Regulatory Toxicology and Pharmacology 63 (2012) 440–452

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Epidemiologic studies of glyphosate and cancer: A review

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ARTICLE INFO

Article history:
Received 3 July 2011
Available online 7 June 2012

Keywords:
Cancer
Glyphosate
Herbicides
Epidemiology

ABSTRACT

The United States Environmental Protection Agency and other regulatory agencies around the world have registered glyphosate as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential, based primarily on results of carcinogenicity studies of rats and mice. To examine potential cancer risks in humans, we reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. We also reviewed relevant methodological and biomonitoring studies of glyphosate. Seven cohort studies and fourteen case-control studies examined the association between glyphosate and one or more cancer outcomes. Our review found no consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or children) or any site-specific cancer and exposure to glyphosate. Data from biomonitoring studies underscore the importance of exposure assessment in epidemiologic studies, and indicate that studies should incorporate not only duration and frequency of pesticide use, but also type of pesticide formulation. Because generic exposure assessments likely lead to exposure misclassification, it is recommended that exposure algorithms be validated with biomonitoring data.

1. Introduction

Glyphosate(N-phosphonomethyl glycine; CAS registry #38641-94-0) is the primary active ingredient in Roundup-branded herbicides produced by the Monsanto Company. The United States (US) Environmental Protection Agency (EPA) and other regulatory agencies around the world have registered this chemical as a broad-spectrum herbicide for use on multiple food and non-food use crops. Glyphosate-based herbicides, which have been sold in the US since 1974 and marketed under the brand names Roundup®, Roundup Pro®, Roundup PowerMAX™, Roundup WeatherMAX®, and AquaMaster®, are now registered in over 130 countries to control annual and perennial weeds, woody brush, and trees in agricultural, industrial, forestry, greenhouse, rights-of-way and residential areas. Other brands and manufacturers of glyphosate products include but are not limited to Glyfos® (Cheminova), Durango® DMA® (Dow AgroSciences), and Touchdown HiTech® (Syngenta). In the US, glyphosate (isopropylamine salt) herbicides were applied to 31% of all planted corn acres in 2005 (USDA, 2006) and 92% of all planted soybean acres in 2006 (USDA, 2007).

Glyphosate is widely considered by regulatory authorities and scientific bodies to have no carcinogenic potential (EC, 2002; US EPA, 1993; WHO/FAO, 2004). US EPA has classified glyphosate as a Group E carcinogen, which is defined as having "evidence of non-carcinogenicity for humans" (US EPA, 1993). This classification was based on "a lack of convincing evidence of carcinogenicity in adequate studies with two animal species, rat and mouse" (US EPA, 1993). Negative results were observed in genotoxicity studies conducted under good laboratory practice conditions and compliant with current regulatory test guidelines (Williams et al., 2000). It was concluded that, in the absence of carcinogenic potential in animals and given the lack of genotoxicity in standard tests, glyphosate is unlikely to pose a carcinogenic risk to humans (WHO/FAO, 2004; Williams et al., 2000). In addition, US EPA has concluded that there is a reasonable certainty that no harm will result to the general population or to infants and children from

Abbreviations: AHS, Agricultural Health Study; CAS, Chemical Abstract Service; CI, confidence interval; FFES, Farm Family Exposure Study; HCL, hairy cell leukemia; IARC, International Agency for Research on Cancer; MGUS, monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin lymphoma; OR, odds ratio; RR, relative risk; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukemia; US EPA, United States Environmental Protection Agency.

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http://dx.doi.org/10.1016/j.yrtph.2012.05.012

aggregate exposure to residues of glyphosate (US EPA, 2007). Nevertheless, there has been no published comprehensive review of the epidemiologic research on this topic.

We reviewed epidemiologic cohort and case-control studies of glyphosate and cancer to evaluate whether exposure to glyphosate is associated causally with risk of developing cancer in humans. In addition, we reviewed methodological and biomonitoring studies of glyphosate to allow for a more comprehensive discussion of issues related to exposure assessment (including exposure misclassification and information bias) and other interpretation issues as they relate to findings from the epidemiologic studies. We did not consider it appropriate to calculate quantitative summary relative risk estimates across studies evaluating different site-specific cancers (e.g., breast cancer, brain cancer, esophageal cancer, etc.), and therefore did not conduct a meta-analysis.

2. Methods

Studies were included in our review if they met the following criteria: (1) published in a peer-reviewed journal; (2) English language; (3) analytic epidemiologic studies (e.g., cohort, case-control) that evaluated the association between glyphosate and a cancer outcome(s). Analyses of more general categories of "pesticides" or "herbicides" did not meet our criteria. Studies of poisonings or other acute effects of glyphosate were not included.

Multiple search strategies were employed to identify literature related to glyphosate exposure and human cancer outcomes. A PubMed search was conducted using the term "glyphosate," as well as its synonyms, chemical name, and Chemical Abstract Service (CAS) number, in conjunction with various terms related to epidemiology studies (e.g., "cohort," "case-control"). In addition, broader searches for articles regarding epidemiologic studies of organophosphorus compounds used as pesticides or herbicides were conducted, as well as a search for case-control studies of pesticides or herbicides.

A separate search was conducted using the STN search service index, which searches multiple databases simultaneously, including Biosis, EMBASE, Medline, Pascal, and SciSearch. The CAS registry number for glyphosate was searched in combination with epidemiologic terms.

After duplicates were removed, abstracts were reviewed to determine if they met the inclusion criteria. Articles meeting the inclusion criteria were then obtained and reviewed.

Literature searches to identify biomonitoring studies of glyphosate were also performed using PubMed. We searched on the terms "glyphosate" and "Round up OR Roundup" in separate searches. Both searches also included the term "biomonitoring" as well as related terms including "sample," "urine," and "blood." Abstracts identified from these searches were reviewed. For all articles of interest, the "related articles" identified by PubMed were also reviewed. All relevant articles were obtained.

For completeness, we examined the reference sections of the primary epidemiology and biomonitoring publications for additional articles that may not have been identified by the PubMed searches.

3. Results

3.1. Cohort studies

Seven "cohort studies" evaluated the association between glyphosate and cancer (see Table 1). All of these analyses were conducted among participants or family members of the Agricultural Health Study (AHS) cohort. We will describe these as separate "studies" but they are really separate analyses and publications from the same cohort study. One study evaluated multiple pesticides and multiple cancer sites in children (Flower et al., 2004), one study examined glyphosate and multiple cancer sites (De Roos et al., 2005), and five studies evaluated multiple pesticides and site-specific cancers, including prostate (Alavanja et al., 2003), breast (Engel et al., 2005), colon/rectum (Lee et al., 2007), pancreas (Andreotti et al., 2009), and cutaneous melanoma (Dennis et al., 2010). There is some overlap between the cases and person-time reported in the De Roos et al. (2005) analyses of multiple cancer sites and analyses of cancers of the prostate (Alavanja et al., 2003), colon/rectum (Lee et al., 2007), pancreas (Andreotti et al., 2009), and cutaneous melanoma (Dennis et al., 2010) in the AHS. Calendar years of follow-up for each study are shown in Table 1. The AHS is a prospective study of private and commercial applicators in Iowa and North Carolina. Participants were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire.

Results of the cohort studies reporting data on glyphosate and cancer are shown in Table 2. Flower et al. (2004) evaluated associations between pesticide application by parents and cancer among children born to Iowa participants in the AHS. Female applicators and spouses of male applicators were asked to complete a questionnaire to collect data on children born after 1975. This information was used to conduct a linkage with the Iowa Cancer Registry to identify cases of cancer among children age 19 and younger, diagnosed between 1975 and 1998. The linkage identified 50 cases of childhood cancer. Exposure to glyphosate was determined by self-reported responses to questionnaires completed by applicators and spouses. There was no positive association between either maternal (odds ratio [OR] = 0.61; 95% confidence interval [CI]: 0.32–1.16) or paternal (OR = 0.84; 95% CI: 0.35–2.34) use of glyphosate and risk of childhood cancer.

De Roos et al. (2005) evaluated associations between glyphosate exposure and incidence of total and specific cancers in the AHS. There was no statistically significant association between glyphosate and "all cancers" or any cancer site in analyses of ever- versus never-exposed to glyphosate, in analyses of tertiles of cumulative exposure days of glyphosate exposure, or in analyses of tertiles of intensity-weighted exposure days. Results for analyses of tertiles were reported for the models that excluded never-exposed participants and used the lowest-exposed category as the reference group. Intensity levels were estimated based on questionnaire responses using the following algorithm: intensity level = [(mixing status + application method + equipment repair status) × personal protective equipment use] (De Roos et al., 2005). The authors stated that they considered p-values less than 0.10 as being indicative of a trend. There were two p-values that met this criterion, but neither corresponded to monotonic positive patterns of association. In the intensity-weighted analysis of glyphosate and lung cancer, the relative risk for the highest tertile was 0.6 (95% CI: 0.3–1.0) and the corresponding p-value for trend was 0.02. For similar analyses of pancreatic cancer, the relative risk in the highest tertile was 0.5 (95% CI: 0.1–1.9) and the p-value for trend was 0.06. The corresponding relative risk for multiple myeloma was 2.1, but the corresponding 95% confidence interval was wide (0.6–7.0), and the p-value for trend was above the 0.10 threshold ($p = 0.17$). De Roos et al. also reported results of secondary analyses of multiple myeloma using "never exposed" to glyphosate as the referent; the relative risk for the highest tertile was higher but less precise (RR = 4.4; 95% CI: 1.0–20.2) than in analyses using the lowest tertile as the referent. Thus, there was