Exposure to Glyphosate-Based Herbicides and Risk for Non-Hodgkin Lymphoma: A Meta-Analysis and Supporting Evidence

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Abstract

Glyphosate is the most widely used broad-spectrum systemic herbicide in the world.

Recent evaluations of the carcinogenic potential of glyphosate-based herbicides (GBHs)

by various regional, national, and international agencies have engendered controversy.

We investigated whether there was an association between high cumulative exposures

to GBHs and increased risk of non-Hodgkin lymphoma (NHL) in humans. We conducted

a new meta-analysis that included the most recent update of the *Agricultural Health*

Study (AHS) cohort published in 2018 along with five case-control studies. Using the

highest exposure groups when available in each study, we report the overall meta-

relative risk (meta-RR) of NHL in GBH-exposed individuals was increased by 41%

(meta-RR = 1.41, 95% CI, confidence interval: 1.13–1.75). For comparison, we also

performed a secondary meta-analysis using high-exposure groups with the earlier AHS

(2005), and we determined a meta-RR for NHL of 1.45 (95% CI: 1.11–1.91), which was

higher than the meta-RRs reported previously. Multiple sensitivity tests conducted to

assess the validity of our findings did not reveal meaningful differences from our primary

estimated meta-RR. To contextualize our findings of an increased NHL risk in

individuals with high GBH exposure, we reviewed available animal and mechanistic

studies, which provided supporting evidence for the carcinogenic potential of GBH. We

documented further support from studies of malignant lymphoma incidence in mice

treated with pure glyphosate, as well as potential links between GBH exposure and

immunosuppression, endocrine disruption, and genetic alterations that are commonly

associated with NHL. Overall, in accordance with evidence from experimental animal

and mechanistic studies, our current meta-analysis of human epidemiological studies

suggests a compelling link between exposures to GBHs and increased risk for NHL.

(273/300 words)

Abbreviations: AHS, Agricultural Health Study; c-NHEJ, canonical non-homologous end joining pathway; CI, confidence interval; EDC, endocrine disrupting chemical; EFSA, European Food Safety Authority; EPA, Environmental Protection Agency; ETS, environmental tobacco smoke; GBHs, glyphosate-based herbicides; IARC, International Agency for Research on Cancer; IFN-γ, interferon gamma; IL-2, Interleukin-2; JMPR, Joint Meeting on Pesticide Residues by the Food and Agriculture Organization of the United Nations and World Health Organization; meta-RR, meta-analysis relative risk; mg/kg/day, milligrams per kilogram per day; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio; ppm, parts per million; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RR, relative risk.

Table of Contents

115

116   **1. Background**

117   *1.1 Global Usage of Glyphosate-Based Herbicides*

118   Glyphosate is a highly effective broad spectrum herbicide that is typically applied

119   in mixtures known as glyphosate-based herbicides (GBHs) and commonly sold under

120   the trade names of *Roundup®* and *Ranger Pro®*. Use of GBHs has increased

121   dramatically worldwide in recent decades. In the United States alone, usage increased

122   nearly sixteen-fold between 1992 and 2009 [1]. Most of this increase occurred after the

123   introduction of genetically modified glyphosate-resistant "Roundup-ready" crops in 1996

124   [1]. In addition, there have been significant changes in usage. In particular, the practice

125   of applying GBHs to crops shortly before harvest, so-called "green burndown," began in

126   the early 2000s to speed up their desiccation; as a consequence, crops are likely to

127   have higher GBH residues [2]. By the mid-2000s, green burndown became widespread,

128   and regulatory agencies responded by increasing the permissible residue levels for

129   GBHs [3, 4].

130   *1.2 Ubiquitous Exposure in Humans*

131   Glyphosate and its metabolites persist in food [5-7], water [8], and dust [9],

132   potentially indicating that everyone may be exposed ubiquitously. Non-occupational

133   exposures occur primarily through consumption of contaminated food, but may also

134   occur through contact with contaminated soil [9], dust [9] and by drinking or bathing in

135   contaminated water [8]. In plants, glyphosate may be absorbed and transported to parts

136   used for food; thus, it has been detected in fish [5], berries [6], vegetables, baby formula

137   [7], and grains [10], and its use as a crop desiccant significantly increases residues.

138   GBH residues in food persist long after initial treatment and are not lost during baking.

139   Limited data exist on internal glyphosate levels among GBH-exposed individuals

140   [11]. Average urinary glyphosate levels among occupationally exposed subjects range

141   from 0.26-73.5 µg/L, whereas levels in environmentally exposed subjects have been

142   reported between 0.13-7.6 µg/L [11]. Two studies of secular trends have reported

143   increasing proportions of individuals with glyphosate in their urine over time [12, 13].

144   Given that more than six billion kilograms of GBHs have been applied in the world in the

145   last decade [2], glyphosate may be considered ubiquitous in the environment [14].

146   ***1.3 Controversy Surrounding the Carcinogenic Potential of GBHs***

147   Exposure to GBHs is reportedly associated with several types of cancer, among

148   which the most-well studied in humans is non-Hodgkin lymphoma (NHL). Some

149   epidemiological studies have reported an increased risk of NHL in GBH-exposed

150   individuals [15-17]; however, other studies have not confirmed this association [18, 19].

151   GBHs have recently undergone a number of regional, national, and international

152   evaluations for carcinogenicity in humans [20-23], resulting in considerable controversy

153   regarding glyphosate and GBHs' overall carcinogenic potential. Hence, addressing the

154   question of whether or not GBHs are associated with NHL has become even more

155   critical. Here, we evaluated the all the published human studies on the carcinogenicity

156   of GBHs and present the first meta-analysis to include the most recently updated

157   Agricultural Health Study (AHS) cohort [24]. We also discuss the lymphoma-related

158   results from studies of glyphosate-exposed animals as well as mechanistic

159 considerations to provide supporting evidence for our analysis of the studies of human

160 exposures to GBHs.

2. Current Meta-Analysis of GBHs and NHL

2.1 Meta-Analysis Objective

163   Epidemiological studies may vary in several ways, such as by study design,

164 sample size, and exposure assessment methods. Results among individual studies vary

165 and may appear to conflict, which poses challenges in drawing an overall conclusion.

166 Meta-analysis is a quantitative statistical tool that is frequently applied to consolidate the

167 results from similar but separate individual studies so that an overall conclusion about

168 the effects of exposure can be drawn. Here, we conducted a meta-analysis using

169 published human studies to better understand whether the epidemiological evidence

170 supports an association between exposures to GBHs and increased NHL risk. Although

171 three previously published meta-analyses have examined the same association and

172 reported positive meta-risks for GBH-associated NHL [22, 25, 26], our analysis differs

173 from earlier ones by focusing on an *a priori* hypothesis targeting biologically relevant

174 exposure magnitude and by including the newly updated AHS study [24].

2.2 A Priori Hypothesis

176   Our *a priori* hypothesis is that the highest biologically relevant exposure to GBHs,

177 *i.e.*, higher levels, longer durations and/or with sufficient lag and latency, will lead to

178 increased risk of NHL in humans. The hypothesis is based on the understanding that

179 higher and longer cumulative exposures during a biologically relevant time window are

180 likely to yield *higher* risk estimates, given the nature of cancer development [27]. Hence,

181 when cumulative exposure is higher, either due to higher level or longer duration

182 exposures, an elevated association with the cancer of interest is more likely to be

183 revealed if a true association exists. This *a priori* approach has been employed to

184 estimate meta-risks for benzene [28] and formaldehyde [29, 30], but not in any of the

185 previous meta-analyses exploring the GBH-NHL association [22, 25, 26].

186   Risk estimates, including relative risks (RRs) and odd ratios (ORs), in high

187 exposure groups are less likely to be dominated by confounding or other biases

188 compared to RRs or ORs from groups experiencing average or low exposure [31].

189 Furthermore, including people with very low exposure in the exposed group can dilute

190 risk estimates. Studying the most highly exposed group is also useful to ensure an

191 adequate exposure contrast, given the potential that most people have been exposed

192 either directly or indirectly to GBHs. Because our main goal is to determine whether

193 there is an exposure effect and not to conduct a precise dose-response assessment or

194 to evaluate risks in people with low exposures, we assert that this *a priori* hypothesis is

195 appropriate for testing whether or not a GBH-NHL association exists.

196 ***2.3 Agricultural Health Study (AHS) Update***

197   A recently published update [24] from the large AHS cohort of American pesticide

198 applicators (N > 50,000) has been included for the first time in our primary meta-

199 analysis. Although the original AHS report [19] was used in previous meta-analyses [22,

200 25, 26], the 2018 AHS update [24] contributes 11-12 additional years of follow-up with

201 over five times as many NHL cases (N = 575 compared to N = 92 in the original study

202 [19]), and >80% of the total cohort was estimated to be exposed to GBHs. As the

203 largest and most recently published study, it adds substantial weight to the new meta-

analysis [24]. We also performed a secondary comparison analysis using our *a priori*

hypothesis with the original AHS report [19] for the purpose of comparing results with

our primary meta-analysis (using the 2018 AHS update) and with meta-analyses

published previously.

2.4 Identifying Relevant Human Studies

The literature search was conducted according to the guidelines of the *Preferred*

Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [32]. The

screening process and results are shown in Figure 1. We conducted a systematic

electronic literature review using PubMed in November 2017, and we updated it in

March 2018 and again in August 2018. We used the following keywords: (glyphosat*

OR pesticide [MeSH] or herbicides [MeSH]) AND (lymphoma, non-Hodgkin [MeSH] OR

lymphoma [tiab] OR non–Hodgkin [tiab] OR non–hodgkins [tiab] OR lymphoma[tiab] OR

lymphomas[tiab] OR NHL OR cancer OR cancers) AND ("occupational

exposure"[MeSH] OR occupational exposure[tiab] OR occupational exposures[tiab] OR

farmers [MeSH] OR farmer OR applicators OR applicator OR agricultural workers OR

agricultural worker or workers or worker).

Searches included all cohort, case-control, and cross-sectional studies. No

language restrictions were applied, although non-English language articles needed to

be obtained in full and translated completely in order to be eligible for inclusion. From

the PubMed search, we identified 857 studies. Additionally, we identified 52 studies

from the IARC [22] evaluation of the carcinogenicity of glyphosate, the U.S. EPA [20]

review of glyphosate, and the WHO JMPR [21] report on glyphosate, for a total of 909

studies.

227   After 43 duplicates were excluded, 866 studies were initially screened by title and

228   abstract, of which 850 were excluded because they were reports, correspondence,

229   reviews, irrelevant studies (animal, mechanistic, para-occupational), or did not include

230   the exposure or outcome of interest (Figure 1). When the final 16 qualified

231   epidemiological studies of GBHs and NHL were identified, 10 studies were further

232   excluded because (1) they did not report RRs, ORs, or the data needed to calculate

233   either [33-35], (2) the cohort overlapped with another study [19, 36-40], or (3) they did

234   not specify whether the lymphomas were specifically NHL [41]. For studies including

235   overlapping cohorts, we used results from the most complete and updated analysis with

236   the greatest number of participants. Although overlapping, we kept the earlier AHS

237   (2005) [19] for comparison with our primary meta-analysis (using the updated AHS 2018

238   publication) and with previous meta-analyses. The impact of selecting these studies

239   was evaluated in sensitivity analyses (Section 3.5).

240   **2.5 Review and Assessment of Selected Human Studies**

241   *2.5.1 Data Collection and Extraction*

242   In total, six studies (one cohort [24] and five case-control control studies [15-18,

243   42]) with nearly 65,000 participants were eligible for inclusion in the meta-analysis. Two

244   studies were conducted in the United States, one study was from Canada, two studies

245   were from Sweden, and one study was from France. All six studies reported NHL risks

246   (RRs or ORs) above or close to 1.0, three of which were statistically significant in the

247   original analyses (Table 1). From each study, we abstracted information on study

248   design, location, dates, sample size, participation rates, age, sex, case/control source,

249   diagnosis, histologic verification, exposure assessment, results, and statistical

250   adjustments. Table 1 summarizes key aspects of the design and exposure assessment,

251   the results, strengths, and weaknesses of all the studies evaluated in this meta-

252   analysis, including both versions of the AHS report (n = 6+1). As described above, the

253   early AHS data [19] were also evaluated in Table 1 and in a comparison meta-analysis

254   described later.

255   *2.5.2 Study Quality Evaluation*

256   The methodological quality of the cohort (Table 2) and case-control studies

257   (Table 3) included in the meta-analyses was assessed independently by two co-authors

258   using the Newcastle Ottawa Scale (NOS) [43]. Studies were evaluated based on

259   selection, comparability, and outcome or exposure (in nine categories).

260   Cohort studies were evaluated based on (1) representativeness of the cohort, (2)

261   selection of non-exposed, (3) ascertainment of exposure, (4) demonstration that

262   outcome of interest was not present at the start of study, (5) comparability of cohort on

263   the basis of controlling for other pesticide use and (6) age, (7) assessment of NHL

264   outcome, and (8) sufficiency of follow-up length, and (9) response rate.

265   Case-control studies were evaluated on (1) the validation of cases, (2)

266   representativeness of cases, (3) selection of controls, (4) absence of disease in the

267   controls, (5) whether the study controlled for other pesticide use and (6) age, (7)

268   exposure assessment, (8) concordance of method among cases and controls, and (9)

269   similarity of response rate among both groups. Each study was awarded a maximum of

270   one point for every item that was satisfied, with a total of 9 available points.

271   According to our quality assessment (Tables 2-3), the highest quality study in

272   either design category was the AHS 2018 cohort [24]. The highest quality case-control

273   study was Eriksson *et al.* [16], while the lowest quality studies were McDuffie *et al.* [42]

274   and Orsi *et al.* [18].

275   ***2.6 Selection of the Most Highly Exposed Category***

276   Based on our *a priori* hypothesis, when multiple RRs or ORs were given in the

277   original studies, we selected estimates in the following order: (1) highest cumulative

278   exposure and longest lag (the time period preceding NHL onset, which is excluded from

279   the exposure estimate) or latency (time between first lifetime exposure and NHL

280   diagnosis); (2) highest cumulative exposure; (3) longest exposure duration and longest

281   lag or latency; (4) longest exposure duration; (5) longest lag or latency; and (6) ever-

282   exposure. The definition of cumulative exposure includes duration and intensity. As we

283   discuss in more detail in Section 5.2, in both AHS reports [19, 24] cumulative exposure

284   was calculated as an intensity-weighted exposure (lifetime exposure days multiplied by

285   an intensity score) [44, 45].

286   We prioritized highest cumulative exposure based on evidence of glyphosate's

287   persistence in the environment [46-48] and because chronic disease, including cancer,

288   is usually the result of cumulative exposures [49]. We selected the longest lag or latency

289   because decades may be needed for the health effects of many environmental toxicants

290   to manifest as detectable cancers. If no high exposure data were available, we used the

291   ever-exposure estimate. Given the relatively few human epidemiological studies

292   published to date on the topic, we made this decision because we did not want to

293   exclude any potentially relevant data, even though the inclusion of minimally exposed

294   individuals in the "exposed" category could attenuate any potential association of

295   interest.

296   Although there are different perspectives on the best way to account for other

297   pesticide exposures, we selected RR estimates that adjusted for other pesticide use

298   over their unadjusted counterparts to mitigate potentially substantial confounding by

299   other pesticide use. Five of the seven studies adjusted for a combination of different

300   pesticides [15-17, 19, 24], indicating they accounted for confounding by other

301   pesticides. However, if these multiple pesticides acted synergistically or on different

302   points along a pathway, this approach to adjustment may no longer be the appropriate,

303   and alternatives such as interaction analysis should be considered. Reanalysis of the

304   raw data, which is beyond the scope of this paper, would be helpful to address this

305   possibility.

306   We evaluated the impact of our *a priori* exposure selection criteria in sensitivity

307   analyses. We also conducted a separate meta-analysis of all ever-exposed individuals

308   to assess the magnitude of potential bias caused by adding subjects with low exposures

309   (ever-RR from De Roos *et al.* [19] was used; the ever-RR estimate from Andreotti *et al.*

310   [24] was not available). In Table 4 we summarize the risk estimates selected from each

311   original study and the study weights used in the meta-analyses.

312   ***2.7 Statistical Methods***

313   We calculated the meta-analysis summary relative risk (meta-RR) and

314   confidence intervals using both the fixed-effects inverse-variance method [31] and the

315   random-effects method [50]. In the fixed-effects model, the weights assigned to each

13

316 study are directly proportional to study precision, whereas in the random-effects model,

317 weights are based on a complex mix of study precision, relative risk (RR), and meta-

318 analysis size. One benefit of the random-effects model is the ability to incorporate

319 between-study variance into the summary-variance estimate and confidence intervals,

320 which may help prevent artificially narrow confidence intervals resulting from use of the

321 fixed effects model in the presence of between-study heterogeneity [51]. However, a

322 feature of the random-effects model is that study weighting is not directly proportional to

323 study precision, and greater relative weight is given to smaller studies, which may result

324 in summary estimates that are less conservative than the fixed-effects model [51]. For

325 these reasons, our primary results focus on the fixed-effects model, although the

326 random-effects model estimates are also reported. We also estimated between-study

327 heterogeneity, defined as the X^2-test statistic for heterogeneity being greater than its

328 degrees of freedom (number of studies minus one), using the summary-variance

329 method [51].

330   We evaluated publication bias through funnel plots, Egger's test, and Begg's test

331 [52, 53]. All statistical analyses were conducted with Stata IC 15.1 [54] and Microsoft

332 Excel 2013 [55].

333 **3. Meta-Analysis Findings**

334 *3.1 Increased Meta-Relative Risk of NHL*

335   Table 5 includes the results from our two meta-analyses, which included the

336 primary analysis using the most recently updated AHS cohort [24] and the secondary

337 comparison analysis using the original report [19]. Using the updated AHS results [24],

14

338   we observed a meta-RR of **1.41** (95% CI: 1.13-1.75), which indicates a statistically

339   significant increased risk (41%) of NHL following high cumulative GBH exposure. With

340   the original AHS 2005 cohort results, we observed a meta-RR of **1.45** (95% CI: 1.11-

341   1.91) for NHL. The results did not change appreciably when comparing the fixed effects

342   model to the random-effects model.

343   Forest plots (Figure 2A-B) and Funnel plots (Figure 2C-D) from these two major

344   meta-analyses are reported in Figure 2. We observed little evidence of publication bias

345   in the Funnel plots (Figure 2C-D), Eggers (p = 0.185), and Beggs tests (p = 0.851).

346   ***3.2 Sensitivity Analyses***

347   We conducted several sensitivity analyses to evaluate the impact of excluding or

348   including different studies as well as using different RRs/ORs from original studies

349   (Tables 5 and 6). In general, results were similar across our sensitivity analyses,

350   demonstrating the robustness of our findings.

351   *3.2.1 Alternative Exposure Criteria*

352   As a sensitivity analysis, we also conducted a meta-analysis using the longest

353   exposure duration results to compare with our primary analysis using the highest

354   cumulative exposure results. When RRs corresponding to exposures with the longest

355   duration were selected from the AHS 2018, the meta-RR remained the same at **1.41**

356   (95% CI: 1.13-1.74). When the AHS 2005 report was included, the meta-RRs increased

357   to **1.56** (95% CI: 1.17-2.06) (Table 5).

358   When evaluating studies with only the highest levels of exposure [16, 24, 42], the

359   meta-RR was **1.36** (95% CI: 1.06-1.75, Table 6). In studies that combined all exposures

360   as ever exposed [15-19, 42], the meta-RR was **1.30** (95% CI: 1.03-2.64). Although the

361   higher exposure group was used in the main analysis, Eriksson *et al.* [16] also provided

362   results for greater than 10 years latency, which contributed to a meta-RR of **1.40** (95%

363   CI: 1.13-1.75). [Note: AHS 2018 did not provide ever-exposure, so AHS 2005 was used

364   to calculate this statistic and *ever* exposure above].

365   *3.2.2. Study Inclusion*

366   When we limited our analysis to case-control studies (Table 5), there was little

367   inter-study heterogeneity. We estimated a doubling of the NHL risk (meta-RR = **1.84**,

368   95% CI: 1.33-2.55) from 41% to 84% compared to the estimate that included the cohort

369   study.

370   To ensure that one individual study was not artificially inflating the meta-risk

371   estimate, we excluded the case-control studies one at a time and found that they all

372   nominally lowered the meta-RR, except for the exclusion of Orsi *et al.* [18], where the

373   meta-RR increased to **1.46** (1.16-1.83) (Table 6).

374   *3.2.2 NHL vs. Cell-type Specific Lymphomas*

375   Although our primary meta-analysis included six studies, there was a possibility

376   to include a seventh study [41]. We excluded this study from the primary analysis

377   because it included all B-cell lymphomas (4 cases), which account for approximately

378   85% of all NHL [56]; however, not all four cases were confirmed to be NHL. When we

379   added Cocco *et al.* [41] to the meta-analysis (n = 7, Table 6), the resulting RR remained

380   fairly similar at **1.43** (95% CI: 1.15-1.78).

381   Similar to our inclusion of the Cocco *et al.* [41] study, another cell-type specific

382   study evaluated all cases of hairy cell leukemia (HCL), a subtype of NHL [39]. It was

383   one of two studies [38, 39] included in the Hardell *et al.* [17] analysis, with the other

384   study examining NHL only [38]. Excluding HCL cases had no effect on the meta-RR

385   (**1.41,** 95 % CI: 1.13-1.77, Table 6). Similarly, using only hairy cell leukemia cases from

386   Hardell *et al.* [17] (reported in Nordstrom *et al.* [39]) did not impact the meta-RR (1.43,

387   95% CI: 1.14-1.78).

3.2.4 Study Location and Adjustment

389   Studies in North America [15, 24, 42] had a meta-RR of **1.38** (95% CI: 1.08-

390   1.76), whereas European studies [16-18] had a meta-RR of **1.53** (95% CI: 0.93-2.52).

391   On average, when studies were adjusted for other pesticide use [15-17, 19], the meta-

392   RR for ever-exposure was lower than unadjusted risk estimates from the same studies

393   (meta-RR$_{adjusted}$ = **1.46**, 95% CI: 1.05-2.02; meta-RR$_{unadjusted}$ = **1.69**, 95% CI: 1.29-2.23).

3.2.5 Logistic vs. Hierarchical Regressions

395   Consistent with the two previous meta-analyses by IARC [22] and Schinasi and

396   Leon [25] discussed in Section 4.1 below, we selected the RR estimated using the more

397   traditional logistic regression over the hierarchical regression estimate in the case-

398   control study by De Roos *et al.* [15] and found that there was little impact of this

399   selection (meta-RR = **1.36**, 95% CI: 1.09-1.70). When Cantor *et al.* [37] or Lee *et al.*

400   [36] were used instead of De Roos *et al.* [15], the meta-RR decreased to **1.29** (95% CI:

401   1.04-1.59) and **1.35** (95% CI: 1.11-1.65), respectively. Similarly, using Hohenadel *et al.*

402 [40] instead of McDuffie *et al.* [42] caused the meta-RR to decrease to **1.23** (95% CI:

403 0.99-1.53).

404 **4. Comparison with Previous Meta-Analyses**

405   Three meta-analyses of NHL in relation to GBH exposure have been published

406 [22, 25, 26], all of which report lower, albeit also positive, risk estimates. In contrast to

407 our work, these analyses did not focus on the highest exposed groups. Table 7

408 summarizes the major results from all GBH-NHL meta-analyses conducted to date,

409 including the current one.

410   Schinasi and Leon [25] first reported a meta-RR of **1.45** (95% CI: 1.08-1.95).

411 Although their selection criteria stated that they used the most adjusted effect estimate

412 for the dichotomously defined exposure with the greatest number of exposed cases,

413 they did not use adjusted effect estimates in the two Swedish studies [16, 17]. The

414 IARC Working Group subsequently corrected this discrepancy in an otherwise identical

415 meta-analysis [22], resulting in a meta-RR of **1.30** (95% CI: 1.03 -1.65). Although both

416 studies are listed in Table 7 for completeness, we consider IARC 2015 to be the most

417 accurate and updated version of this meta-analysis.

418   Most recently, Chang and Delzell [26] reported a meta-RR of **1.27** (95% CI: 1.01-

419 1.59) in their primary analysis (model one). For each included study, the authors

420 selected the most fully adjusted RR from the publication with the most recent and

421 complete study population with the largest number of exposed cases. (In their

422 publication, the meta-RR was rounded to one digit to the right of the decimal point.)

423   Whereas the three previous meta-analyses focused on general exposure (ever

424   versus never), our new meta-analysis differs primarily because of our *a priori* selection

425   of risk estimates from the most highly exposed groups when available (from three

426   studies [16, 19, 42]). In our secondary comparison meta-analysis with the same six

427   studies (including AHS 2005), we document an additional 0.15-0.18 (or 15-18%) higher

428   NHL RR than previous meta-RRs [22, 26] (not including Schinasi and Leon, because it

429   was corrected in IARC 2015). Similarly, in our primary analysis with AHS 2018, our

430   meta-RR estimate adds an additional 0.11-0.14 (11-14%) increase in NHL relative risk

431   to the previous meta-RRs [22, 26]. Overall, the meta-RR obtained using our *a priori*

432   hypothesis, while generally consistent with previous analyses, gave somewhat higher

433   estimates and suggested increased risk of NHL in individuals highly exposed to GBHs.

434   **5. Strengths and Limitations**

435   In this section, we evaluate the strengths and limitations of our meta-analyses, as

436   well as of the cohort study and the case-control studies utilized.

437   *5.1 Current Meta-Analyses*

438   The strengths of these meta-analyses are the inclusion of the updated AHS 2018

439   study and our novel *a priori* hypothesis. By using the highest exposure group in each

440   study when it was reported, we maximized the ability to detect the presence of an

441   exposure-disease association. The current meta-analysis is also the first study to

442   include the newly updated AHS.

443   There are several weaknesses of our analysis that should be noted, however.

444   First, there were only limited published data available for inclusion. Although meta-

445   analysis prevents overemphasis on any single study [57], we cannot exclude the

446   potential for publication bias, given the relatively few published studies to date. Second,

447   there was imbalance in study design: among the only six included studies, five were

448   case-control and one was a cohort. The collection of NHL findings from the cohort study

449   was consistent with a wide range of risks [24], while, by contrast, most of the case-

450   control studies did suggest an increased risk [15-17, 42]. There were also important

451   differences in the comparison group utilized in the studies; some used the lowest

452   exposure group as the reference, while others used the unexposed group. Because of

453   this heterogeneity, and because no statistical tests can confirm elimination of

454   publication bias or heterogeneity in a meta-analysis [58], our results should be

455   interpreted with caution. Finally, as depicted in Figure 3 illustrating key milestones

456   related to glyphosate use in society and in epidemiological studies, none of the

457   available studies capture the effects of the significant increased usage of glyphosate

458   that began with the introduction of "green-burn-down" in the mid-2000s.

459   **5.2 AHS Cohort Study**

460   In general, cohort studies are considered the gold standard among observational

461   studies because of their ability to estimate exposure before disease occurrence (which

462   allows for clarity of temporality and can minimize recall bias), to estimate incidence, to

463   examine multiple outcomes, and for some target populations, to study a large number of

464   exposed subjects. Our new meta-analysis is the first to include the AHS 2018 update,

465   which is the largest, newest, and most heavily weighted study (>50%, Table 4). Given

466   its importance and because it was the only cohort study in our analyses, we discuss

467   below several aspects of the AHS 2018 study and its comparison with the AHS results

468   reported in 2005. Key differences between the AHS 2018 and AHS 2005 are

469   summarized in Table 8.

470   *5.2.1 Exposure Assessment and Quantification*

471   Exposures were self-reported using questionnaires. AHS 2005 used the

472   exposures reported at baseline only, whereas AHS 2018 supplemented this information

473   with responses to a follow-up questionnaire returned by 63% of AHS participants.

474   The risk estimates generated from the follow-up AHS 2018 report depended on a

475   "multiple imputation" approach with multiple steps to generate GBH exposure

476   information for the 37% of participants who did not complete the follow-up questionnaire

477   [24]. A standard imputation model captures the full distribution of the exposure by

478   relying on two parts of a model: the regression or predictable part and the residual error

479   part. The validity of the imputed exposures and the resulting risk estimates relies on the

480   validity of both parts of the imputation model. The AHS imputation method for

481   ever/never pesticide use conditioned on the reported pesticide use and other data,

482   including demographics, medical history at baseline, and farming characteristics at

483   enrollment, with some covariates chosen by stepwise regression (see Table 2 in

484   Heltshe *et al.* [59]). Based on their analysis of a 20% holdout dataset, the prevalence of

485   glyphosate use was underreported by 7.31%, suggesting some lack of validity in the

486   predictable part of the imputation model that may in turn affect the NHL risk estimates.

487   The imputations of days of use per year and most recent year of farming activity relied

488   upon a stratified sampling with replacement approach, with values sampled from Phase

489   2 respondents based on strata defined using Phase 1 information.

490   The imputations did not use the NHL or any other cancer outcome information

491   reported by Andreotti *et al.* [24]. This approach is problematic because of how the

492   residual error part of the imputation model is handled. It is known that multiple

493   imputation of a covariate (*i.e.,* glyphosate exposure) in a model that omits the outcome

494   variable to be used in the inference leads to attenuation of the effect estimate for that

495   covariate due to lack of correlation with the outcome in the residual error part of the

496   imputed exposures [60]. As we discuss further in the next paragraph, this approach

497   effectively "bakes into the results" the null hypothesis of no increased risk of NHL

498   exposure due to glyphosate risk.

499   Because the NHL outcome information was not used in the imputation

500   procedure, the exposure "imputation" method used in the AHS 2018 report can be

501   better named "exposure simulation" as described by Gryparis *et al.* [61]. This term gives

502   a much more accurate understanding of the impact of the imputation of the data on the

503   risk estimates because when exposure is simulated in a model that does not take the

504   NHL outcome into account, the uncertainty in the "imputed" exposure behaves like

505   classical measurement error and, thus, will bias the effect estimate towards the null [62].

506   AHS 2018 authors argue that their imputation approach "likely did not materially

507   impact risk estimates" [63]. However, their argument has to do with the impact on the

508   average change in the number of predicted events in an outcome-augmented

509   imputation model and not the role of classical measurement error in the imputed

510   exposure estimates.

511   There was also a subtle yet important difference in the categorization and

512   quantification of exposure data between AHS 2005 and 2018. As depicted in Table 8,

22

513   both studies classified exposure based on (1) ever/never, (2) cumulative exposure days,

514   and (3) intensity-weighted exposure days. However, the algorithm utilized to calculate

515   intensity-weighted exposure days was updated between 2005 and 2018. Key

516   differences include rescaling of scores by a factor of 10 and altering the weights for

517   mixing, certain pesticide application techniques, and the use of chemically resistant

518   gloves [44]. Therefore, these metrics cannot be directly compared.

519   Additionally, it is crucial to highlight the difference in reference groups between

520   these two studies, which further limits the comparability of their estimates. AHS 2005

521   utilized the lowest exposed tertile as the comparison group for risk estimation. They

522   justified this decision as an attempt to control residual confounding, because of the

523   presence of significant differences in key characteristics between the never-exposed

524   and lowest-exposed groups. By contrast, AHS 2018 utilized the unexposed group as

525   the reference group even though our comparison of the demographics reported in each

526   paper's Table 1 does not suggest there is substantially better comparability between

527   groups in AHS 2018. Furthermore, because the exposure information by which these

528   groups were classified was based on their imputation procedure, the limitations of which

529   are highlighted above, the actual comparability between groups may differ from the

530   values reported. Not only would it be helpful to be able to compare directly the risk

531   estimates across the two papers, it would be useful to investigate whether there was

532   residual confounding introduced into the AHS 2018 analysis by the use of the

533   "unexposed" group as the reference.

534   *5.2.2 Exposure Misclassification*

535   Differential misclassification is unlikely in a cohort study when exposure is

536   assessed prior to the disease occurrence. In AHS 2018, however, we believe there is

537   some potential for differential misclassification. Sixty-three percent of the original

538   cohort provided updated exposure information by questionnaire one time between the

539   years of 1999 and 2005. Although details are not provided, it is likely that some of the

540   cases reported their exposure after disease occurrence, allowing for potential

541   differential misclassification in the self-reported exposures in this cohort similar to

542   general concerns with case-control studies. Furthermore, noting large societal trends in

543   GBH exposure between initial exposure ascertainment and the follow-up questionnaire,

544   and the 7.3% under-prediction of glyphosate exposures in the holdout dataset [59], the

545   prediction part of the imputation modeling was likely differentially under-predicting

546   exposures.

547   Non-differential misclassification occurs when exposure status is equally

548   misclassified among exposed cases and unexposed controls[64]. The approach in AHS

549   2018 to exposure imputation is one theoretically well-understood source of non-

550   differential misclassification. In addition, it may be more problematic in the context of a

551   ubiquitous exposure because it is hard for participants to know to what extent or how

552   long they have been exposed. Glyphosate's ubiquity in the environment leads to

553   profound concerns that even "unexposed" individuals in the cohort are likely to have

554   been exposed to GBHs; consequently, the magnitude of any potential association

555   relative to the unexposed group may be attenuated due to this misclassification. This

556   problem is encountered with other environmental exposures such as environmental

557   tobacco smoke (ETS): never smokers with ETS exposure carry some cancer risk and

558 are not the ideal true reference group in studies of smoking and tobacco-related

559 cancers [65]. As we noted above, non-differential misclassification is likely to attenuate

560 measures of association, biasing the RR toward the null of 1.0 [66]. Although it is

561 difficult to ascertain exactly, the extent of this source of non-differential misclassification

562 can be estimated through smaller-scale validation studies [66].

563 *5.2.3 Disease Classification & Latency*

564 The updated AHS 2018 included multiple myeloma (MM) in their NHL cases, but

565 the previous AHS 2005 did not. Although MM traditionally did not belong to NHL, WHO

566 recently revised the classification of lymphoid neoplasms and suggested some types of

567 MM (e.g., IgM mutation-related MM) are related more closely to lymphomas, including

568 NHL, than to myelomas [67].

569 There is much uncertainty surrounding the latency period for NHL. The latency

570 period for short-term high-dose exposures to carcinogens may be as short as two years,

571 but it may also be as long as 15 years or more. Low-dose long-term exposures are

572 expected to have longer median latencies between 15 to 20 years for NHL [68, 69]. It is

573 possible that different NHL subtypes may also have different latencies. Given the

574 uncertainty surrounding NHL latency, it is possible that the follow-up period (median =

575 6.7 years) in the 2005 AHS study [19], which was unlagged, may have been too short

576 for a sufficient number of exposure-related cancer events to manifest. Given that

577 participants had been exposed to GBHs prior to enrolling in the study (median = 8

578 years; mean = 7.5 years; SD = 5.3 years), participants could have had an exposure

579 duration ranging from as low as 0 years to as high as 18 years at the time of enrollment,

580 assuming a normal distribution. Hence, although some AHS members may have had

581   sufficient exposure durations to develop NHL, many fell short of the median 15-20 years

582   of expected NHL latency.

583   The 2018 AHS publication added 11-12 further years of follow-up for all study

584   participants, an additional 483 cases of NHL, and considered five, ten, fifteen, and

585   twenty year exposure lags, which was not possible in AHS 2005 due to its short

586   duration. Epidemiologic studies often lag exposures to account for disease latency

587   under the assumption that recent exposures have little impact on disease development.

588   Theoretically, longer exposure durations and/or lags would present more biologically

589   plausible associations with NHL. For AHS 2018 specifically, not only are the risk

590   estimates associated with longer lag times more plausible that unlagged risk estimates

591   in AHS 2005 and 2018, but the twenty-year exposure lag, specifically, may also be free

592   of the bias caused by exposure imputation described above, given that at this lag

593   exposure information may have been derived exclusively from the baseline

594   questionnaire.

595   *5.2.4. Summary*

596   Overall, the study features highlighted above related to exposure assessment

597   and quantification; misclassification; and latency and lag suggest caution in direct

598   comparisons between AHS 2005 and 2018. Additionally, the limitations with AHS 2018

599   with regard to exposure simulation, potential residual confounding, and misclassification

600   may have accounted for the weaker meta-RR estimate that we obtained when

601   incorporating this study into the meta-analysis.

602   **5.3 Case-Control Studies**

603   Although cohort studies are the gold standard in observational epidemiology,

604 they are often challenging to conduct due to the small number of incident cases for rare

605 diseases such as NHL. Case-control studies can be more efficient for evaluation of rare

606 diseases. For example, the AHS had to recruit tens of thousands of participants (N =

607 53,760) and follow them for more than a decade in order to gather 575 new cases of

608 NHL, whereas the 5 case-control studies assembled 2,836 NHL cases among all

609 participants (N = 8,868) in a much shorter period of time (Tables 1 and 4). Though the

610 case-control studies are smaller and carry less weight than the large cohort study, it is

611 worth noting that results from multiple case-control studies displayed little heterogeneity

612 (Table 5) and reported similar findings pointing away from null (Table 4).

613   However, there are other challenges and concerns relevant to the case-control

614 studies utilized in our meta-analysis, which we briefly discuss below.

615 *5.3.1 Control Selection and Exposure Quantification*

616   Four of the five case-control studies utilized here are population-based, while one

617 is hospital-based. There may be important differences between hospital-based controls

618 and population-based controls that could impact the interpretability and comparability of

619 the resulting risk estimates. Of relevance to this concern is that, as noted above in our

620 sensitivity analyses, exclusion of Orsi *et al.* [18] (the hospital-based case-control study)

621 resulted in an increased meta-RR of 1.46 (95% CI: 1.16-1.83), while sequential

622 exclusion of each of the population-based case control studies produced decreased

623 meta-RRs.

624   Exposure was also quantified differently between the selected case-control

625   studies, further impacting their comparability. While all the studies considered in our

626   meta-analysis conducted exposure assessment based on self-reported questionnaire

627   data, some studies considered ever/never exposure, while others evaluated exposure

628   based on number of days per year (see Tables 1 and 4). Some studies also relied on

629   proxy respondents such as next of kin.

630   *5.3.2 Exposure Misclassification*

631   It is always possible for the internal validity of case-control studies to be

632   threatened by recall bias, a form of differential exposure misclassification that occurs

633   when exposures are remembered differently by cases (or their proxies) and controls.

634   Cases may have been more motivated to recall GBH exposure, and the exposures may

635   be more vivid or meaningful due to awareness of the risk factors for their disease. While

636   differential misclassification can bias the OR in either direction, differential

637   misclassification due to cases being more likely to report exposure tends to artificially

638   inflate the OR.

639   *5.3.3 Latency and Lag*

640   As discussed in Section 5.2.3, the latency for NHL is uncertain and could be

641   anywhere from 2 years to greater than 15 years. There were differences in how the

642   case-control studies considered and incorporated latency and lag into their analyses.

643   For example, De Roos *et al.* [15] and McDuffie *et al.* [42] do not mention these

644   considerations; by contrast, Hardell *et al.* [17], Orsi *et al.* [18], and Eriksson *et al.* [16]

645 each incorporate latency and lag, albeit differently. These differences suggest caution in

646 the integration of these results.

6. Summary of the GBH and NHL Association in Humans

648 Overall, the results from our new meta-analysis employing the *a priori* hypothesis

649 and including the updated AHS 2018 study (1) demonstrated a significantly increased

650 NHL risk in highly GBH-exposed individuals (meta-RR = **1.41**, 95% CI: 1.13-1.75; Table

651 5 and Figure 2A), (2) are aligned with findings (Table 7) from previous meta-analyses

652 [22, 26], and (3) revealed an additional 11-14% and 15-18% increase in NHL relative

653 risk due to high levels of GBH exposure (Table 7) when using the AHS 2018 and the

654 AHS 2005 cohort, respectively.

655 Together, all of the meta-analyses conducted to date, including our own,

656 consistently report the same key finding: exposure to GBHs are associated with an

657 increased risk of NHL.

658 Because most people in these epidemiological studies were not exposed to pure

659 glyphosate, but rather glyphosate-based formulations (e.g. Roundup® or Ranger Pro ®)

660 with a number of adjuvants, it could be argued that the NHL manifested as a result of

661 exposure to the mixture or an ingredient other than glyphosate in the formulation. To

662 investigate causal inference regarding the association between glyphosate exposure

663 and NHL, we discuss briefly whether or not the association identified from

664 epidemiological studies could be supported further by experimental animal and

665 mechanistic studies.

7. Animal Data: Lymphoma Prevalence in Glyphosate-Exposed Mice

The animal study outcome most closely linked to human NHL is malignant lymphoma. We identified six unpublished glyphosate and lymphoma studies in mice that are in the public domain from two sources: a presentation by the European Food Safety Authority [70] at the EPA FIFRA Scientific Advisory Panel on Carcinogenic Potential of Glyphosate and a report by The Food and Agriculture Organization of the United Nations and World Health Organization Joint Meeting on Pesticide Residues [21]. EFSA [70] reported results from five unpublished studies: four in CD-1 [71-74] and one in Swiss albino mice [75], whereas JMPR [21] also reported data from a study in female CD-1 mice [76]. Each study reported four glyphosate doses and corresponding lymphoma incidence in males and females except for Takahashi [76], where the only data available in the public domain was for female mice [21].

7.1 Results of Murine Lymphoma Studies

Results from all studies (n = 6) of malignant lymphomas in mice available in the public domain are presented in Table 9. Study durations ranged from 1.5 to 2 years. All studies administered glyphosate through the diet [71-76], and the concentrations tested ranged from 100 ppm to 50,000 ppm [21]. EFSA [70] and JMPR [21] reported slightly different doses, with JMPR [21] further stratifying by sex. Lymphoma incidence was abstracted from EFSA [70], with slightly different numbers for one study [71]. Table 9 provides the dietary concentration of glyphosate (reported in ppm), the doses (reported in mg/kg/day) provided by EFSA [70] and JMPR [21], and lymphoma incidence in males and females. One study [73] reported food consumption, which was recorded for each treatment group, and weekly mean achieved-dose levels were averaged to calculate

689   actual doses for males and females. Information on how doses were calculated for the

690   other studies [71, 72, 74-76] was not available.

691   In summarizing these studies, EFSA [70] noted that Sugimoto [72] and Wood *et*

692   *al.* [73] showed statistically significant dose-response in males according to the

693   Cochran-Armitage test for linear trend, whereas Kumar [75] showed a statistically

694   significant Z-test for both males and females. In agreement, JMPR [21] noted that

695   Sugimoto [72] and Wood *et al.* [73] showed a statistically significant trend in males and

696   that Kumar [75] reported statistically significant increases in malignant lymphoma in

697   high-dose groups of both males and females. JMPR [21] further reported Takahashi [76]

698   had a statistically significant increased incidence in lymphoma among females by their

699   trend test. The remaining two studies did not report evidence of a statistically significant

700   dose-response effect.

701   ***7.2 Additional Considerations and Recommendations***

702   One challenge with these studies is that at face value they appear to be

703   inconsistent because some show statistically significant findings whereas others do not.

704   However, based on EPA's Cancer Guidelines, evidence of increased lymphoma

705   incidence should not be discounted due to lack of statistical significance in trend and/or

706   pairwise comparison tests. Additional factors that should not be used to exclude study

707   findings are the use of high doses and/or incidence rates that are consistent with levels

708   seen in historical controls [77].

709   Another consideration is that the study lengths in these animal experiments may

710   have been insufficient for development of NHL. There are proposals that the standard

711   timeframe of two years for a cancer bioassay to approximate long-term cancer

712   incidence in humans should be extended to account for potentially longer latencies.

713   Eighty percent of all human cancers occur after the age of sixty. A two-year-old rat

714   approximates a human of 60-65 years, indicating a traditional two-year bioassay may

715   not be sufficient for late-developing tumors [78].

716   Future work should combine the results from these six studies into an overall

717   pooled analysis to give a more robust assessment of the evidence. A pooled analysis

718   would take into account the varying study durations (of 18 or 24 months) as well as

719   other between-study differences in dose regimens and mouse strains.

720   These studies, in which mice were exposed to only glyphosate, may have

721   underreported incidence of malignant lymphoma given evidence of increased toxicity of

722   GBHs compared to glyphosate alone [79-81]. GBH mixtures, which contain a number of

723   adjuvants, have been reported to exert synergistic toxic effects in mechanistic studies

724   (Section 6). Therefore, we also recommend the evaluation of GBHs in chronic animal

725   carcinogenicity studies to better capture representative exposure of humans.

726   **8. Potential Mechanistic Context**

727   There are several possible mechanistic explanations for the increased NHL risk

728   in humans and lymphomas in animals. The etiology of NHL remains largely unknown;

729   however, potential risk factors include autoimmune diseases, infection with viruses

730   and/or bacteria, immunosuppressant medications, and exposures to some pesticides

731   [82, 83]. Although not a formally recognized risk factor for NHL, endocrine disruptors

732   have been associated recently with risk of B-cell neoplasms [84], most of which are

733 NHL [56]. Furthermore, a genetic hallmark of NHL is the recurrence of chromosomal

734 translocations, such as t(14;18), involving the immunoglobulin heavy chain gene fusion

735 (*BCL2-IGH*), which are frequently detected in subgroups of NHL patients [85] and in

736 pesticide-exposed farmers [86, 87]. Hence, immunosuppression, viral/bacterial

737 infections, endocrine disruption, and genetic alterations have been suspected as key

738 underlying mechanisms in the development of lymphoma (lymphomagenesis). Although

739 not specifically linked to NHL, oxidative stress is a general mechanism of

740 carcinogenesis that could contribute to lymphomagenesis.

741 *8.1 Immunosuppression/Inflammation*

742 The strongest factors known to increase NHL risk are congenital and acquired

743 states of immunosuppression [88]. Several studies suggest that glyphosate alters the

744 gut microbiome [79, 89] and cytokine IFN-γ and IL-2 production [90]. These changes

745 could impact the immune system, promote chronic inflammation [91], and contribute to

746 susceptibility of invading pathogens, such as *H. pylori* [92].

747 *8.2 Endocrine Disruption*

748 Disruption of sex hormones may contribute to lymphomagenesis/NHL [93].

749 Glyphosate may act as an endocrine disrupting chemical (EDC) because it has been

750 found recently to alter sex hormone production. Several in vivo studies of male rats

751 exposed to glyphosate have reported significantly lower testosterone levels [94-96],

752 spermatid numbers [94], altered sperm and testicular morphology [94, 95], greater

753 development of the mammary gland [97], and a surge in mast cell infiltration and

754 proliferation accompanied by increased estrogen receptor (ESR1) [97]. In ovarian

755   granulosa cells, glyphosate exposure resulted in decreased cell proliferation and

756   estradiol production [98], which may contribute to lymphomagenesis [93].

757   **8.3 Genetic Alterations**

758   Several studies report that glyphosate can induce single- and double-strand DNA

759   breaks [99-102], purine and pyrimidine oxidation [100], increased comet tail moment

760   [103], and activation of the canonical non-homologous end-joining pathway (c-NHEJ)

761   [101] that stimulates DNA repair. Glyphosate was also reported to induce micronuclei

762   [104-110], sister chromatid exchanges [109], and chromosomal aberrations [111], but

763   other studies found no change in these parameters [112-116]. Conclusions on the

764   genotoxicity of glyphosate remain controversial in the debate on its carcinogenic

765   potential [117]. A recent review reported that this discrepancy could be attributed to

766   differences in the literature analyzed (published versus unpublished), exposure type

767   (glyphosate versus GBHs), and exposure magnitude (low everyday exposures versus

768   higher exposure groups) [118].

769   **8.4 Oxidative Stress**

770   Numerous studies indicate glyphosate causes oxidative stress [119-

771   122]. Biomarkers of oxidative stress have been reported in a number of tissues in rats

772   and mice, including liver, skin, kidney, brain, and plasma. In a study of *albino male rats*,

773   levels of hepatic reduced glutathione were significantly decreased in GBH-exposed

774   animals (1.64 mmol/g) compared to controls (2.64 mmol/g) [80]. A different

775   study in glyphosate-exposed *Wistar rats* reported increased lipid peroxidation across all

776   tissues studied and reactive nitrogen species in the brain and plasma [119]. A proteomic

777   analysis of *Swiss albino mice* reported overexpression of carbonic anhydrase 3, a

778   cytoplasmic protein that plays a role in cellular response to oxidative stress [123]. These

779   mechanisms, among others, provide evidence of biological plausibility for the observed

780   link between glyphosate exposure and human NHL, though further work is needed to

781   better understand these pathways.

782   **9. Conclusions and Future Directions**

783   The rise of glyphosate as the most widely used herbicide raises serious health

784   concerns, given its potential links with NHL. Using our high-exposure *a priori* hypothesis

785   and including the recently updated AHS cohort in a meta-analysis for the first time, we

786   report that GBH exposure is associated with increased risk of NHL in humans. Our

787   findings are consistent with results reported from prior meta-analyses but show higher

788   risk for NHL because of our focus on the highest exposure groups. However, given the

789   heterogeneity between the studies included, the numerical risk estimates should be

790   interpreted with caution. Additionally, as noted above and depicted in Figure 3, the

791   available studies do not capture the possible effects of increased population exposures

792   due to secular increases in use where "green burn-down" practices introduced in the

793   mid-2000s may be a particularly important source of population exposures. The totality

794   of the evidence from six studies of glyphosate-exposed mice support this association in

795   humans. Although the underlying mechanisms remain unknown, mechanistic studies of

796   glyphosate-induced immunosuppression/inflammation, endocrine disruption, genetic

797   alterations, and oxidative stress suggest plausible links between GBH exposure and

798   NHL development. The overall evidence from human, animal, and mechanistic studies

799   presented here supports a compelling link between exposures to GBHs and increased

800   risk for NHL.

801

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1196   Steen, C. Samanic, M. Dosemeci, M.C. Alavanja, Reliability of reporting on life-style and
1197   agricultural factors by a sample of participants in the Agricultural Health Study from
1198   Iowa, Epidemiology, 13 (2002) 94-99.

1199

1200

Table 1 Epidemiologic studies of GBHs and cancer: studies used in the main meta-analyses[a]

Author/location	Subject ascertainment	Participation rates	Exposure assessment	Exposure level	Results for NHL[b]	Weaknesses	Adjustments	Notes
Andreotti et al. [24] (Agricultural Health Study) Where: Iowa and North Carolina Design: Prospective cohort Years: 1993-97 to 2012-13 Percent exposed: 82.8%	Who: 54,251 pesticide applicators recruited between 1993-97 Cases: NA Source of cases: Iowa and North Carolina Cancer Registries, state and national death registries Histologic verification: Not mentioned Controls: NA Source of controls: NA Similar demographics (exposed and unexposed): Similar age, sex, race, and smoking. Exposed higher education, alcohol consumption, and family history of cancer Final size: 575 NHL cancers, 53760 subjects without missing data Follow-up: from enrollment through December 31, 2013 in Iowa and December 31, 2012 in North Carolina (16-20 years)	Exclusions: 3059 excluded (mostly missing data) Percent proxy interviews: None Missing Follow-Up Questionnaire: 37% (Pesticide use imputed)	Collection: Self-administered and take home questionnaire at time of recruitment: 22 specific pesticides application methods, PPE, years of use, and days per use. Review: No Blinded: Prospective design Validation: Similar questions asked 1 year apart in 4,088 subjects, agreement on glyphosate ever use = 82%, days per year mixed = 52% [124]	Exposed: Quartiles 1-4 calculated by multiplying lifetime exposure days by an intensity score. Intensity based on (mixing + application method + equipment repair) * PPE in Coble et al. 2011 [44] Unexposed: No glyphosate use Latency: 5, 10, 15, and 20 years	Adjusted Intensity Weighted Cumulative Exposure (Days): RRs for Q1: 1–598.9; Q2: 599–1649.9; Q3: 1650–4339.9; and Q4: ≥4340.0, = 1.0 (Ref), 0.83 (0.59-1.18), 0.83 (0.61-1.12), 0.88 (0.65-1.19), 0.87 (0.64-1.20); p-trend = 0.95; n=54251 total, 111 cases in the high exposure group Similar results comparing highest to lowest quartile. Latency with Adjusted Intensity Weighted Cumulative Exposure: RRs for 20-year lag quartiles: Q1: 1–281.3; Q2: 281.4–895.9; Q3: 896–2609.9; Q4: ≥2610.0 = 1.00 (Ref), 1.22 (0.91-1.64), 1.15 (0.86-1.55), 0.98 (0.71-1.36), 1.12 (0.83-1.51) Latency with Adjusted Lifetime Cumulative Exposure: RRs for 20-year lag quartiles: Q1: 1-8.74; Q2: 8.75-21.24; Q3: 21.25-59.4; Q4: ≥59.5 = 1.00 (Ref), 1.52 (1.16-2.00), 0.95 (0.68-1.32), 0.97	1. Possible fairly short follow-up for some people 2. Somewhat weak validation 3. Imputed exposure data for participants who did not complete the follow-up questionnaire.	Matched: NA Adjusted: adjusted for age, state of recruitment, education, cigarette smoking status, alcohol per month, family history of cancer, atrazine, alachlor, metolachlor, trifluralin, 2,4-D. Other: NA	Censored on date the subjects left the state. Increased RR for AML (RR=2.6, 0.7-9.4); highest exposure group (RR = 2.44, 0.94 - 6.32). 79.3% of all cases ever used glyphosate Used updated Surveillance Epidemiology End Results (SEER) coding scheme for NHL which includes multiple myeloma [67] Update of De Roos et al. [19]

					(0.71-1.33), 1.13 (0.85-1.52) Change with adjustment: No			
De Roos (2005) [19] (Agricultural Health Study) Where: Iowa and North Carolina Design: Prospective cohort Years: 1993-97 to 2001 Percent exposed: 75.5%	Who: 54,315 pesticide applicators recruited between 1993-97 Cases: NA Source of cases: Iowa and North Carolina Cancer Registries, state and national death registries Histologic verification: Not mentioned Controls: NA Source of controls: NA Similar demographics (exposed and unexposed): Similar age, sex, smoking, alcohol. Exposed higher education and family history of cancer Final size: 92 NHL cancers, 36,509 subjects without missing data Follow-up: from enrollment through Dec. 2001 (5-8 years, median=6.7 years)	Exclusions: 20,802 excluded (mostly missing data) (36.3%) 298 people lost to follow-up Percent proxy interviews: None	Collection: Self-administered and take home questionnaire at time of recruitment: 22 specific pesticides application methods, PPE, years of use, and days per use. Review: No Blinded: Prospective design Validation: Similar questions asked 1 year apart in 4,088 subjects, agreement on glyphosate ever use = 82%, days per year mixed = 52% [124]	Exposed: Ever or upper tertiles Intensity based on (mixing + application method + equipment repair) * PPE in Dosemeci et al. 2002 [45] Unexposed: Never or lower tertile Latency: Not mentioned	Ever exposed: Age adjusted: RR=1.2 (0.7-1.9) Adjusted: RR=1.1 (0.7-1.9) Intensity-weighted exposure days: For exposures of 0.1-79.5, 79.6-337.1, and 337.2-18241, 1.0 (Ref), 0.6 (0.3-1.1), and 0.8 (0.5-1.4); p-trend = 0.99; n=36,823 total, 22 cases in the high exposure group Similar results comparing highest to lowest tertile. Adjusting for other pesticides did not change RR by more than 20% Change with adjustment: No	1. Possible fairly short follow-up for some people 2. Large numbers of people excluded from dose-response analysis due to missing data 3. Somewhat weak validation	Matched: NA Adjusted: Age, education, smoking, alcohol, family cancer history, state, 10 other pesticides most strongly correlated with glyphosate (if RR changes by >20%) Other: NA	Censored on date the subjects left the state. Increased RR for multiple myeloma (OR=2.6, 0.7-9.4) but with large change after adjustment (unadjusted OR=1.1, 0.5-2.4) 75.5% ever used glyphosate
De Roos (2003) [15] Where: US Design: Case-control Years: 1979-86 Percent exposed: 5.5%	Who: White men only. Combines data from three NCI case-control studies: Hoar et al. [33], Zahm et al. [34], and Cantor et al. [37]. Cases: Nebraska [34]: White subjects ≥ 21 years, 66 counties in eastern Nebraska, diagnosed 1983-86 Iowa/Minn [37]: White men ≥ 30 years, diagnosed 1980-83. Iowa: entire state. Minnesota: entire state except four large cities	Exclusions: >25% (missing data and worked on farm before 18 years old) Interview rates: Kansas Cases: Unclear but likely >90% Controls: 93%	Collection: Telephone (Kansas, Nebraska) or in-person (Iowa/Minn) interviews: SES, medical history, smoking, and family history Nebraska: Specific pesticides,	Exposed: Any reported use, no further details Unexposed: No use of glyphosate Latency: Not mentioned	Unadjusted (calculated): OR=1.80 (1.18-2.74) Adjusted: OR=2.1 (1.1-4.0), 36 exposed cases Hierarchical adjustment: OR=1.6 (0.9-2.8), 36 exposed cases	1. Unknown whether there was full case ascertainment in some areas. For example, incidence rates in Nebraska were 77% of those in SEER [34]. Few details provided on Minnesota case surveillance system 2. Only includes White male subjects	Matched: Race, sex, age, and vital status Adjusted: Age study site, and 47 pesticides. Hierarchical models included pesticide class, and prior knowledge on carcinogenicity from IRIS and IARC	Farmers: 59.9% among controls Exclusions: Subjects who did not work on farms after age 18; subjects with missing data on any of 47 pesticides

	Kansas [33]: White men ≥ 21 years diagnosed 1979-81, entire state, 200 of 297 randomly selected Source of cases: **Nebraska:** Nebraska Lymphoma Study Group and area hospitals, **Iowa/Minn:** Iowa State Health Registry, surveillance system of Minnesota hospitals and pathology laboratories (not described) **Kansas:** State wide registry run by the University of Kansas Cancer Data Service, mandatory cancer reporting in the state Histologic verification: Yes, in all three studies (Kansas 90%) Controls: Randomly selected from the same areas Source of controls: Random digit dialing, Medicare, and state mortality records for deceased cases Similar demographics: Similar education; family history higher in cases; few other variables described Final size: 650 cases and 1933 controls	**Iowa/Minn** Cases: 89% Controls: 76-79% **Nebraska:** Cases: 91% Controls: 85% Percent proxy interviews: 30.9% in cases and 39.7% in controls	number years used, average days used per year, PPE Iowa/Minn: Specific pesticides, first and last year used, method of use, personal application, and PPE Kansas: Open ended question about pesticides used, duration and days per year only for pesticide groups, and PPE Review: No Blinded: Partial (see individual studies) Validation: Kansas: Sought to confirm purchases in 110 subjects, suppliers usually reported fewer purchases, no consistent differences between cases and controls, few details given Iowa/Minn: No Nebraska: No		Change with adjustment: Yes Other results: Iowa/Minn [37]: OR=1.1 (0.7-1.9), 26 exposed cases Kansas: No glyphosate data in Hoar et al. [33] Nebraska: No glyphosate data in Zahm et al. [34] In non-asthmatics OR=1.4 (0.98-2.1) in Lee et al. [36]	3. Large number of proxy interviews 4. No details regarding timing of pesticide use in relation to disease onset	Other: Family cancer history, education, and smoking had little impact on results	(about 25% of subjects) In Nebraska, larger percentage of farmers reported no pesticide use Overlapping study with Cantor et al. [37][c] and Lee et al. [36][d]; both of which were evaluated in the sensitivity analysis.
Eriksson et al. [16] Where: Sweden Design: Case-control Years: 1999-2002	Who: Population based, men and women Cases: Age 18-74 diagnosed 1999-2002 Source of cases: 4 of 7 health service regions in Sweden associated with four University Hospitals, from physicians and pathologists Histologic verification: Yes	Exclusions: 134 of 1163 (11.5%) with medical conditions or deceased Interview rates: Cases: 91% Controls: 92%	Collection: Mailed questionnaire on work history, specific pesticides, number of years, days per year, hours per day, with follow-up telephone	Exposed: One full day, or median number of days exposed in the controls. Unexposed: Unexposed to	Unadjusted: Not provided Adjusted: ≥1 day (univariate): OR=2.02 (1.10-3.71) ≤10 days: OR=1.69 (0.70-4.07)	1. Deceased cases not included 2. True participation rates may be lower 3. Use of PPE not assessed 4. Population based: not a high exposure group	Matched: Age and sex Adjusted: Age, sex, and year of diagnosis. Adjusted for other pesticides in some analyses (MCPA, mercurial seed dressing…)	Authors state that all lymphoma treating clinics and all lymphoma pathologists in the study regions were

Percent exposed: 1.8%	Controls: Randomly selected from the same health regions, matched on age and sex Source of controls: Sweden population registry for the same health service regions Similar demographics: Data not provided Final size: 910 cases and 1016 controls	Percent proxy interviews: Deceased cases were not included (n=88)	interviews as needed Review: No Blinded: Partial, interviewers blinded to case-control status Validation: No	any included pesticide Latency: Exposures in the year of and the year before diagnosis disregarded	>10 days: OR=2.36 (1.04-5.37, n=17 exposed cases) ≥1 day adjusted for other pesticides (multivariate): OR=1.51 (0.77-2.94) Latency (≥1 day) 1-10 years: OR=1.11 (0.24-5.08) >10 years: OR=2.26 (1.16-4.40) Change with adjustment: Yes	5. Adjustments for other pesticides not completely clear	Other: NA	covered by the study. Also gives RR by subtype Percent farmers unknown, but only 51 controls (5.0%) used herbicides
Hardell et al. [17] Where: Sweden Design: Case-control Years: 1987-90 Percent exposed: 0.7%	Combines two published studies, one of NHL [38] and one of hairy cell leukemia (HCL) [39] Who: Population based, males ≥25 years old NHL cases (n=404): All male cases, living or deceased, diagnosed 1987-1990 from 7 Swedish counties HCL cases (n=121): All living male cases in whole country 1987-92 Source of cases: Regional cancer registries (compulsory reporting) Histologic verification: Yes Controls: 2-4 per case matched on age, county, and year of death (if deceased). Those closest in age of birth to case were selected Source of controls: National Population Registry and National Registry for Causes of Death Similar demographics: Data not provided Final size: 515 cases and 1141 controls	Exclusions: Deceased HCL cases excluded, numbers unknown. No other obvious major exclusions Interview rates NHL Cases: 91% Controls: 84% HCL Cases: 91% Controls: 83% Percent proxy interviews: Approximately 43.4% of NHL cases and controls. HCL study only living subjects used.	Collection: Mailed questionnaire: complete working history, exposure to specific chemicals (years and total number of days). Supplemented with phone interviews as needed. Review: No Blinded: Subjects blinded to hypothesis, interviewers blinded to case status Validation: None	Exposed: Minimum exposure of 1 day (8 hours) Unexposed: No reported pesticide exposure Latency: At least one year	NHL and HCL combined: Unadjusted: OR=3.04 (1.08-8.52) Adjusted: OR=1.85 (0.55-6.20), 8 exposed cases NHL only: [38] Unadjusted OR=2.3 (0.4-1.3), 4 exposed cases Adjusted OR=5.8 (0.6-54). Adjustment factors and sample sizes not given HCL only: [39] Unadjusted OR=3.1 (0.8-12), 4 exposed cases Adjusted results not given. Age adjustment decreases OR for "herbicides" (2.9 to 1.8) Change with adjustment: Yes	1. Large change in ORs with adjustments, and changes were in opposite directions for NHL only vs. NHL and HCL combined 2. Adjustment factors not listed in some analyses 3. Cut-off for defining exposure is very low 4. Population based: not a high exposure group 5. Small numbers of exposed cases 6. Demographic data not provided 7. Large number of proxy interviews	Matched: Age, county, and year of death (in deceased) Adjusted: Study (NHL vs. HCL), study area, vital status, (unclear, but it seems likely the multivariate analysis adjusted for 2-methyl-4-chlorophenoxyacetic acid, 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid, and other herbicides)	Percent farmers unknown. 184/1141 controls (16.1%) used insecticides so probably low
McDuffie et al. [42] Where: Canada	Who: Population based, males 19 years and older Cases: ICD9 200, 202 newly diagnosed 1991-94	Exclusions: 68 cases in pilot study, all	Collection: Mailed questionnaires: demographics,	Exposed: Not provided	Any exposure Unadjusted: OR=1.26 (0.87-1.80), n=51 exposed cases	1. Unclear if full case ascertainment in Quebec	Matched: Age and province	Farmers: 44.7% in controls had

53

Design: Case-control Years: 1991-94 Percent exposed: 8.8%	Source of cases: Provincial cancer registries, except Quebec (hospitals) Histologic verification: Partial (84%) Controls: Men age 19 or older randomly selected matched on 2-year age groups Source of controls: Randomly selected from provincial health insurance records, telephone listings, or voter lists Similar demographics: Yes for age, farm, smoking, and missing data. Cases less likely to have mumps, measles, and allergy shots/tests; more likely to have previous cancer Final size: 517 cases and 1506 controls	deceased cases (% unknown) Interview rates: Cases: 67.1% Controls: 48.0% Percent proxy interviews: Deceased cases excluded	medical history, family cancer history, lifetime job history, exposure to specific substances, accidental spills, and protective equipment. Phone interviews in those with ≥10 hours/year of cumulative exposure to all pesticides combined. Asked about exposure to pesticides and number of days per year Review: No Blinded: Not mentioned Validation: In a pilot sample of 27 farmers, compared questionnaire data to pesticide purchases. "Excellent concordance" but no actual numbers given	Unexposed: No reported exposure to glyphosate Latency: Not mentioned	(age and province adjusted) Adjusted: OR=1.20 (0.83-1.74) Dose-response: ORs for 0, >0-≤2, and >2 days per year = 1.00 (Ref), 1.00 (0.63-1.57), and 2.12 (1.20-3.73; n=23 exposed cases) (adjusted only for age and province) Unadjusted in high exposure group (calculated) OR=1.88 (1.01-3.21) Change with adjustment: No Other: Glyphosate only: OR=0.92 (0.54-1.55) Glyphosate and malathion: OR=2.10 (1.31-3.37) Hohenadel et al. [40]	2. Is registry compulsory 3. Fairly low participation rates, and difference seen between cases and controls 4. Average exposure in the highest group not given. Duration of exposure not given 5. Deceased cases excluded	Adjusted: Age, province, measles, mumps, cancer allergy shots, and family cancer. Factors with p ≤0.05 retained in the models. Unclear what factors included in the high exposure analysis	residence on farm Similar rural/urban make-up between respondents and non-respondents but other differences not assessed. *See Kachuri et al. [35] for multiple myeloma data* Overlapping study with Hohenadel et al. [40][e] which was excluded from the main meta analysis.
Orsi et al. [18] Where: France (6 cities) Design: Case-control Years: 2000-04 Percent exposed: 5.5%	Who: Population-based, males age 20-75 years old Cases: Diagnosed in one of the main hospitals in the 6 cities, ICD-0-3 codes (listed in their Table 1) Source of cases: Hospitals Histologic verification: Yes Controls: Hospital controls Source of controls: Men from the same hospitals, mostly orthopedic and rheumatology. Unclear if randomly selected.	Exclusions: History of immuno-suppression (% unknown) Interview rates: Cases: 95.7% Controls: 91.2%	Collection: Self-administered questionnaire: all jobs, years, tasks and products handled (open-ended); followed by structured personal interview including non-occupational and occupational use	Exposed: Any, possible or definite; duration greater than the median in the exposed Unexposed: Never exposed to glyphosate, similar results	Unadjusted: OR=0.89 (0.44-1.81) Adjusted: OR=1.0 (0.5-2.2), 12 exposed cases for any exposure Change with adjustment: No	1. Deceased cases probably not included 2. Private clinics not included 3. Unknown if control selection is population based 4. Population based: not a high exposure group or high risk group	Matched: Center and age Adjusted: Age and center Other: Rural vs. urban, type of housing, education, infection, family history, skin characteristics,	Also has multiple myeloma results (OR=2.4; 0.8-7.3) Results for a few subtypes also given but with small numbers

54

	Similar demographics: Similar for SES, education, rural vs. urban Final size: 244 cases and 436 controls	Percent proxy interviews: Not mentioned	(in farmers) of pesticides, mixing or spraying, number and duration of applications Review: Questionnaires reviewed by occupational hygienist and agronomist Blinded: Interviewer and subject blind to hypothesis, and reviewer blind to case status. Unclear if interviewer was blinded Validation: Partial (see "Review"), pesticides compared to annual directories that list recommended pesticides by crop and pest	with "never used any pesticide" Latency: Not mentioned or assessed for glyphosate			smoking, and alcohol had little impact on results	Farm, agriculture, or forestry work in 92 of 426 controls (21.1%)

Abbreviations: HCL, Hairy Cell Leukemia; IARC, International Agency for Research on Cancer; ICD, International Classification of Disease; IRIS, US Environmental Protection Agency Integrated Risk Information System; Minn, Minnesota; NA, not applicable; NCI, National Cancer Institute; OR, odds ratio; PPE, personal protective equipment; Ref, reference; RR, relative risk; SEER, Surveillance Epidemiology End Results; SES, socioeconomic status

[a] Although there is no overlapping study used in the main analysis, Cocco et al. [41] was excluded because only results for all B-cell lymphomas combined were reported (two cases of NHL, one case of multiple myeloma, and one unspecified B-cell lymphoma; n=4). It is evaluated in the sensitivity analysis.

[b] 95% confidence intervals in parentheses

[c] Cantor et al. [37] was excluded because it was combined with two other U.S. case-control studies in De Roos et al. [15].

[d] Lee et al. [36] was excluded because it presents results comparing asthmatics to non-asthmatics and results are not adjusted for other pesticide use. It is evaluated in the sensitivity analysis.

[e] Hohenadel et al. [40] was excluded because it presents results in subjects exposed and unexposed to malathion, which has not been consistently linked to NHL; the OR for glyphosate only was used in the sensitivity analysis.

1201

Table 2. Quality assessment of the cohort studies in meta-analysis.*

Study	Selection				Comparability		Outcome			Overall Quality Scores
	Representative-ness of Exposed	Selection of Non-Exposed	Exposure Assessment	NHL Absent at Start	Controls for Other Pesticides	Controls for Age	Assessment of Outcome	Follow-up Length	Adequacy of Follow-up	
Andreotti *et al.* [24]	1	1	1	1	1	1	1	1	0	8
De Roos (2005) [19]	1	1	1	1	1	1	1	0	0	7

* The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for cohort studies [43]. One point was awarded for yes, and zero points were awarded for no, unable to determine, or inadequate.

1202

Table 3. Quality assessment of the case-control studies in meta-analysis.*

Study	Selection				Comparability		Exposure			Overall Quality Scores
	Adequate Case Definition	Representative-ness of cases	Control Selection	Definition of Controls	Controls for Other Pesticides	Controls for Age	Exposure Assessment	Method Consistency	Non-response Rate	
De Roos (2003) [15]	1	1	1	0	1	1	0	1	0	6
Eriksson *et al.* [16]	1	1	1	0	1	1	0	1	1	7
Hardell *et al.* [17]	1	1	1	0	1	1	0	1	0	6
McDuffie *et al.* [42]	1	1	1	1	0	1	0	0	0	5
Orsi *et al.* [18]	1	1	0	1	0	1	0	0	1	5

* The study quality was assessed according to the Newcastle Ottawa Quality assessment scale for case-control studies [43]. One point was awarded for yes, and zero points were awarded for no, unable to determine, or inadequate.

Table 4: Description and weight of studies selected for the current meta-analyses.

Study (Author, Year)	Case No. (Exp/Tot)	Exposure Category	Risk Estimate[a] (95% CI)	Weight[b] AHS 2018	AHS 2005
AHS Cohort					
Andreotti *et al.* [24]	55/575	≥2610 d/l [c,d]	1.12 (0.83, 1.51)[e]	54.04	--
De Roos (2005) [19]	22/92	≥337.2 d/l [c]	0.8 (0.5, 1.4)[f]	--	28.43
Case-Control					
De Roos (2003) [15]	36/650	Ever, log	2.10 (1.10, 4.00)	11.61	18.08
Eriksson *et al.* [16]	17/910	>10 d/y	2.36 (1.04, 5.37)	7.18	11.18
Hardell *et al.* [17]	8/515	Ever	1.85 (0.55, 6.20)	3.30	5.14
McDuffie *et al.* [42]	23/517	>2 d/y	2.12 (1.2, 3.73)	15.05	23.43
Orsi *et al.* [18]	12/244	Ever	1.0 (0.5, 2.2)	8.82	13.73

Abbreviations: AHS, Agricultural Health Study; d, days; exp, exposed; l, lifetime; log, logistic regression; tot, total; y, year.

[a] Relative risk (RR) reported in both AHS analyses and odds ratio (OR) reported in all case-control studies.

[b] Weight given to each study in the fixed effects model.

[c] Intensity-weighted lifetime exposure days (cumulative exposure days multiplied by intensity score)

[d] 20 years or more lag (time between study recruitment and NHL onset).

[e] Reference group is unexposed

[f] Reference group is lowest exposed

1203

Table 5. Major Findings from Current Meta-Analyses

Analysis	N	Fixed Effects meta-RR (95% CI)	Random Effects meta-RR (95% CI)	Heterogeneity[a] X^2	p
Highest cumulative exposure					
AHS (2018) [24]	6	1.41 (1.13, 1.75)	1.56 (1.12, 2.16)	8.26	0.14
AHS (2005) [19][b]	6	1.45 (1.11, 1.91)	1.52 (1.00, 2.31)	10.59	0.06
Longest exposure duration					
AHS (2018) [24]	6	1.41 (1.13, 1.74)	1.56 (1.12, 2.16)	8.21	0.15
AHS (2005) [19][b]	6	1.56 (1.17, 2.06)	1.57 (1.06, 2.26)	7.81	0.17
Study design					
Case-control [15-18, 42]	5	1.84 (1.33, 2.55)	1.86 (1.39, 2.48)	3.36	0.50
Cohort (AHS 2018) [24]	1	1.12[c] (0.83, 1.51)			

Abbreviations: AHS, Agricultural Health Study; meta-RR, meta-relative risk; N, number of studies.

[a] Heterogeneity is present when X^2 heterogeneity statistic is greater than degrees of freedom (number of studies minus 1).

[b] De Roos *et al.* [19] used instead of Andreotti *et al.* [24] for comparison. See Table 4 for clarifications about the risk estimates used.

[c] Since there was only one cohort study, the RR is presented instead of a meta-RR.

Table 6. Sensitivity tests for meta-analysis

Analysis	N	Fixed Effects meta-RR (95% CI)	Random Effects meta-RR (95% CI)	Heterogeneity[1] X^2	p
Alternate Exposure Categories					
High level[2]	3	1.36 (1.06, 1.75)	1.63 (0.97, 2.76)	5.70	0.06
Ever (AHS 2005)	6	1.30 (1.03, 1.64)	1.26 (1.07, 1.48)	3.73	0.59
Latency[3]	6	1.40 (1.13, 1.75)	1.54 (1.12, 2.13)	8.01	0.16
Cell Type Specific					
Add Cocco *et al.* [41][4]	7	1.43 (1.15, 1.78)	1.59 (1.16, 2.18)	9.10	0.17
Exclude HCL [17][5]	6	1.41 (1.13, 1.77)	1.61 (1.11, 2.34)	9.58	0.09
Only use HCL [17][6]	6	1.43 (1.14, 1.78)	1.62 (1.14, 2.31)	9.36	0.10
Study Location					
North America	3	1.38 (1.08, 1.76)	1.61 (0.99, 2.60)	5.70	0.06
Europe	3	1.53 (0.93, 2.52)	1.55 (0.88, 2.71)	2.43	0.30
Other pesticides[7]					
Adjusted (AHS 2005)	4	1.46 (1.05, 2.02)	1.43 (1.06, 1.92	2.61	0.46
Unadjusted (AHS 2005)	4	1.69 (1.29, 2.23)	1.70 (1.26, 2.30)	3.47	0.33
De Roos *et al.* [15]					
Hierarchal OR[8]	6	1.36 (1.09, 1.70)	1.46 (1.08, 1.96)	6.80	0.24
Cantor *et al.* [37][9]	6	1.29 (1.04, 1.59)	1.36 (1.02, 1.80)	7.07	0.22
Lee *et al.* [36][10]	6	1.35 (1.11, 1.65)	1.41 (1.09, 1.82)	6.63	0.25
Other					
Hohenadel vs. McDuffie[11]	6	1.23 (0.99, 1.53)	1.30 (0.96, 1.76)	7.34	0.20
Exclude one study[12]					
Andreotti *et al.* [24]	5	1.84 (1.33, 2.55)	1.86 (1.39, 2.48)	3.36	0.50
De Roos *et al.* [15]	5	1.34 (1.06, 1.69)	1.47 (1.02, 2.11)	6.59	0.16
Eriksson *et al.* [16]	5	1.35 (1.08, 1.70)	1.47 (1.04, 2.07)	6.62	0.16
Hardell *et al.* [17]	5	1.40 (1.12, 1.75)	1.56 (1.08, 2.24)	8.06	0.09
McDuffie *et al.* [42]	5	1.31 (1.03, 1.66)	1.43 (1.01, 2.03)	5.90	0.21
Orsi *et al.* [18]	5	1.46 (1.16, 1.83)	1.69 (1.16, 2.45)	7.36	0.12

Abbreviations: CI, confidence interval; HCL, hairy cell leukemia; meta-RR, meta-relative risk

1. Heterogeneity is present when X^2 heterogeneity statistic is greater than degrees of freedom (number of studies minus 1).

2. Risk estimates for the most highly exposed group available in the three studies that stratify by exposure level.

3. Eriksson *et al.* [16] results for any glyphosate exposure >10 years latency was used instead of the higher exposure group used in the main analysis.

4 The study combined all B-cell lymphomas and is added to the analysis on highest cumulative exposure (AHS 2018).

5. Hairy cell leukemia cases excluded—results presented in Hardell and Eriksson [38].

6. NHL cases excluded; only HCL results used—results presented in Nordstrom *et al.* [39].

7. Studies that provided RRs that are both adjusted and not adjusted for other pesticide use for ever exposure, or reported that adjusting for pesticide use had little impact on the RR estimate. AHS (2018) did not report ever exposure, so AHS (2005) was used instead.

8. Hierarchical model RR used instead of the standard logistic regression model RR.

9. Cantor *et al.* [37] used instead of De Roos *et al.* [15]. Cantor *et al.* [37] was the only of the three studies combined by De Roos *et al.* [15] that presented data for glyphosate.

10. Lee *et al.* [36] used instead of De Roos *et al.* [15]. Lee *et al.* [36] used same subjects as De Roos *et al.* [15] but did not adjust for other pesticide exposure, did not exclude those with missing data on other pesticide use, and used only non-asthmatics.

11. Hohenadel *et al.* [40] used same subjects as McDuffie *et al.* [42] but presented results in subjects exposed to glyphosate but not malathion (OR=0.92; 95% CI: 0.54-1.55).

12. One study excluded at a time to evaluate the impact of each individual study on the overall meta-RR.

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Table 7. Comparison of current meta-analysis to other published meta-analyses

Studies	Schinasi and Leon [25][a]	IARC [22]	Chang and Delzell [26][a, b]	Current Meta-Analysis with AHS 2005 [19]	Current Meta-Analysis with AHS 2018 [24]
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Andreotti *et al.* [24]	N/A	N/A	N/A	N/A	1.12 (0.83-1.51)
De Roos (2005) [19]	1.1 (0.7, 1.9)	1.1 (0.7, 1.9)	1.1 (0.7, 1.9)	0.8 (0.5, 1.4)	N/A
De Roos (2003) [15]	2.1 (1.1, 4.0)	2.1 (1.1, 4.0)	1.6 (0.9, 2.8)	2.1 (1.1, 4.0)	2.1 (1.1, 4.0)
Eriksson *et al.* [16]	2.0 (1.1, 3.7)	1.51 (0.77, 2.94)	1.51 (0.77, 2.94)	2.36 (1.04, 5.37)	2.36 (1.04, 5.37)
Hardell *et al.* [17]	3.0 (1.1, 8.5)	1.85 (0.55, 6.20)	1.85 (0.55, 6.20)	1.85 (0.55, 6.20)	1.85 (0.55, 6.20)
McDuffie *et al.* [42]	1.2 (0.8, 1.7)	1.20 (0.83, 1.74)	1.20 (0.83, 1.74)	2.12 (1.20, 3.73)	2.12 (1.20, 3.73)
Orsi *et al.* [18]	1.0 (0.5, 2.2)	1.0 (0.5, 2.2)	1.0 (0.5, 2.2)	1.0 (0.5, 2.2)	1.0 (0.5, 2.2)
meta-RR (95% CI)	**1.45 (1.08, 1.95)[c]**	**1.30 (1.03, 1.64)**	**1.27 (1.01, 1.59)**	**1.45 (1.11, 1.91)**	**1.41 (1.13, 1.75)**

Abbreviations: CI, confidence interval; meta-RR, meta-relative risk; RR, relative risk;
[a] In their published reports, meta-RRs and their 95% confidence intervals were rounded to one digit right of the decimal point.
[b] Findings from Model 1, the primary analysis, are reported here.
[c] Random effects model.

1209

Table 8: Key differences between AHS 2005 and AHS 2018, with an emphasis on exposure quantification

1211

	AHS 2005 [19]			AHS 2018 [24]				
Exposure assessment	Self-report at baseline			Self-report at baseline and follow-up questionnaire with exposure simulation[1]				
Exposure quantification	Ever/never	Cumulative exposure days	Intensity-weighted exposure days[2]	Ever/never[3]	Cumulative exposure days[3]	Intensity-weighted exposure days[2]		
Lag period	Unlagged			Unlagged			5-year lag	20-year lag[4]
Exposure groups among exposed (days)[5]	Ever exposed	T1: 1-20; T2: 21-56; T3: 57-2678	T1: 0.1-79.5; T2: 79.6-337.1; T3: 337.2-18,241	Ever exposed	T1: 1-19.9; T2: 20.0-61.9; T3: >62.0	Q1: 1–598.9; Q2: 599–1649.9; Q3: 1650–4339.9; Q4: ≥4340.0	Q1: 1–530.9; Q2: 531.0–1511.9; Q3: 1512.0–4063.4; Q4: ≥4063.5	Q1: 1–281.3; Q2: 281.4–895.9; Q3: 896–2609.9; Q4: ≥2610.0
Exposure duration (years)[6]	Maximum possible range= 20-24;[7] Actual maximum: 7.3[8] Median =*not provided*; IQR = *not provided*			Maximum possible range = 26-32;[9] Actual maximum: *not provided* Median = 8.5; IQR = 5-14			Max. possible range = 21-27;[9] Actual max: *not provided* Median = 4.1;[10] IQR = *not provided*	Max. possible range = 6-12;[9] Actual max: *not provided* Median = 2.5;[10] IQR = *not provided*
Reference group	Unexposed	Lowest exposure tertile	Lowest exposure tertile	Unexposed				
Potential Exposure misclassification	Differential misclassification unlikely; Non-differential misclassification likely			Differential misclassification possible; Non-differential misclassification likely				
Follow-up (years)	Median = 6.7; Maximum possible = 9[11]			Median = *not provided* Maximum possible = 20[11]				
Outcome inclusion	Multiple myeloma (MM) not included in NHL cases			Multiple myeloma (MM) included in NHL cases				

62

1212   [1]*This was referred to as "multiple imputation" by study authors; see manuscript text for further details*

1213   [2]*The algorithm for calculating "intensity-weighted exposure days" was updated between 2005 and 2018. Key differences include rescaling of*
1214   *scores by a factor of 10 and altering the weights for mixing, certain pesticide application techniques, and the use of chemically resistant gloves*
1215   *[44]. Therefore, these metrics cannot be directly compared.*

1216   [3] *Ever/never and cumulative exposure days were only presented in the AHS 2018 supplement but are presented here to facilitate comparisons*
1217   *with AHS 2005*

1218   [4] *Results and quartiles for 10- and 15-year lags are presented in the AHS 2018 supplement*

1219   [5] *Exposure group abbreviations are as follows: Tertiles = "T;" Quartiles = "Q."*

1220   [6]*The values provided in this row are based on the subset of individuals who reported using glyphosate*

1221   [7]*This theoretical maximum duration value was calculated based on the year that glyphosate entered the market (1974) and the end of AHS*
1222   *enrollment (1993-1997), since AHS 2005 used only baseline exposure information*

1223   [8]*This value was calculated based on the upper bound of the cumulative exposure days tertiles*

1224   [9]*These theoretical maximum duration values were calculated based on the year that glyphosate entered the market (1974) and the end of AHS*
1225   *follow-up exposure questionnaire (1999-2005), with the appropriate adjustments for the lag times as indicated.*

1226   [10]*These medians were calculated using the information provided in the footnote in Table 3 of the AHS 2018 publication*

1227   [11]*These follow-up times were calculated based on timing of study enrollment and follow-up*

Table 9. Data from Publically Available Studies of Malignant Lymphomas in Mice Exposed to Glyphosate[a]

Study	Strains	Study Duration	Concentration in Diet (ppm)	Dose (mg/kg/day) EFSA [70]	Dose (mg/kg/day) JMPR [21][c]	Incidence[b] (%) Male	Incidence[b] (%) Female
Wood et al. [73]	CD-1	1.52 years (79 weeks)	0	0	0, 0	0/51 (0)	11/51 (22)
			500	71	71.4, 97.9	1/51 (2)	8/51 (16)
			1500	234	234.2, 299.5	2/51 (4)	10/51 (20)
			5000	810	810, 1081.2	5/51(10)*	11/51 (22)
Kumar [75]	Swiss Albino	1.5 years	0	0	0, 0	10/50 (20)	18/50 (36)
			100	15	14.5, 15.0	15/50 (30)	20/50 (40)
			1000	151	149.7, 151.2	16/50 (32)	19/50 (38)
			10000	1460	1453, 1466.8	19/50 (38)*	25/50 (50)*
Sugimoto [72]	CD-1	1.5 years	0	0	0, 0	2/50 (4)	6/50 (12)
			1600	153	165, 153.2	2/50 (4)	4/50 (8)
			8000	787	838.1, 786.8	0/50 (0)	8/50 (16)
			40000	4116	4348, 4116	6/50 (12)*	7/50 (14)
Atkinson et al. [74]	CD-1	2 years	N/A	0	0	4/50 (8)	14/50 (28)
			N/A	100	100	2/50 (4)	12/50 (24)
			N/A	300	300	1/50 (2)	9/50 (18)
			N/A	1000	1000	6/50 (12)	13/50 (26)
Knezevich and Hogan [71]	CD-1	2 years	0	0	0, 0	2/48 (4)	6[d]/50 (12)
			1000	157	157, 190	5[d]/49 (10)	6/48 (13)
			5000	814	814, 955	4/50 (8)	7[d]/49 (14)
			30000	4841	4841, 5874	2/49 (4)	11[d]/49 (22)
Takahashi [76]	CD-1	1.5 years	0		0, 0		3/50 (6)
			500	N/A	67.6, 93.2	N/A	1/50 (2)
			5000		685, 909		4/50 (8)
			50000		7470, 8690		6/50 (12)*

Abbreviations: N/A, not available.
[a] Data sources: EFSA [70] and JMPR [21] for both males and females.
[b] Number of lymphomas / total mice in group.
[c] Data for male, female mice.
[d] Reported slightly differently in JMPR [21] ($N \pm 1$).
* $p_{trend} < 0.05$ reported by at least one test for trend in EFSA [70] or JMPR [21].
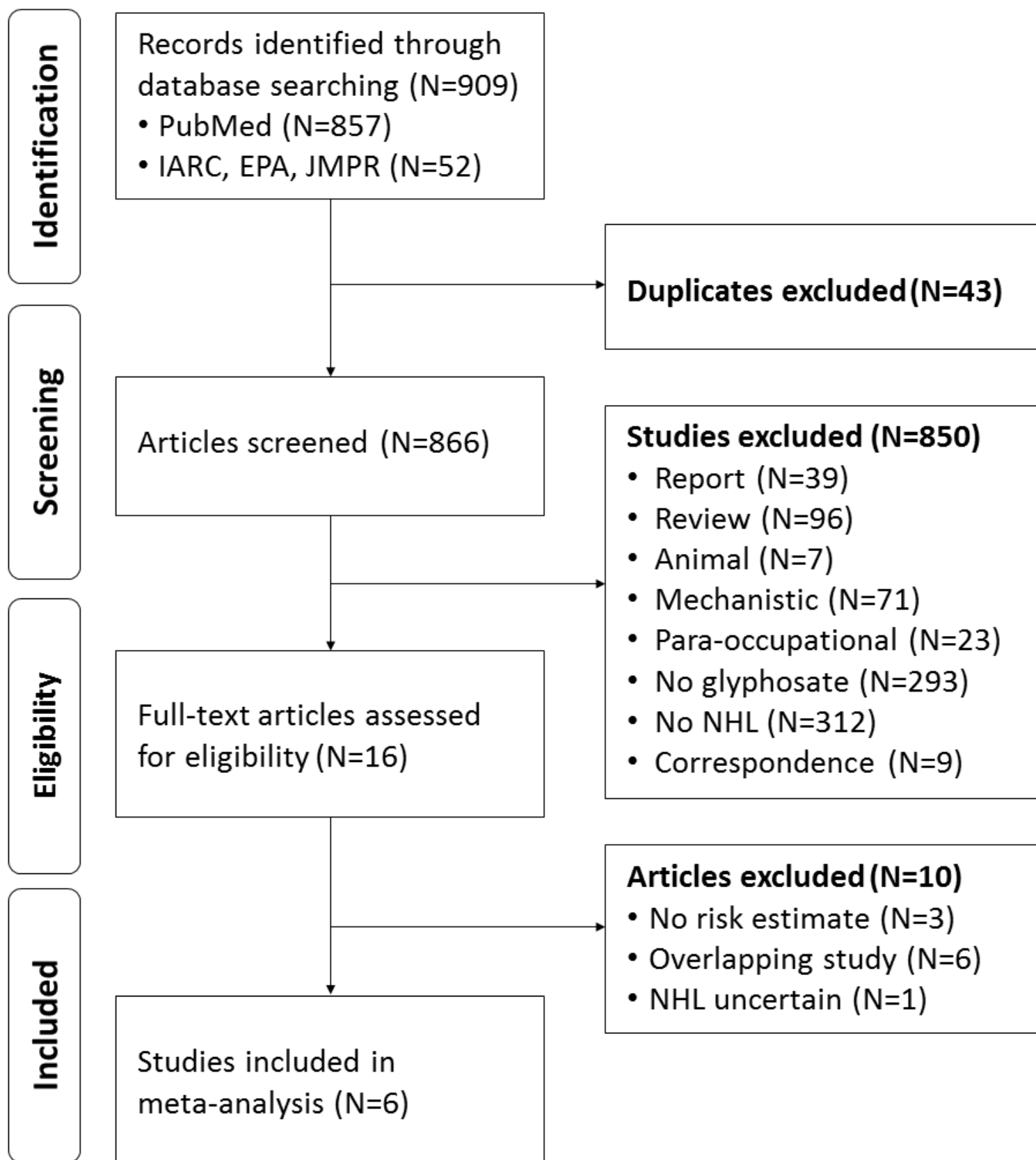
1229

1230 **Figure Captions**

1231

1232 **Figure 1.** Study Selection Process for Meta-Analysis using PRISMA Guidelines.
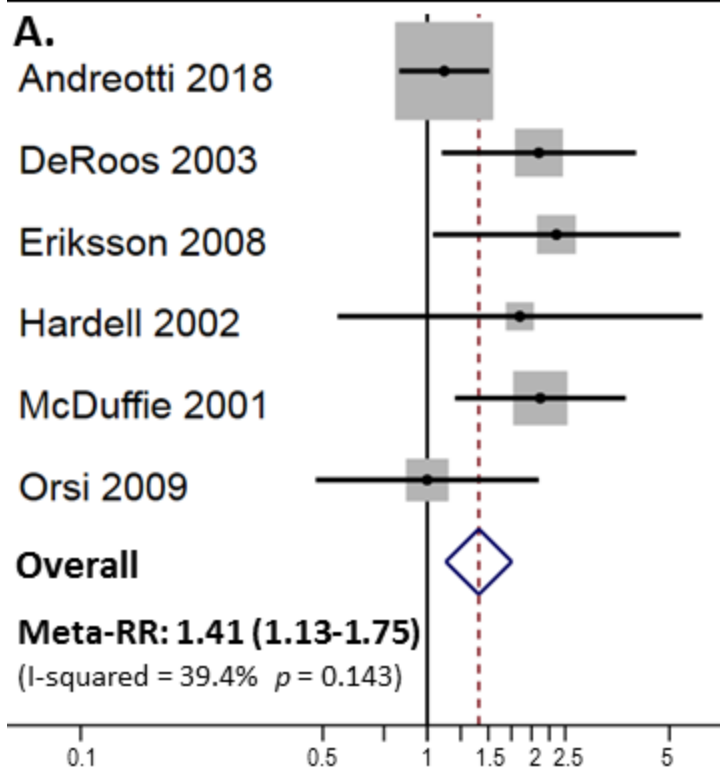
1233 **Figure 2.** Major meta-analysis results. A) Forest plot for meta-analysis using AHS 2018

1234 and B) using AHS 2005. C) Funnel plot for meta-analysis using AHS 2018 and D) using

1235 AHS 2005.

1236 **Figure 3.** Timeline of glyphosate use milestones in relation to cohort and case-control
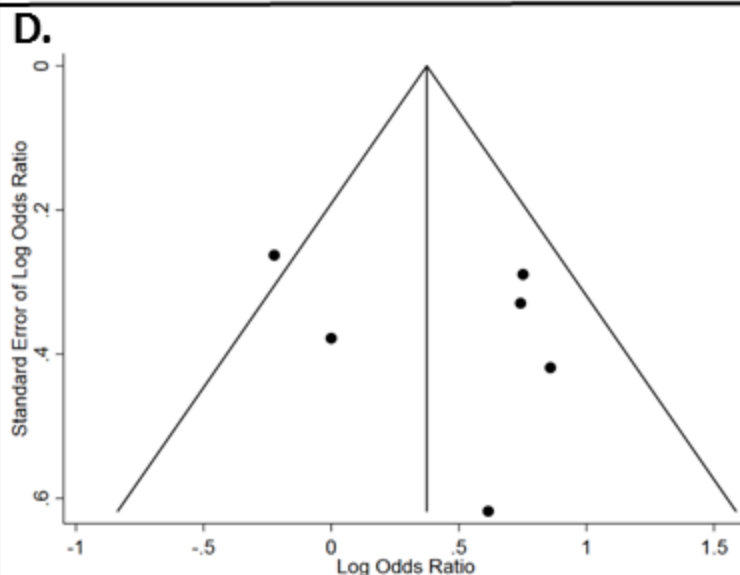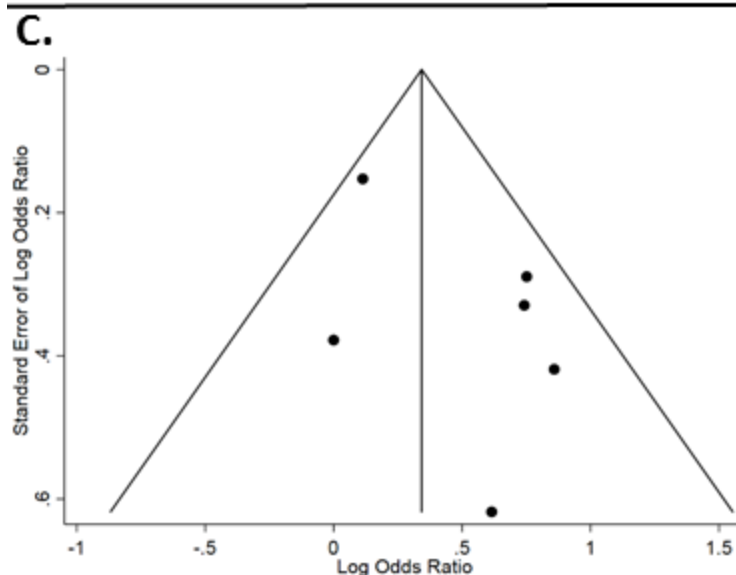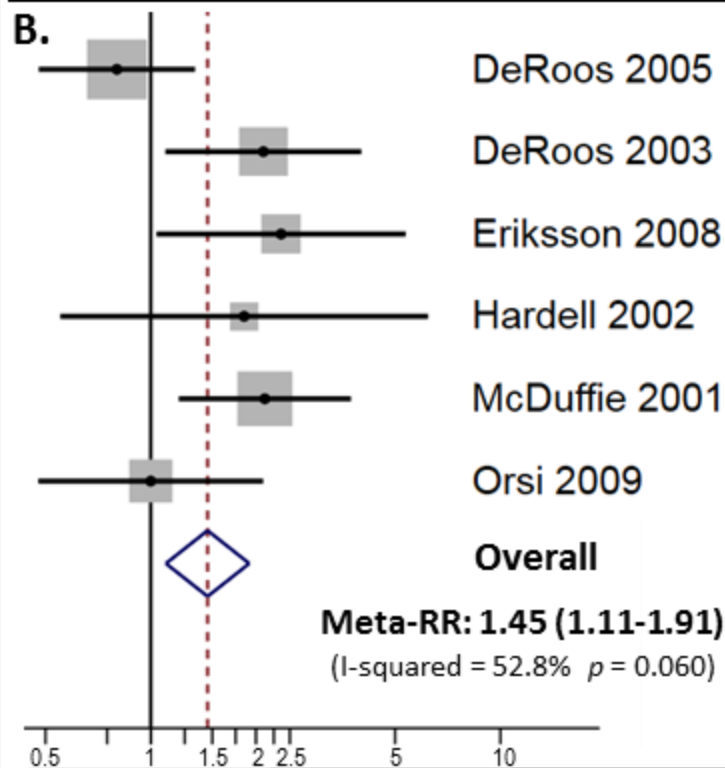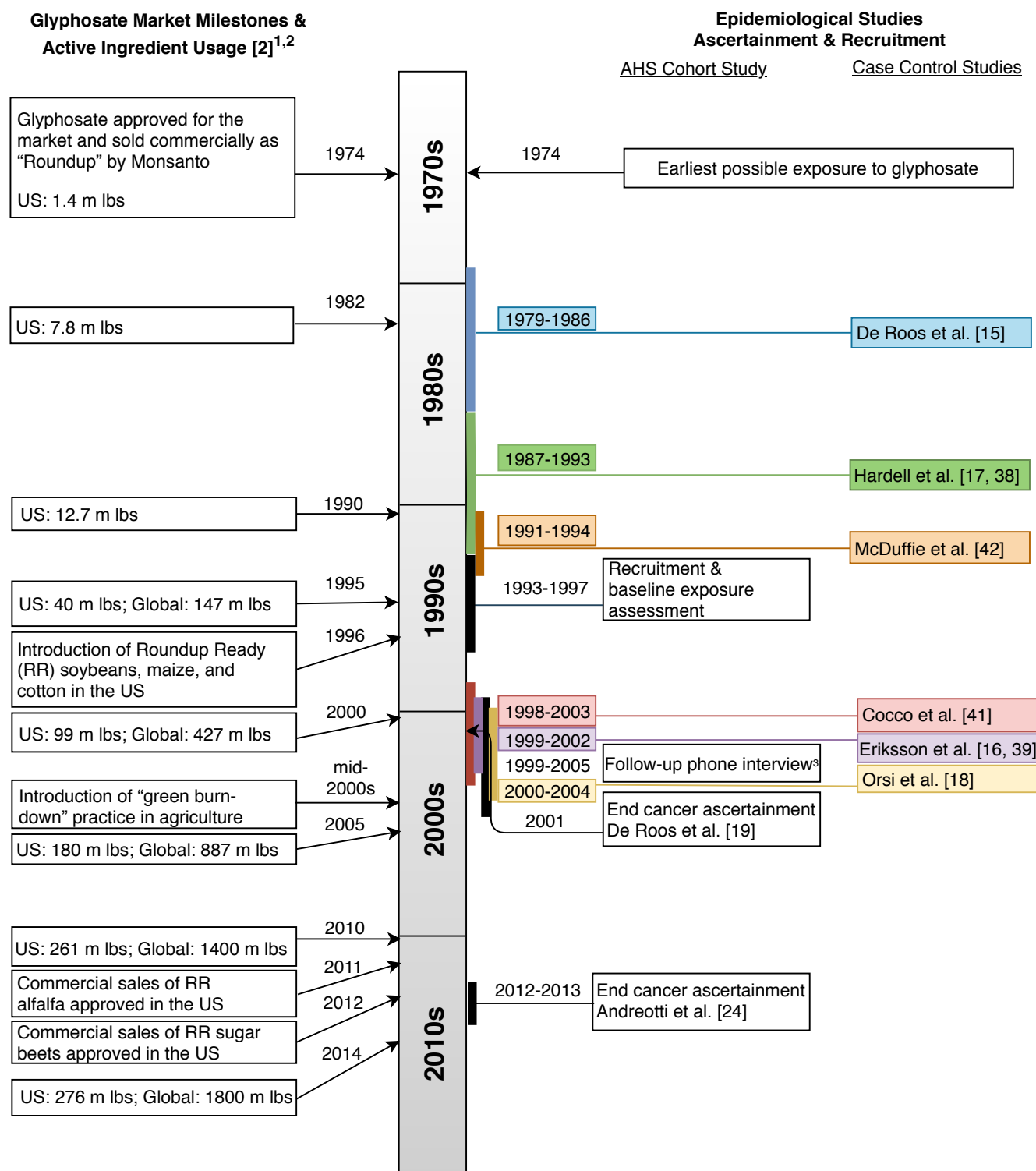
1237 study events.

with AHS 2018

A.

Andreotti 2018

DeRoos 2003

Eriksson 2008

Hardell 2002

McDuffie 2001

Orsi 2009

Overall

Meta-RR: 1.41 (1.13-1.75)
(I-squared = 39.4% *p* = 0.143)

0.1   0.5   1   1.5 2 2.5   5

with AHS 2005

B.

DeRoos 2005

DeRoos 2003

Eriksson 2008

Hardell 2002

McDuffie 2001

Orsi 2009

Overall

Meta-RR: 1.45 (1.11-1.91)
(I-squared = 52.8% *p* = 0.060)

0.5   1   1.5 2 2.5   5   10

C.

Standard Error of Log Odds Ratio

-1   -.5   0   .5   1   1.5
Log Odds Ratio

D.

Standard Error of Log Odds Ratio

-1   -.5   0   .5   1   1.5
Log Odds Ratio

Figure 3: Timeline of glyphosate use milestones in relation to cohort and case-control study events

[1] Glyphosate active ingredient usage includes agricultural and non-agricultural applications
[2] m = millions; lbs = pounds
[3] Completed by 63% of AHS participants

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7-9
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	9-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	9-10
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	9-10
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10-13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-13
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	10-12
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12-13
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13-14