in 2016 (Ministerial Authorization N° 710/2015-PR, issued on
127 17/7/2015) where both glyphosate alone and its formulation Roundup have been
128 tested. In fact glyphosate alone and its formulations could have different effects. For
129 example, the adjuvants present in the formulation might potentiate the toxic effects of
130 glyphosate [13]. To set this study in motion, the Institute built up a network of
131 authoritative partners including the University of Bologna (Faculties of Agriculture,
132 Veterinary Science and Biostatistics), the Genoa Istituto Tumori, the Istituto
133 Superiore di Sanità (ISS), the Icahn School of Medicine at Mount Sinai, New York,
134 and the George Washington University, Washington, DC.

135 The study was designed to assess the techniques and methods for detecting
136 glyphosate and its metabolites in different matrices [14] and to develop methods for
137 assessing organ toxicity, genotoxicity, molecular toxicity, reproductive/developmental
138 toxicity, endocrine disruption and microbiome alteration [15]. In this pilot study,
139 glyphosate and Roundup were both tested at a dose considered to be “safe”-
140 corresponding to the ADI of glyphosate currently allowed in the US, defined as the
141 chronic Reference Dose (cRfD) determined by the US EPA [16], namely 1.75 mg/kg
142 bw/day .

143 Initial results from this pilot study were presented during the Annual Ramazzini
144 Days (26-29 October 2017). These preliminary findings suggest that glyphosate and
145 Roundup – even at doses deemed safe, i.e., at doses equivalent to the current ADI and
146 with relatively short exposure time, from pregnancy until 13 weeks after weaning in
147 human-equivalent terms from pregnancy to approximately 18 years of age – might be
148 able to alter certain important biological parameters related to sexual development,
149 genotoxicity and alteration of the intestinal bacterial flora. Other important parameters
150 are under investigation that pertain to effects on target organs such as mammary
151 gland, kidney and liver, the hormonal status in the blood, and chromosome alterations
152 in sperm. All the results will be submitted for publication in this journal [14, 15].

153 A pilot study is, by definition, of short duration and involves fewer animals than a
154 comprehensive experiment. Therefore, it can provide only limited information and is
155 not designed to detect chronic effects and diseases of late onset such as cancer. Thus
156 the Ramazzini Institute pilot study is not able to resolve the current regulatory
157 uncertainty around glyphosate. However, the findings of the pilot study do highlight
158 potentially serious health effects that might manifest as long-term oncologic
159 pathology and could affect very large numbers of people, given the great and growing

160 global use of the GBHs. Clearly these findings deserve further follow-up.

161

162 **Future research.** To follow up on the Ramazzini Institute pilot study, a more
163 comprehensive investigation is necessary and it must examine the effects of a range of
164 different environmentally relevant doses of glyphosate alone and GBHs. Therefore,
165 in 2015, the Ramazzini Institute designed a comprehensive, integrated experimental
166 approach to a long-term project following an already published protocol through
167 which numerous parameters bearing on human health might be simultaneously
168 monitored, thereby sparing animals [17]. In fact, proprietary studies conducted on
169 behalf of the manufacturers often represent a limited investigation of the various
170 toxicological effects now studied by academic and government scientists. The
171 integrated study proposed by the Ramazzini Institute is based on a stepwise process
172 that includes the priority end points of the Economic Co-operation and Development
173 and the National Toxicology Program guidelines on carcinogenicity and chronic
174 toxicity in addition to developmental and reproductive toxicity, exploring multiple
175 windows of susceptibility of specific interest for risk assessments and public health
176 decision-making such as prenatal, lactational and neonatal exposures. Such an
177 integrated toxicological study is needed, together with further epidemiological
178 evidence, for an independent and comprehensive assessment of the possible risks
179 resulting from the ubiquitous exposure to GBHs.

180 As in the pilot study, both glyphosate and the commercial formulation Roundup
181 will be tested in the integrated study. A human-equivalent model will be used to
182 determine the dose-levels to be administered and the exposure period, which will
183 include mating and gestation. Detailed assessments will examine the toxic effects in
184 terms of the intestinal microbiome, gene expression and parameters relating to

185 fertility, defects in development, effects on the nervous system and any treatment-
186 related differences in the incidence of various tumours. This will be the most
187 comprehensive study on GBHs to date and it will last 3-4 years.

188 To preserve independence from the pesticide-manufacturing industry and from its
189 competitor (i.e. organic food industry), this integrated study will be supported through
190 a global crowd-funding campaign that will be open to the world's citizens, non-
191 governmental organizations (NGOs) and national/international institutions. Details of
192 this campaign are available at: www.glyphosatestudy.org.

193 To provide ongoing review of the integrated study, we intend to set up an external
194 international scientific committee that will evaluate the study plan, the conduct of the
195 study and review study results as they become available. We also plan to gather
196 together all stakeholders interested in using our results to ascertain the degree of
197 hazard involved in GBH exposure. These will include: IARC, EFSA, ISS, the
198 National Institute of Environmental Health Sciences, and others, including NGOs
199 representatives. Study results will be available by the time of the next EU decision on
200 the reauthorization of glyphosate in 2022.

201

202 **CONCLUSIONS**

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

208

209 **ABBREVIATIONS:**

210 GM: genetically modified; IARC: International Agency for Research on Cancer;
211 EFSA: European Food Safety Agency; GBH: Glyphosate Based Herbicides; RAR:
212 renewal assessment report; EU: European Union; ECHA: European Chemicals
213 Agency; ISS: Istituto Superiore di Sanità;

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215 **DECLARATIONS:**

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