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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	**ADMINISTRATIVE MOTION TO FILE UNDER SEAL**

Pursuant to Civil Local Rules 79-5 and 7-11 and the Amended Protective and Confidentiality Order entered by the Court on September 6, 2017 ("Amended Protective Order"), Plaintiffs hereby submit this Administrative Motion to File Under Seal. Pursuant to the Amended Protective Order, "[w]hen a Party wishes to use a document that has been designated as confidential in support of a motion or other filing with the court, it will move the Court to file the document under seal pursuant to Civil Local Rule 79-5…." *See* Amended Protective Order, ¶ 18.

I. Plaintiffs Conditionally Lodge Under Seal Document Designated as Confidential by Defendant Monsanto Company.

Pursuant to Civil Local Rule 79-5(e), Plaintiffs hereby notify the Court that they have conditionally filed under seal a document which has been designated Confidential by Monsanto

Company, or which contains or references information so designated. Specifically, Plaintiffs have conditionally filed under seal Exhibit No. 50 – part 2, which was originally and incorrectly filed as ECF No. 651-3, to their Opposition to Monsanto Company's *Daubert* and Summary Judgment Motion and in Support of Plaintiffs' *Daubert* Motion. Pursuant to the Amended Protective Order, "the designating party will have 10 court days to file the responsive declarations required by Civil Local Rule 79-5(e) ." *See* Amended Protective Order, ¶ 18.

This application is also based on the information set forth in the Declaration of Aimee H. Wagstaff in Support of this Administrative Motion to File Under Seal, filed concurrently herewith.

Dated: November 1, 2017

/s/ Aimee Wagstaff

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For MDL 2741

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

DATED: November 1, 2017

/s/ Aimee Wagstaff
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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	**WAGSTAFF DECLARATION IN SUPPORT OF ADMINISTRATIVE MOTION TO FILE UNDER SEAL**

I, Aimee H. Wagstaff, declare:

1. I am a member of the executive committee of MDL 2741. I make this declaration in support of Plaintiffs' Administrative Motion to File Under Seal filed on November 1, 2017. I have personal knowledge of the facts stated herein and, if called as a witness, I could and would competently testify thereto.

2. Plaintiffs have filed conditionally under seal Exhibit No. 50 – part 2 as this document contains or references material and information designated Confidential by Monsanto. This document was originally and incorrectly filed as ECF No. 651-3 and should have been lodged under seal.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 1st day of November, 2017.

/s/ Aimee H. Wagstaff

Aimee H. Wagstaff

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

DATED: November 1, 2017

/s/ Aimee Wagstaff

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UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

SAN FRANCISCO DIVISION

IN RE ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741
This Document Relates To All Actions	**[PROPOSED] ORDER REGARDING ADMINISTRATIVE MOTION TO FILE UNDER SEAL**

Having reviewed Plaintiffs' Administrative Motion to File Under Seal and the Declaration of Aimee H. Wagstaff in support thereof, the Court ORDERS that:

Plaintiffs' Exhibit 50 – part 2 to their Opposition to Monsanto Company's *Daubert* and Summary Judgment Motion and in Support of Plaintiffs' *Daubert* Motion shall remain filed conditionally under seal for ten (10) days after the date they were originally filed conditionally under seal, pursuant to the Amended Protective and Confidentiality Order in this case and Civil Local Rule 79-5(e).

Dated:_____

_____
Hon. Vince Chhabria
Judge of the United States District Court

EXHIBIT 50

(Part 2)

Human and Ecological Risk Assessment: Vol. 6, No. 1, pp. 47-71 (2000)

The Federal Government's Agricultural Health Study: A Critical Review with Suggested Improvements

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ABSTRACT

The Agricultural Health Study (AHS) has approximately 90,000 pesticide applicators and their spouses enrolled in a number of studies to determine whether exposures to specific pesticides are associated with various cancers and other adverse health outcomes. Although the AHS was intended to be an integrated program of studies, some significant difficulties have emerged. In this report, we examine the design of the AHS, identify important program strengths and flaws, suggest various improvements in the program, and recommend ancillary studies that could be undertaken to strengthen the AHS.

Overall, the AHS is collecting a large amount of information on potential determinants of health status among farmers and farm families. A promising feature of

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1080-7039/00/$.50

the AHS is the prospective cohort study of cancers among farmers in which the research design determines exposures prior to the diagnosis of disease. More effort needs to be devoted to reducing selection bias and information bias. Success of the cohort study will depend in part on follow-up surveys of the cohort to determine how exposures and disease states change as the cohort ages. The cross-sectional and case-control studies planned in the AHS are less promising because they will be subject to some of the same criticisms, such as potentially biased and imprecise exposure assessment, that have characterized the existing literature in this field.

Important limitations of the AHS include low and variable rates of subject response to administered surveys, concerns about the validity of some self-reported non-cancer health outcomes, limited understanding of the reliability and validity of self-reporting of chemical use, an insufficient program of biological monitoring to validate the exposure surrogates employed in the AHS questionnaires, possible confounding by unmeasured, nonchemical risk factors for disease, and the absence of detailed plans for data analysis and interpretation that include explicit, *a priori* hypotheses. Although the AHS is already well underway, most of these limitations can be addressed by the investigators if adequate resources are made available. If these limitations are not addressed, the large amounts of data generated in the AHS will be difficult to interpret. If the exposure and health data can be validated, the scientific value of the AHS should be substantial and enduring.

A variety of research recommendations are made to strengthen the AHS. They include reliability and validity studies of farmer reporting of chemical use, biological monitoring studies of farmers and members of farm families, and validity studies of positive and negative self-reports of disease status. Both industry and government should consider expanded research programs to strengthen the AHS.

Key Words: epidemiology, pesticides, farmworkers, health effects

INTRODUCTION

The Agricultural Health Study (AHS) was launched in 1993 by scientists at the National Cancer Institute, the National Institute of Environmental Health Sciences, and the Environmental Protection Agency. The primary impetus for the study is a concern that exposures to chemicals on the farm, particularly certain fungicides, insecticides, and herbicides, may be responsible for a variety of adverse health effects, including cancer, neurological damage, reproductive problems, immunologic defects, nonmalignant respiratory disease, kidney disease, and impairments to the growth and development of children (Alavanja *et al.*, 1996).

As a result of this concern, just over 90,000 farmers, commercial applicators of farm chemicals, and their families in two states, Iowa and North Carolina, have been enrolled in a long-term health study. Most of the data in the study are being obtained from farmers through self-administered questionnaires and telephone interviews. Numerous questions were already asked of enrollees regarding their experiences as a farmer, their patterns of chemical use, their lifestyles, and their current health status. For some diseases, such as cancer, some of the future health information about enrollees will be obtained from state-wide registries.

The AHS is not a single study. Although the population of primary interest is the farmers ("private applicators"), there will also be studies of the health of commercial applicators and the spouses and children of private applicators. The AHS includes studies with at least four different designs and makes use of a variety of data sources.

First, the main prospective cohort study is expected to follow the 90,000 enrollees for many years or until death, to determine whether use of particular chemicals or other features of the farm environment and personal behavior are associated with poor health outcomes. This main study will not be completed until sufficient numbers of the cancers of interest have occurred or, ultimately, until most of the enrollees have died and the collected data on health outcomes have been fully analyzed. Interim reports on the cohort can be expected when the frequency of specific health problems supports a quantitative analysis of the factors associated with these health outcomes. An important design feature of the main cohort study is that much of the information on chemical use is obtained from farmers via survey methods *prior to the diagnosis of disease.* Although some enrollees had chronic diseases when they entered the study, the AHS investigators should consider analyzing the data with and without inclusion of these prevalent cases of disease.

Second, cross-sectional studies are being undertaken to determine the prevalence of certain noncancer health outcomes among farmers and farm families. The three initial cross-sectional studies are investigating (1) history of spontaneous abortion, menstrual function, and fertility in young women; (2) menopausal states, reproductive history, and selected chronic diseases in older women; and (3) neurologic symptoms and visual impairment in farmer-applicators. A cross-sectional design entails comparing the prevalence of reported adverse health outcomes with the reported use of or exposure to specific chemicals. Telephone interviews of subsamples of the cohort are being used to compare those people who responded to take-home questionnaires and those who did not as well as to obtain the information to augment the cross-sectional studies of non-cancer health outcomes (Sandler, 1998).

Third, nested case-control studies are planned for a variety of diseases including non-Hodgkin's lymphoma, leukemia, and cancers of the prostate, brain, ovary, breast, lung, colon, and stomach (Agricultural Health Study, 1993). Farmers in the cohort who develop a particular disease will be compared with controls selected from the cohort. Unlike the main cohort study, the nested case-control studies may entail obtaining some information from farmers or next of kin after a disease has been diagnosed. The investigators will examine whether cases report greater use of agricultural chemicals than selected controls. Cases and controls may also be invited to complete more detailed questionnaires aimed at obtaining a better understanding of possible differences in their exposure to a variety of farm and nonfarm factors.

Finally, some effort is being undertaken to determine how much farmers and their families have been exposed to selected chemicals. Biological monitoring, which typically entails the collection and analysis of urine and/or blood samples for multiple chemicals, is expensive. Biomonitoring was originally proposed to take place at 200 farms. Pilot studies found low participation rates (about 23%) and higher costs than anticipated and thus the program of exposure assessment has been scaled back. The current experimental design calls for samples to be gathered

from people at 125 farms, but unexpected obstacles have surfaced in obtaining funds for even this reduced program of biological monitoring.

The design and implementation of any research program as large and complex as the AHS requires many tradeoffs and compromises. Not every analyst would make the same choices, but on the whole we commend the AHS investigators for making a variety of sound choices in the face of limited resources and a complex challenge. As we emphasize below, we are particularly enthusiastic about the prospective cohort study of cancer outcomes because it responds directly to some of the methodological weaknesses of prior epidemiologic studies of farmers and pesticides. Other aspects of the AHS, such as the cross-sectional studies of disease prevalence, have serious problems. In this report we focus on what the strengths and limitations of the various AHS studies are, how the AHS can be improved, and what steps can be taken by the government and industry to enhance what is being done in the AHS through complementary efforts.

Information about the AHS used in this review was obtained primarily from publicly available documents and information presented at the AHS's annual public Advisory Panel meetings.[1] We recognize that more detailed plans may have been made but are not publicly distributed. Although the cohort has already been defined and enrolled in the study, numerous decisions have yet to be made about how the data will be analyzed and how future surveys of the cohort will be refined and improved. Thus, the emphasis in our report is on two issues: those that can be addressed by the principal investigators of the AHS through expansions or modifications of the workplan and those that need to be understood as inherent limitations when the findings of studies are published and disseminated.

The report is organized as follows. Section 1 addresses "Data Sources, Response Rates and Data Quality". Sections 2 and 3 address "Pesticide Exposure" and "Pesticide Use", respectively. Section 4 examines "Risk Factors Other Than Pesticides". In Sections 5 and 6 we examine the "Study Design Issues" and "Data Analysis Plans". Section 7 summarizes our recommendations on how the study can be improved and what additional studies can be undertaken to advance the field.

DATA SOURCES, RESPONSE RATES, AND DATA QUALITY

The AHS includes four types of data that could play important roles in epidemiologic analyses: health outcome data, pesticide use and exposure data, and data on potential confounders (risk factors) for disease. In this section, possible limitations in the scope or quality of each type of data are identified, and we present some suggestions aimed at enhancing data quality. Since most of the data used in the study are based on surveys of farmers and members of farm families, we begin with a discussion of the response rates obtained for the AHS questionnaires (Tarone *et al.*, 1997).

Response Rates to Questionnaires

The target population for the AHS is all persons required by the states of Iowa and North Carolina to obtain a pesticide applicator license. This includes "private"

applicators (farmers) and "commercial" applicators. Both states require periodic retraining to maintain a license for either type of pesticide applicator. The enrollment questionnaire was given to all attendees at training courses in the two states over a 3-year period. A 3-year cycle for licenses assured that all users had a chance to enroll. In January, 1997, enrollment through training classes was completed.

Not all applicators at training sessions agreed to participate. Some special recruitment efforts were undertaken to increase participation rates. In Iowa, the response rate for the enrollment questionnaire was 81.9% for private applicators and 42.2% for commercial applicators. In North Carolina, 84.8% of private applicators enrolled and the study design did not include commercial applicators. Overall, enrollment questionnaire data are available from about 53,000 private applicators and 5,000 commercial applicators (out of about 76,000 possible). Questionnaire data have also been collected from about 32,000 spouses of farmers (about 73% of those eligible).[2]

After pesticide applicators filled out the enrollment questionnaire at the training session, they were given three supplemental questionnaires (applicator; spouse; female and family health) to complete at home and return. The AHS uses the supplemental questionnaires to enroll spouses and other family members. The response rates for the supplemental questionnaires are low. Overall, about 44% of *enrolled* applicators completed and returned the additional questionnaire (33.5% of all eligible applicators). The Spouse Questionnaire, or a telephone administered version, was completed by 73% of eligible spouses. The Female/Family Health questionnaire was returned by about 39% of female applicators or spouses of enrolled farmers (64.6% of enrolled spouses).

The questionnaires are the primary source of data for the AHS. The enrollment questionnaire, which is used to define membership in the cohort, gathers personal identifiers on the applicator and his or her spouse. It also asks about work on and off of the farm, frequency of use of 22 pesticide compounds (*e.g.*, ever/never used and frequency of application) and ever/never used information on 28 more, one question about application methods and another about protective equipment, whether a doctor has ever diagnosed any of 16 diseases, and several questions on some lifestyle activities (including smoking) and the specific crops or livestock raised on the farm. These data are available for all applicators in the cohort except when there are missing responses.

The supplemental questionnaires are intended to gather more detailed information from the applicator and his or her spouse about pesticide use, family history of cancer, personal history of infectious and chronic diseases, over-the-counter medicine use, and diet. The Spouse Questionnaire, for the wife or husband of the applicator, asks for information about pesticide use and farm activities, along with information about factors such as laundering and vacuuming and information about the home that might influence pesticide exposure. Information about dietary and cooking practices is also collected. A self-reported medical history elicited from each subject includes about 55 diseases or disease symptoms. The Female and Family Health questionnaire is intended for female applicators or female spouses of pesticide applicators. This questionnaire collects information about the woman's reproductive cycle, pregnancies, and children. Identifiers, birthweight, nursing history, and whether the child ever worked on a farm are recorded for each child.

The low and variable response rates to the supplemental questionnaires seriously affect the quality of the AHS. Steps have been taken to increase response rates but the rate of non-response remains substantial. We encourage more efforts to increase the response rate, to reduce the potential for selection bias and increase statistical power. An evaluation of the potential for selection bias to influence risk estimates should be undertaken.

In the prospective cohort study, low response rates to questionnaires designed to obtain information on subject identifiers, exposures, and baseline disease status will clearly diminish statistical power and may create bias. The success of the cohort study also depends upon acceptable response rates to future follow-up surveys of the cohort. Periodic follow-up surveys are necessary to determine how exposures and disease states change as the cohort ages, thereby maintaining the prospective character of the study. If low response rates occur with the follow-up questionnaires, the potential for bias will increase, partly from misclassification of subjects (and person-years) with regard to chemical exposure and partly from residual confounding stemming from inaccurate measurement of risk factors other than pesticides. According to the AHS protocol (Agricultural Health Study, 1993), follow-up questionnaires will be administered every 5 years. Since no follow-up has yet been administered, response rates are unknown.

Selection bias should be reduced in the prospective cohort study if persons who already have the disease(s) of interest are identified and excluded from the cohort at the beginning. Identification of diseases diagnosed at the time of enrollment into the cohort may be done well for conditions, such as some cancers, that have an easily defined point of diagnosis but is more difficult for certain neurological conditions and for renal, respiratory, and cardiovascular diseases. For instance, bias will occur if persons who are at risk of cancer and are exposed are more likely to participate by returning questionnaires. There are plans for cohort studies of kidney, neurologic, respiratory and cardiovascular disease that might be biased by the erroneous inclusion of subjects with disease onset before enrollment, if the probability of study participation depends on exposure status. Furthermore, if response rates are low for questionnaires designed to obtain information on medical conditions occurring during the follow-up period, the likelihood of bias is high.

In cross-sectional and case-control studies, low response rates have most of the same potentially detrimental effects on precision and accuracy as mentioned above. In addition, poor response raises the likelihood that selection bias will occur because it is likely that participation will depend both on exposure status and on "disease" status in a manner that could bias estimates of prevalence ratios or odds ratios (*e.g.*, through underrepresentation of exposed persons without disease).

Health Outcomes

Accurate ascertainment of the presence or absence of disease among farmers and members of farm families is critical to the success of the AHS. Some of the diseases of interest in the study are relatively rare and only a small number of cases of these diseases can be expected. Thus, it is appropriate to consider the quality of the health-outcome data being collected in the AHS, looking at the potential for both false-positive and false-negative errors.

Cancer

The statewide cancer registries in Iowa and North Carolina will be used by the AHS investigators to determine which subjects develop various types of cancer. The Iowa registry is well established and is believed to provide accurate and reasonably complete data on incidence of cancer in the state. The North Carolina registry is newer but should provide data of sufficient accuracy.

Use of the cancer registries will be hampered if personal identifiers such as name, birth date, Social Security number, and gender are not available from both the cancer registries and the AHS cohort. Such identifiers are critical to linking subjects in the AHS cohort to registry records. In February 1997 it was reported that in Iowa the four identifiers mentioned above were available for 94.0% of commercial applicators, 86.3% of private applicators, and 53.4% of enrolled spouses of married private applicators. In North Carolina the four identifiers were available for 86.6% of private applicators and 76.5% of spouses. Linkage with registries may be acceptable with current identifiers but AHS investigators are making efforts to increase the completeness and quality of data needed for record linkage. There are other ways to determine whether enrollees have developed cancer, but they are generally more expensive.

Non-Cancer Health Outcomes

Mortality from kidney, neurologic, respiratory, cardiovascular, and other diseases can also be assessed through objective measures that do not entail self-reporting by subjects in the cohort. For example, mortality from specific causes can be monitored through periodic follow-up through the National Death Index and state and local vital statistics records. Yet even for data from objective sources, potential validity problems need to be identified and addressed.

In order to accelerate the opportunity to cover a wide range of non-cancer outcomes, the AHS relies on self-reporting of health states by farmers and members of farm families on both the enrollment and supplemental questionnaires. The self-reporting occurs either through return of written questionnaires or responses to telephone interviews. Telephone surveys of special subgroups of the cohort are being employed to reduce the potential for selection bias in the cross-sectional studies, but it is possible for a modest amount of selection bias to have a substantial effect on results. Diseases of particular interest to the AHS investigators include kidney disease, neurotoxicity and neurological disease, reproductive and developmental impairments, and immunologic effects. Several questions ask about possible acute toxicity episodes associated with pesticide use.

Section IV of the main enrollment questionnaire has two questions regarding health. Question #28 inquires whether "a doctor has ever told you that you had any of the following conditions": A list of 16 conditions is supplied (asthma, tuberculosis, other chronic lung disease, pneumonia, melanoma of skin, other skin cancer, leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, other cancer, heart disease, diabetes, Parkinson's disease, kidney disease, nervous disorder, and depression), each to be answered yes or no. For the cancer outcomes, it will ultimately be

feasible to compare the self-reports of subjects to the data obtained through the statewide cancer registries. A strategy for addressing discordant data is needed.

Question #29 inquires whether "your parents, brothers, sisters, or children related to you by blood ever had any of the following?" A list of 14 conditions is supplied, again with yes or no responses. If the subject has multiple blood relatives, the implicit understanding is that the question refers to any of them.

In addition to these questions about diseases, questions #14 and #15 provide additional information about acute health effects that may be related to pesticides. These questions do not ask about a medical diagnosis, and no effort is being made to validate the answers.

Question #14 asks "How often, if ever, have you had the following symptoms that you think may be related to your using pesticides?" There are seven listed symptoms: "been excessively tired", "had headaches/dizziness", "had nausea or vomiting", "had skin irritation", "had eye irritation", "had chest discomfort", and "felt nervous or depressed". For each symptom, the respondent is asked to respond on a scale of never/rarely, sometimes, frequently, almost always. This set of questions seems to combine elements of symptom frequency and causal attribution. It is not clear how the respondent is expected to judge whether such symptoms were "related to your using pesticides" unless the effects were immediate and unambiguous. It may be preferable to ask separate questions about the frequency of these symptoms and the respondent's view about whether they are associated with pesticide use, although questions about validity might remain. It is also not clear what would be meant by "frequently/almost always", since no frequency context is suggested to the respondent. The response may represent symptom frequency in absolute terms or as a percentage of the total number of pesticide applications. Given the ambiguous nature of this question, the meaning of the information that is elicited will be uncertain.

Question #15 asks subjects: "As a result of USING PESTICIDES (emphasis in original), how often have you: a. seen a doctor, b. been hospitalized." The possible responses are never, once, twice, or three or more times. Again, this question presumes that the respondent knows something about the causative role of pesticides in particular situations, perhaps because he or she experiences unusual symptoms in short order after the chemical is applied. Some visits may be after exposure but before symptoms appear. In ambiguous situations involving common symptoms and longer time lags, the respondent may not realize that the chemical exposure was responsible for the symptom or may attribute to the chemical a symptom that was not caused by the exposure. If the question is intended to provide a surrogate measure of exposure to chemicals, it needs to be used with caution if it is used at all.

Although there is limited information on noncancer health outcomes in the main enrollment questionnaire, the supplemental questionnaire includes a fairly detailed self-reported "medical history" from each subject. The low overall rate of response to the supplemental questionnaire, despite efforts to increase response, will prevent full understanding of the cohort's exposure and health states.

Questions #87 through #102 in the supplemental questionnaire ask about numerous aspects of the applicator's health status. For example, Question #87 asks about

each of 41 listed diagnoses (*i.e.*, whether a doctor has ever told the subject that he or she has that condition). Question #90 asks how frequently, during the last 12 months, the subject has experienced each in a list of 23 symptoms ranging from dizziness and headaches to feeling tense or depressed. Questions #96 through #102 focus on the respondent's vision and use of eyeglasses. Responses to these questions need to be validated.

It may be that any biases will cancel out because potential cases and non-cases interpret questions in roughly the same manner, as may be expected in a prospective cohort study, but it will be very difficult to know for sure the overall or net impact of any resulting biases.

Applicators who are women, and the spouses of male applicators, are also asked to complete a "Female and Family Health Questionnaire" that includes numerous questions on the subject's reproductive and pregnancy history, and about the health status of children. The AHS is also using a specialized "Women's Health Questionnaire" and a separate "Young Women's Health Questionnaire" to obtain specific pesticide use information and more detailed health information on subgroups of women who have enrolled in AHS. The former questionnaire has a special section on menopause while the latter questionnaire emphasizes menstrual functioning and pregnancy history.

Epidemiologists do not expect perfect concordance between self-reports and medical records. Although subjects may supply inaccurate data, medical records are themselves not free from error. The accuracy of self-reports presumably vary by type of health endpoint, questionnaire design, period of recall, and population studied. For many reproductive endpoints, the results of reliability and validity studies are reassuring, while for others there is concern (Bean *et al.*, 1979; Wilcox and Horney, 1984; Olson *et al.*, 1997). For some endpoints, such as menstrual function, there is no practicable gold-standard to compare with self-reports. It is important for the investigators to address how they will incorporate uncertainty about self-reports into their analyses and interpretation of results.

The AHS is collecting a large amount of self-reported health information on non-cancer health outcomes. Most of the specific questions on non-cancer health outcomes used in the questionnaires have not been assessed for validity or reliability and there appear to be no plans to initiate such studies by the AHS team. Apparently, follow-up questionnaires will not repeat questions about past health outcomes, preventing assessment of reliability. Some of these questions have already been used in previous studies and may have been subjected to some reliability and validity checks but study context can influence responses. More such studies would help users understand the quality of the non-cancer outcome information that will be analyzed in the AHS. It is crucial that reports of both the presence and absence of specific outcomes be validated in order to ascertain false-positive and false-negative errors.

Bias can occur when subjects know the purpose of a study and when they also know their exposure status and disease status. For example, "exposed" subjects (*e.g.*, heavy users of chemicals) with disease may be more willing to participate in the AHS cross-sectional studies than nonexposed subjects who also have the same disease. The prospective cohort design provides an important protection against such bias,

as long as a subject's exposure truly precedes the onset or diagnosis of the disease being investigated. The prospective cohort study also provides a good opportunity to obtain valid information on exposure and disease status. This strength may be enhanced through various analyses designed to detect and diminish information bias and other problems with the AHS data. It would probably be necessary to gather additional data to support such methodological substudies. It is preferable to minimize the potential for bias by obtaining valid information from all subjects.

PESTICIDE EXPOSURE

Although the primary goal of the AHS is to assess the relationship between human exposure to pesticides and a variety of adverse health outcomes, direct measurement of human exposure to pesticides will be limited by cost considerations. Most of the analyses will be based on surrogates for exposure.

As of early 1998, the U.S. USEPA team planned to select a sample of 125 farms and evaluate total exposure for several chemicals through measurement of environmental media, personal exposure (*e.g.*, through patches on clothing), and samples of urine and blood, taken soon after application. These samples will then be analyzed for a limited number of chemicals of greatest interest. Unexpected funding problems may prevent implementation of USEPA's plan.

Since no direct measures of pesticide exposure will be available on most of the 90,000 members of the AHS cohort, the investigators will rely primarily or exclusively on surrogates for pesticide exposure derived from the questionnaires administered to farmers and members of farm families. For example, previous studies have considered as surrogate factors such measures as frequency of application per year, number of years of application, and application practices that may be related to exposure (*e.g.*, method of application and type of protective equipment used) (Hoar *et al.*, 1986; Zahm *et al.*, 1990). It is not known how well any of these surrogates indicate biologically significant exposures or whether any is appropriate. A case can be made that exposure surrogates should be validated before initiating a major epidemiologic study, or at least before exposure-response analyses are undertaken.

A key goal of the USEPA portion of the AHS is calibration of reported work practices with actual farmer exposures, using the information obtained from the measurements gathered on the sample of farms. Ideally, this information would allow at least a ranking of exposure potential by method of application and protective equipment used. For example, some pesticides are formulated as liquids, and gloves may provide a great deal of protection. Others are formulated as dusts or sprays and thus gloves may make little difference, while a respirator or mask may greatly reduce exposure. Still others are large granules and neither type of protective equipment may have much influence on exposure.

Because of its limited size, the USEPA study is unlikely to provide a rigorous validation of the numerous exposure surrogates derived from the AHS questionnaire data. A larger sample of farms, pesticides, and work practices would be useful in validating the surrogates against the background of other significant determinants of exposure such as the subject's age and role in pesticide use. There are also

questions about the representativeness of sampled farms. The USEPA has had difficulty obtaining the participation of farmers. In a pilot study in North Carolina, fewer than 10% of farmers asked agreed to participate (U.S. Environmental Protection Agency, 1997). It seems unlikely that the farmers who agree to participate will be representative of all of the farmers in the AHS. The timing of the USEPA exposure study is also a source of concern. USEPA's exposure study is just getting underway but the AHS enrollment questionnaires have already been administered to the 90,000 enrollees. If the USEPA study raises questions about the validity of the exposure surrogates contained in the enrollment questionnaire, the data that have already been collected from farmers on work practices will be of diminished utility. If done in a timely fashion, it may be feasible to revise future follow-up questionnaires in a way that will benefit from the insights generated from the USEPA's exposure study.

Previous studies have relied on the assumption that total lifetime exposure to one or more pesticides is determined by annual frequency of application and number of years of application. Although this assumption may seem logical, there is no plan to validate it. It is possible that those farmers who apply pesticides frequently and have done so for many years do so with particular experience and care, which might suggest that their absorbed dose per application is less than the exposure of farmers who apply chemicals less frequently or have fewer years of experience in farming. Of course, bias may also run in the opposite direction if some applicators become careless or even contemptuous of risks as the substances and application practices become familiar. A particular task, such as mixing, may lead to much greater exposure than frequent application. If rare but serious mishaps or spills have a powerful influence on total lifetime exposure, number of applications may be a poor surrogate for total exposure, since the probability of mishap/spill may be smaller among high-frequency applicators. The USEPA study may not be large enough to detect these rare yet serious incidents. Thus, it is not obvious that total exposure to pesticides in a farmer's lifetime, on average, will be a straightforward multiple of the number of applications in a farmer's lifetime.

The use of inappropriate or imperfect exposure surrogates may compromise the validity of the study by producing erroneous measures of association. Errors due to misclassification can produce bias toward the null (attenuation of the magnitude of a true positive or inverse association) or bias away from the null (exaggeration of the strength of a true weak or true null association). In large prospective follow-up studies of relatively common exposures and diseases, exposure misclassification tends to be nondifferential with regard to disease status. Nondifferential exposure misclassification will produce bias toward the null if exposure is classified dichotomously (*e.g.*, exposed vs. unexposed, high vs. low exposure). If more than two categories of exposure are evaluated, however, nondifferential misclassification has an unpredictable impact and can produce bias away from the null (Correa-Villasenor, A., Stewart, W. F., Franco-Marina, F., and Seacat H. (1995); Thomas, 1995). In small studies or studies in which exposure is rare or disease rates are low, the impact of misclassification, again, is unpredictable. There is no guarantee that exposure misclassification will be nondifferential even if objective exposure assessment pro-

cedures are used. Misclassification will reduce the power of the study to detect any genuine cause-effect relationships and will also reduce the validity of findings. Reductions in power are a serious issue because they will undermine the ability of government and industry to regulate harmful exposures and to reassure farmers with "negative" results.

Biomonitoring studies of farmers who mix and apply pesticides with different frequencies might help resolve this matter, but such studies would need to be large in size and would be logistically complex. Such studies may induce behavioral changes (*e.g.*, extra safety precautions) on the part of some farmers that are not typical of their normal behavior.

Although it will be difficult to validate whether number of applications is a strong predictor of total exposure, it may be more feasible to study the impact of work practices and method of application on the amount of actual pesticide exposure. A farmer's personal habits can have an enormous influence on pesticide dose, as measured by urinary excretion, even when the same protective equipment is used (Lavy, Walstad, Flynn, and Mattice, 1982; Forbess *et al.*, 1982; Leng, Ramsey, Braun, and Lavy, 1982). It will be difficult to characterize this source of variability in the small sample of farmers being evaluated by the USEPA. Broader studies of the type planned by the USEPA, with a focus on the AHS pesticides and work practice and protective equipment questions, would be very useful. Some information on the role of work practices and protective equipment is already available in USEPA's Pesticide Use Handlers Database and our understanding is that the AHS investigators have begun to exploit this source of data. We encourage more efforts in this direction. The Department of Defense has conducted large programs of research on the efficiency, safety, and comfort of protective gear, and some of the results (*e.g.*, points of leakage or tolerance by the protected person) may be directly applicable to pesticide applicators.

There are also practical and technical concerns associated with any urine biomonitoring program. The USEPA investigators are aware of many potential pitfalls but still may have difficulty dealing with them. One of the biggest problems is time. If a pesticide is rapidly excreted, measurements must be made quickly after a single application to be useful for exposure assessment. If, however, the material is cleared slowly from the body, the amount of the chemical measured in urine will be highly dependent on the frequency of applications and the time interval between applications. There are significant differences in pharmacokinetics across compounds that will influence the relationship between frequency/pattern of use and exposure. Thus, a serious biomonitoring program must have a protocol that tailors the measurement regime to the behavior of the compounds under study. Yet the USEPA plans to sample only a fraction (perhaps as few as 10) of the 50+ chemicals being assessed in the AHS, and funding obstacles are jeopardizing even this modest level of effort.

Another key assumption of the AHS is that exposure of farm family members to pesticides is associated with the farmer's patterns and frequencies of use. Little is known about the nature of this relationship or how it varies for different compounds and farm types (Lowenherz *et al.*, 1997). The existing studies are small in size and are quite limited in the number and type of pesticides evaluated. Assuming partici-

pation obstacles can be overcome, biomonitoring could be used productively to better understand the presence and magnitude of indirect exposures to farm families that are assumed in the Spouse Questionnaire and the Female and Family Health Questionnaire. USEPA has limited plans in this area that will need to be expanded considerably if they are to be useful in the AHS.

The NCI also plans a biomarker component, collecting buccal DNA samples from a subsample of the AHS cohort, to store for later analysis of genetic polymorphisms potentially related to susceptibility to pesticide-induced disease. Although this effort is of considerable scientific interest, it is not likely to assist in validation of the exposure surrogates to be used in epidemiologic analyses.

In general, a major limitation of the current design of the AHS study is that so few direct measurements of human exposure to chemicals will be available. The information that USEPA plans to collect may be useful in its own right but, for the reasons stated above, is not likely to be as useful as it could be for use in the epidemiologic analyses to be performed in the AHS. Pesticide exposure studies that are linked to epidemiologic investigations are urgently needed if a major advance is to be made in our understanding of the relationship between pesticides and human disease. The significant cost associated with such an effort is noted, but the scientific value of this major epidemiologic study is questionable without a valid exposure assessment.

PESTICIDE USE

In the AHS, the questionnaires filled out by subjects elicit information on various aspects of pesticide use rather than on exposure directly. This approach is sensible because the respondent is in a better position to report accurate information on whether and how a chemical is used than information on the amount of exposure to chemicals. However, there are still serious questions about the quality of the pesticide use data that are being collected in the AHS. Since these data are likely to be critical to the interpretation of the epidemiologic analyses, the associated quality concerns need to be considered carefully.

In the AHS enrollment questionnaire, the primary questions (Qo, #11A-D) ask: "During your lifetime have you ever personally mixed or applied this pesticide?; how many years did you mix or apply this pesticide?; in an average year when you personally used this pesticide, how many days did you use it?; and when did you first personally use this pesticide?" (Paraphrased). These questions are posed for 22 named pesticides. For an additional 28 compounds, there is a simple question about whether that pesticide had ever been used.

In order to answer these questions, respondents must remember with some accuracy when they first used products and their frequency of use of each pesticide product, and they must be able to compute averages in their head involving multiple years of use. For older subjects who have many years of farm experience, accurate responses will be difficult to supply. Moreover, some pesticides are sold and applied as mixtures and thus the exact ingredients may not be known to farmers. It can reasonably be expected that there will be inaccuracies in these data.

In the AHS enrollment questionnaire, there are two important questions about work practices. Question 16 asks: "how do you personally apply pesticides?" The offered answers include 20 options that are not differentiated by livestock or crop farming, by specific crop, or by pesticide used. Question 17 asks "what type of protective equipment do you generally wear when you personally handle pesticides?" The offered answers include 8 options, again making no distinction between farm types or pesticides used. Since most farmers will have had different practices for different crops or pesticide products, it is not clear how they will answer these questions in a meaningful way since multiple answers do not appear to be allowed.

There are, of course, real concerns about the ability of farmers to recall use of specific pesticides, let alone their frequency of use, when confronted with a long list of compounds. Many farmers know pesticides by trade names, not technical names. The AHS questionnaires list some trade names for all chemicals but the list is not exhaustive. In addition, farmers now often use formulations that contain several pesticides. A respondent who knows only one of the compounds or trade names could underreport the use of other pesticides in the mixture. Errors of recall may occur differentially between controls and diseased persons.

Due to a change in enrollment procedures, the AHS investigators do have duplicate enrollment questionnaires from 1223 applicators from Iowa (Alavanja, 1998). Reliability was reported as both the percent agreement (the fraction of applicators giving the identical answer to a question on both questionnaires) and kappa statistic, often used as a measure of reliability. For example, smoking had an agreement of about 90% and a kappa of 0.88. Reports of ever/never use of specific pesticides had agreement around 80% with kappas around 0.60. The agreement of frequency of use questions was not reported. Some questions, especially those about vegetable and fruit consumption, had quite low agreements (30 to 40%) and kappas (about 0.50). Of course, this analysis does not address the validity of the responses. It may be useful to include some more important use questions on future follow-up surveys to gauge reliability in the whole cohort.

A weakness of the AHS is that adequate information is not being collected on excipients such as solvents, stabilizers, diluting agents, preservatives and other chemical substances that are used with pesticide products. Confusion may occur about whether reported health effects are attributable to active ingredients or excipients. For regulators and firms interested in the design of pesticide products, it is crucial to know what precisely is causing a reported health effect.

There is no reason to believe that large numbers of subjects were deliberately dishonest in the enrollment questionnaire about their patterns of pesticide use. However, the questions about use of protective equipment may have induced some "socially desirable" but inaccurate answers, especially when questionnaires were administered at training sessions. It is also quite possible that pesticide products near the bottom of the lists of 22 and 28 were checked less frequently by respondents who became weary filling out this rather arduous aspect of the questionnaire. This problem could be smoothed out in the future follow-up surveys by rotating the order of the products.

A study of the magnitude of the AHS requires good understanding of the validity and reliability of each major data set. The AHS will obtain pesticide use data from

responses to a written questionnaire of farmers. Data will be collected both at the beginning of the study and with follow-up questionnaires of unspecified frequency, for either the whole cohort or a select subsample, in later years. On the subject of validity, purchase records have been used in the past to ascertain whether written answers to a "yes/no" question on use of specific products are accurate. One study reported a 60% agreement rate between purchase records and reported use of specific products (yes/no) (Blair and Zahm, 1993). Agreement between farmer's recall of years of use and the records of their suppliers ranged from 38% to 68% depending on type of pesticide and crop. Measures of frequency of use in a year have never been subjected to a validation study.

When social scientists find it difficult to validate questionnaire data, it is typical to at least conduct reliability studies, such as repeated administrations of the same (or similar) questionnaire(s) to respondents, to determine whether answers to the same question are stable. Few reliability studies of self-reported pesticide use, particularly the quantitative responses, have been published in the literature (Johnson *et al.*, 1993). In addition, since reliability is influenced by the particular wording of questions and response choices, there probably would be limited generalizability from reliability studies of other questionnaires.

The questions of reliability and validity regarding the reported data could be addressed in several ways. In addition to the small study already mentioned, a comparison of the responses of farmers to selected questions that have been included on both the enrollment and supplemental questionnaires will provide some ideas about reliability. Studies comparing self-reported use to purchase records for a subsample of the AHS farmers could provide an idea of the validity of self-reported use estimates. Even if recent purchase data can be obtained, it is likely that purchase records for earlier years will be less complete. Thus, it will be more difficult to verify the accuracy of self-reports of pesticide use in the past. Another opportunity to check self-reports might come from the Extension Service recommendations for each crop in Iowa and North Carolina. Consistency between self-reports and the recommendations of the Extension Service is one possible measure of accuracy. However, if such recommendations are widely known, farmers may be reluctant to report actual use patterns that deviate significantly from these recommendations.

The chemicals, formulations, and application methods used on farms have changed significantly over time. Herbicides once applied at rates of pounds of active ingredient per acre are now applied in ounces per acre. Formulations have been developed to reduce exposure by making the pesticide in large granules or as packets that are dropped into an application tank, with no need for mixing or loading. These changes in patterns of pesticide use mean that data gathered about farming practice today are not a valid reflection of what was done in the past. The amount of exposure per application is probably smaller today than it was years ago, further complicating any calculation of cumulative exposure.

These details are important because if pesticides cause chronic diseases such as cancer and neurological disease, the biologically meaningful measure of exposure may be a cumulative dose figure that accounts for farming practices years or even decades ago. For chronic diseases diagnosed over the next 5 years or so, the exposure of interest probably occurred many years ago. Yet information about

changes in farming practices over time is not being gathered in the AHS. In addition, the extent of pesticide use information to be collected in follow-up surveys of the cohort is not clear. If most of the pesticide use assessment in the AHS proves to be retrospective, the AHS will have little advantage over previous studies.

RISK FACTORS OTHER THAN PESTICIDES

Numerous factors other than pesticide use are known or suspected to contribute to the development of various diseases and health impairments under study in AHS. These factors are important because they may confound (exaggerate or attenuate) the effects of pesticides, they may interact with the effects of pesticides, or they may prove to be of much greater quantitative importance than pesticides even if they are not confounders or interacting variables.

Confounding Variables

In epidemiologic analysis, a confounding variable is a risk factor for the disease of interest that is associated with the exposure of interest (in this case, pesticides). For example, in an analysis to determine whether frequent application of a particular pesticide is a risk factor for a particular type of skin cancer, exposure to sunlight is a potentially confounding (or interacting) variable. The ultraviolet radiation from exposure to sunlight is known to be a cause of skin cancer and farmers who engage in frequent application of pesticides may have more exposure to the sun than other farmers. If exposure to sunlight is a confounding variable and is omitted from the epidemiologic analysis, the estimated risks associated with pesticide exposure will be biased. This bias can be reduced or eliminated by collecting information on the confounder and including such information in a multivariate analysis of the disease in question.

Concern about possible confounding may arise if certain patterns of pesticide misuse (*e.g.*, failure to use protective equipment) are used as a surrogate for pesticide exposure without consideration of the farmer's lifestyle. Farmers who do not use protective equipment (or engage in risky application practices) may be more likely to engage in a wide range of risky behaviors at work and at home than farmers who use protective equipment (or engage in low-risk application practices). Some of those risky personal actions may be linked to the health outcomes under study.

The AHS collects data on numerous variables that might confound the relationship between pesticide use/exposure and disease outcomes. Yet we know of no effort to identify such confounding variables and include them in the AHS study plans. Information about some risk factors other than pesticides is being collected in the AHS study (*e.g.*, aspects of the diets of farmers) but it is not clear whether such variables are correlated with pesticide exposure and are likely to cause the same types of tumors that chemicals may cause. In addition, since these data are collected in the supplemental questionnaires, they are not available for the entire cohort.

Interacting Variables

The effects of pesticide exposure on human health may be magnified or attenuated by other behavioral and/or environmental factors. For example, it has been

shown that the risk of lung cancer due to radon exposure among uranium miners is much larger among smokers than nonsmokers (Hornung, Deddens, and Roscoe, 1995). We do not know of any interaction effects to be expected in the AHS data, but if others know or suspect of such interactions, they should be postulated explicitly prior to data analysis and then tested rigorously in the statistical analyses.

Other Important Risk Factors

Although pesticide exposures are certainly worthy of study, these exposures are not necessarily the most biologically plausible determinants of disease in farmers or farm families and they may not prove to be as quantitatively important as a variety of risk factors such as smoking, diet, and obesity. Even accepting that chemicals are a major priority for study, more effort might be devoted to understanding farmer exposures to such agents as veterinary pharmaceuticals, engine oils, consumer products, animal viruses, and the crops themselves.

If modified appropriately, the AHS could be used to generate comparative information that might help farm families develop a sense of perspective about the relative risks associated with different risk factors in farm life. In order to serve this function, future surveys of the cohort planned by the AHS investigators need to devote more attention to risk factors other than pesticides and compare their relative significance to those of pesticides based on rigorous epidemiologic analysis. Nevertheless, a significant focus on pesticides is worthwhile.

STUDY DESIGN ISSUES

From a methodological perspective, the AHS employs several different study designs in various phases of the epidemiologic inquiry. They include a prospective cohort design, a nested case-control design, and a cross-sectional design. These different study designs have inherent strengths and weaknesses that need to be understood when the findings of the study are interpreted and compared to the findings of other investigators.

Prospective Cohort Study

A typical prospective cohort study follows subjects from the time of enrollment in a study until a particular disease is diagnosed or some other event occurs and/or death. The subjects' frequency and/or degree of exposure to the chemical or physical agents of interest are typically documented at the time of enrollment and throughout the follow-up period. An advantage of this study design is that exposure determinations are made by the investigators before anyone (including the investigators and the subjects) knows which subjects will develop a particular disease or die prematurely. A disadvantage of the prospective design is that accurate measurement of exposure to pesticides and other disease determinants requires that the cohort be questioned or monitored at intervals during the study period, not just at the beginning. For cancers diagnosed during the first 5 years of study, the exposure assessment in the cohort study is based on recollections of pesticide use patterns from years or even decades ago.

Determining exposure status prior to knowledge of health outcome is particularly critical in the epidemiology of pesticides. Previous findings in the literature, which were based primarily on the case-control design, have been criticized on the grounds that those farmers who developed disease (or their next of kin) may have been motivated (for a variety of reasons) toward more complete and accurate reporting of pesticide use and/or exposure than those farmers who did not develop the diseases of interest (Ibrahim et al., 1991). If such differential misclassification of exposure occurs, it will tend to create a spurious positive association between exposure and disease. The prospective cohort design selected by the AHS investigators reduces, but does not eliminate, the chances that bias from differential exposure misclassification will occur because use and exposure are determined prior to knowledge of health outcome. It is critical that follow-up surveys of the cohort be administered on a regular basis to document how exposure and disease states change as subjects age.

The major disadvantage of the prospective cohort design is that, for some chronic illnesses, it takes a long time for sufficient numbers of subjects to fall ill or for the data to be useful for analysis. It is also an inefficient approach to studying relatively rare tumors such as soft-tissue sarcoma and leukemia. Overall, though, we are very enthusiastic about the decision of the AHS team to invest in the prospective cohort design and encourage the investigators to make every feasible effort to achieve acceptable response rates in the follow-up surveys of the cohort and address potential biases in the study.

Nested Case-Control Study

A typical case-control study will enroll "cases" who are known to have the disease in question and compare them to a random subset of "controls" who do not have the disease in question. If cases and controls are both selected from subjects enrolled in a particular cohort study, the study is referred to as a "nested" case-control study. The strength of this design is that the cases are included in the cohort studied. If exposures to a particular agent cause the disease in question, then the life histories of the cases should exhibit different (and presumably greater) exposures than the life histories of controls. Exposures to the agents of interest are typically assessed retrospectively for cases and controls (*i.e.*, after the death has occurred or the disease determination has been made), sometimes via interviews with next of kin or through reconstruction of job histories and practices. Like the prospective study, the nested case-control aspect of the AHS would be constrained by the time to development of disease and the numbers of persons in the cohort. We do not discuss this design in detail here, because it is currently being given low priority in the AHS and its strengths and weaknesses have been addressed elsewhere (*e.g.*, Monson 1990).

The Cross-Sectional Design

A typical cross-sectional study collects information on exposure and disease simultaneously from a sample of subjects. The association between reported exposure and disease is then investigated within the sample. If exposure causes disease,

it is anticipated that subjects that report more exposure will be more likely to report the health outcome of interest. A major weakness in the cross-sectional approach is the potential for bias. When exposure and disease data are gathered at the same time, it may also be unknown whether the temporality is correct, that is, that the exposure to the presumed cause actually preceded the disease, especially with diseases with no easily identified time of onset. There may be bias if persons change exposure status because of disease (*e.g.*, people with disease may stop working with pesticides). Although this research design has some utility for generating hypotheses, it is not considered useful in defining most cause-effect relationships. There are also concerns about the quality of the data gathered for the AHS cross-sectional studies. Without medical verification of self-reported disease, any associations found in the cross-sectional studies will be a weak basis for planning future studies.

DATA ANALYSIS PLANS

While the AHS study team presumably has some well-defined primary hypotheses, they are not specified in the *Environmental Health Perspectives* article (Alavanja et al., 1996) or in the more detailed study plans that have been made available to the public. By well-defined primary hypotheses, we refer to *a priori* hypotheses regarding specific chemicals, specific tumor types or health outcomes, and specific surrogate measures of exposure. Specific hypotheses and detailed plans for analysis help focus the gathering of data on both exposure and disease outcomes. They may also help investigators to avoid overinterpretation of the random oddities that occur in any large and complex data set.

Given the many possible comparisons of pesticides, methods of use, work practices, and health outcomes, a formal statement of why a particular pesticide/outcome combination should be analyzed seems desirable. Without any precommitment to specific hypotheses, the proper interpretation of any associations that are found will be less clear. Although it is appropriate for the AHS team to explore many possibilities when the data are analyzed, it should be clear to readers and decision makers which results confirm prior evidence or concerns and which are found only in the AHS data.

The large amount of questionnaire data developed by the AHS provides rich scientific opportunities but also particular challenges for analysis and interpretation. For example, information is gathered from respondents on numerous health outcomes (approximately 25 outcomes in the private applicator enrollment questionnaire, 70 outcomes in the farmer applicator and spouse questionnaires, and 35 outcomes in the female and family health questionnaire — a total of 130). For cancer, there will be numerous tumor types available for analysis from registry data. In addition to numerous health outcomes, information is gathered on numerous pesticide products (approximately 50 in the enrollment questionnaire and another 100 in the farmer applicator questionnaire). For exposure (dose)-response analysis, it appears that more than 35 different surrogates of exposure can be constructed from the responses to the questions about pesticide use, application methods and

work practices (*e.g.*, average days of use per year, number of products used, years of use, different types of protective equipment and methods of application).

One can confidently predict that some of the multitude of exposure-response combinations will be statistically significant in the absence of any real effect. Without clearly stated *a priori* hypotheses, the investigators will have to exercise considerable discretion in data analysis and may exercise insufficient or excessive caution in their interpretation. The exercise of this discretion can be evaluated by the scientific community only if a small number of completely specified primary hypotheses are developed prior to any inspection of results. "Completely specified" means that the method of analysis must be given in detail for each primary hypothesis. The benefit of this approach is the increase in plausibility of any "positive" findings among the primary hypotheses; the cost is that all other hypotheses lose some support, though some may still be compelling and others may be examined in subsequent studies.

Important questions arise about the role of conventional measures of statistical significance in the reporting and interpretation of results. Should numerical adjustments be made to published p-values to account for multiple comparisons? Given that many possible associations may be explored prior to publication of final results, what degree of documentation should be provided by the investigators of exploratory analyses? If the documentation requirements are minimal, how will the scientific community understand the importance of the associations that are reported? The importance that may be placed on findings of no association between a specific pesticide and health outcomes raises the question of the reporting requirements for analyses that failed to find an association. Parallel consideration must be given to reporting requirements for "inverse" associations (*e.g.*, relative risks less than 1.0 for a particular exposure). At the same time, it would be helpful if the AHS investigators would publish all data and analytical results in some accessible format. Key findings would especially benefit from documentation of their consistency within the AHS database. Widely accessible electronic media such as the World Wide Web makes this feasible.

A detailed analysis plan and careful interpretation can reduce or eliminate these concerns. Examination of internal consistency can provide information about the plausibility of a particular association. A reasonably consistent dose-response gradient is an important criterion. One implication of this criterion is that statistically significant dose-response trends caused primarily by one dose group, especially if it is an intermediate dose group, should be interpreted cautiously. On the exposure side, a finding that the strength of an association increases with particular use practices that are expected to yield higher exposures (and decreases with increasing farmer care), could be valuable evidence in buttressing study results. Sensitivity analyses involving different exposure surrogates and exposure groupings can also demonstrate whether findings are robust.

A key form of evidence to inform hypotheses and corroborate (or refute) analytic findings is biological plausibility. Pesticides, in addition to prescription drugs, are among the most thoroughly studied of all chemicals from a toxicologic perspective. Pesticides are diverse in mode of action and in excipients, raising doubts about attempts to group pesticides for analysis except under very specific conditions (*e.g.*,

examining insecticides with similar mechanisms of *toxic* action and with similar excipients). In the interpretation of epidemiologic results, dose considerations from toxicology can play an important role in determining the plausibility of the response. Associations with exposures far below those causing effects in animals may be less credible than those demonstrated at higher exposure levels. The nature and limited amount of exposure information in the AHS makes this important use of toxicology difficult. More generally, toxicological reasoning has not yet played a significant role in the design or execution of the AHS but should be an important part of a detailed plan of analysis.

SUMMARY OF RESEARCH RECOMMENDATIONS

The AHS is a major undertaking with the potential to add significantly to our knowledge of possible associations between pesticide use and other factors and the health of farmers. The weight that will be accorded to results from this major study requires care in assuring the accuracy of the findings. Several of the most important limitations of the AHS could be addressed through additional research with the cohort or through complementary studies on different groups. The priorities should be to (1) assess the validity of self-reported health outcomes; (2) explore the reliability and validity of pesticide use data; (3) understand the relationship between exposure surrogates and exposure; (4) examine the biological plausibility of any hypotheses; and (5) develop explicitness on analysis and statistical issues.

Assessing the Validity of Self-Reported Health Outcomes

Many of the early analyses from the AHS will be based on self-reported health data. The validity of these data is crucial to interpretation of the results. There are studies in the literature that raise serious questions about self-reports of disease (Harlow and Linet, 1989; Paganini-Hill and Chao, 1993; Kehoe et al., 1994; The Italian Longitudinal Study on Aging Working Group, 1997). Clinical verification of key self-reported health outcomes, where feasible, is essential. It is important that validity be assessed for both those members of the cohort reporting disease and those who claim none. These studies could also help address some concerns about recall bias in the noncancer studies as well as concerns about whether the disease was indeed preceded by exposure.

Exploring the Reliability and Validity of Pesticide Use Data

Since pesticide use data will be the basis for categorizing potential pesticide exposure in the AHS, the validity of these data is also critical. A simple and pertinent step would be to readminister the questionnaire to a sample of respondents to see how much the answers change. Other studies to validate reported pesticide use, for example, by comparison with purchase records, are also essential. A relatively simple check would consist of questions about number of acres for each specific crop for which a specific pesticide was used. This would allow comparison to label instruc-

tions or Extension Service recommendations to help gauge the validity of use reports. Results of validation studies would suggest the amount of confidence that we could place in the questionnaire data as well as pinpoint ways to enhance the design of follow-up questionnaires. Validation studies will be able to address only relatively recent use since use records from the past are likely to be less complete. Given that many of the pesticides of concern for cancer were used more heavily in the past, and that a substantial period occurs between exposure and detection of disease, there may be significant questions about the validity of self-reported pesticide use in earlier years.

Understanding the Relationship between Exposure Surrogates and Exposure

Complementary studies are needed to assess the accuracy of the assumptions in the AHS that link specific use patterns and work practices with different levels of exposure. Biomonitoring studies could provide critical information to link pesticide use information to actual exposure by measuring pesticide levels in the blood or urine. Biomonitoring studies to correlate farmer exposure and dose to pesticide use patterns and work practices would be extraordinarily valuable in linking chemical use data to exposure categories. Similarly, biomonitoring studies of spouses and children of farmers could help determine whether conditions of pesticide use are associated with family exposures that are frequent enough and high enough to lead to possible adverse effects. This effort would help focus attention and resources on the most critical of possible adverse effects.

Assessing the Biological Plausibility of Any Associations

A key research need is the careful enumeration, in advance of analysis, of the biological effects expected at relevant doses for specific pesticides. This undertaking will help avoid the criticism that identified associations are supported only by toxicologic explanations that are *post hoc* and hence unreliable. This effort should rely on both the existing epidemiologic literature and the immense toxicologic database on pesticide products. Dose-response information must play a key role. Identification of chemicals expected to be capable of affecting health at anticipated exposures can corroborate findings and help focus analysis efforts.

Analysis and Statistical Issues

It is critical that a detailed analysis plan for the AHS be developed. Specifics to be addressed should start with a small number of precise hypotheses about pesticide/disease relationships, including in detail the analytic method. Potential confounders, interacting variables, and other risk factors should be identified in a systematic way, where possible, with a focus on causation of specific diseases. There is a need to specify an analytic framework, including specific statistical procedures, that encompasses decision rules for analysis and reporting.

The general study plan of the AHS is not yet detailed enough to support a confident evaluation of the technical strengths and weaknesses of this major undertaking, and we recommend substantial efforts toward developing such a plan. The level of effort and detail we are suggesting here would be typical of a major

investigator-initiated proposal that is peer reviewed and judged to be worthy of funding by the National Institutes of Health.

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REFERENCES

Agricultural Health Study Protocol, Revision of December 16, 1993.

Alavanja, M. C. R. Agricultural Health Study Information Packet for Advisory Panel Meeting, March 4–5, 1998 — NCI Progress Report.

Alavanja, M. C. R., Sandler, D. P., McMaster, S. B., Zahm, S. H., McDonnell, C. J., Lynch, C. F., Pennybacker, M., Rothman, N., Dosemeci, M., Bond, A. E., and Blair, A. 1996. The agricultural health study. *Environ. Health Perspect.* **104**, 362–369.

Bean, J. A., Leeper, J. D., Wallace, R. B., Sherman, B. M., and Jagger, H. 1979. Variations in the reporting of menstrual histories. *Am. J. Epidemiol.* **109**, 181–185.

Blair, A. and Zahm, S. H. 1993. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* **4**, 55–62.

Correa-Villasenor, A., Stewart, W. F., Franco-Marina, F., and Seacat H. 1995. Bias from nondifferential misclassification in case-control studies with three exposure levels. *Epidemiology*. 6, 276–81.

Forbess, R. C., Morris, J. R., Lavy, T. L., Talbert, R. E., and Flynn, R. R. 1982. Exposure measurements of applicators who mix and spray paraquat in grape vineyards. *Horticult. Sci.* 956–957.

Harlow, S. D. and Linet, M. S. 1989. Agreement between questionnaire data and medical records. *Am. J. Epidemiol.* **129**, 233–248.

Hoar, S. K. *et al.* 1986. Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma. *J. Am. Med. Assoc.* **256**, 1141–1147.

Hornung R. W., Deddens, J., and Roscoe R. 1995. Modifiers of exposure-response estimates for lung cancer among miners exposed to radon progeny. *Environ. Health Perspect.* 103(Suppl. 2), 49–53.

Ibrahim, M. A. *et al.* 1991. Weight of the evidence on the human carcinogenicity of 2,4-D. *Environ. Health Perspect.* 96, 213–222.

Johnson, R. A., Mandel, J. S., Gibson, R. W., Mandel, J. H., Bender, A. P., Gunderson, P. D. and Renier, C. M. 1993) Data on prior pesticide use collected from Self- and proxy respondents. *Epidemiology* **4**, 157–164.

Kehoe, R. *et al.* 1994. Comparing self-reported and physician-reported medical history. *Am. J. Epidemiol.* **139**, 813–818.

Lavy, T. L., Walstad, J. D., Flynn, R., and Mattice, J. D. 1982. (2,4-Dichlorophenoxy)acetic acid exposure received by aerial application crews during spray operations. *J. Agric. Food Chem.* **30**, 373–381.

Leng, M. L., Ramsey, J. C., Braun, W. H., and Lavy, T. L. 1982. Review of Studies with 2,4-Dichlorophenoxyacetic Acid in Humans Including Applicators Under Field Conditions. ACS Symposium Series No. 182. (Plimmer, J. R., Ed.), American Chemical Society.

Lowenherz, C., Fenske, R. A., Simcox, N. J., Bellamy, G., and Kalman, D. 1997. Biological monitoring of organophosphorous pesticide exposure among children of agricultural workers in central Washington state. *Environ. Health Perspect.* **105**, 1344–1353.

Monson, R. R. 1990. *Occupational Epidemiology*, 2nd ed. CRC Press, Boca Raton, FL.

Olson, J., Shu, X., Ross, J., Pendergrass, T., and Robison, L. 1997. Medical record validation of maternally reported birth characteristics and pregnancy-related events: a report from the Children's Cancer Group. *Am. J. Epidemiol.* **145**, 58–67.

Paganini-Hill, A. and Chao, A. 1993. Accuracy of recall of hip fracture, heart attack, and cancer: a comparison of postal survey data and medical records. *Am. J. Epidemiol.* **138**, 101–106.

Sandler, D. P. Agricultural Health Study Information Packet for Advisory Panel Meeting, March 4 to 5, 1998 — NIEHS Progress Report.

Tarone, R. E., Alavanja, M. C. R., Zahm, S. H., Lubin, J. H., Sandler, D. P., McMaster, S. B., Rothman, N., and Blair, A. 1997. The agricultural health study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am. J. Indust. Med.* **31**, 233–242.

The Italian Longitudinal Study on Aging Working Group 1997. Prevalence of chronic diseases in older italians: comparing self-reported and clinical diagnoses. *Int. J. Epidemiol.* 26, 995–1000.

Thomas D. C. 1995. re: When Will Nondifferential Misclassification of an Exposure Preserve the Direction of a Trend? *Am. J. Epidemiol.* **142**, 782–4.

USEPA (U.S. Environmental Protection Agency). Agricultural Health Study Information Packet for Advisory Panel Meeting, February 27 to 28, 1997 — USEPA Summary.

Wilcox, A. and Horney, L. 1984. Accuracy of spontaneous abortion recall. *Am. J. Epidemiol.* **120**, 727–733.

Zahm, S. H. *et al.* 1990. A case-control study of Non-Hodgkin's Lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* **1**, 349–356.

ENDNOTES

1. Agricultural Health Study Information Packet for Advisory Panel Meeting, January 18–19, 1996 — Meeting Overview, NCI Summary, Biomarkers Studies,

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Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma

This Technical Memorandum summarizes the results of a meta-analysis of glyphosate use and risk of non-Hodgkin lymphoma (NHL) using unpublished results from the Agricultural Health Study (AHS) cohort (Alavanja et al. 2013)[1]. For the purpose of sensitivity analysis, this meta-analysis also includes unpublished results from the North American Pooled Project (Pahwa et al. 2015)[2]. We used these two sets of results in place of other results that were included in our previously published systematic review and meta-analysis of the association between glyphosate use and NHL risk (Chang and Delzell 2016)[3]. That meta-analysis relied upon earlier, published results from the AHS cohort (De Roos et al. 2005)[4] and earlier, published results from the case-control studies that contributed to the North American Pooled Project (Cantor et al. 1992; De Roos et al. 2003; Hoar et al. 1986; McDuffie et al. 2001; Zahm et al. 1990)[5].

As stated in our paper (Chang and Delzell 2016), meta-analyses are not intended to identify, validate, or dispute causal relationships. They can provide a statistically precise summary measure of association across multiple studies and aid in identifying heterogeneity of results among studies; however, they also can obscure important differences in methods and results

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1 Alavanja MCR et al. DRAFT- Lymphoma risk and pesticide use in the Agricultural Health Study. March 15, 2013. Received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP.

2 Pahwa M et al. An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma msajor histological subtypes in the North American Pooled Project. Presented at International Society for Environmental Epidemiology Conference, Sao Paolo, Brazil. August 31, 2015. Received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP.

3 Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. J Environ Sci Health B 2016;51(6):402–434.

4 De Roos AJ et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect 2005;113(1):49–54.

5 Cantor KP et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 1992;52(9):2447–2455.

De Roos AJ et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 2003;60(9):E11.

Hoar SK et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986;256(9):1141–1147. The estimated association between glyphosate use and NHL risk was not reported in this paper, although relevant data were available.

McDuffie HH et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10(11):1155–1163.

Zahm SH et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiol 1990;1(5):349–356. The estimated association between glyphosate use and NHL risk was not reported in this paper, although relevant data were available.

among studies that can be more thoroughly evaluated in a detailed qualitative review of study strengths, limitations, and interpretations. In the presence of dissimilar studies, even if heterogeneity of results is not detectable using formal statistical tests, a single summary estimate may not be scientifically meaningful. Additionally, meta-analysis cannot overcome problems in the design and conduct of the underlying studies, and consistent findings across multiple studies may be due to shared biases rather than a true association.

In the meta-analysis described here, earlier results from the AHS cohort were replaced with results from Alavanja et al. (2013). In alternative models used for sensitivity analysis, earlier results from the North American case-control studies were replaced with results from Pahwa et al. (2015)[6]. However, Pahwa et al. (2015) did not describe in detail the eligibility criteria or the numbers of subjects included from each underlying study that contributed to their analysis. The numbers of total and reportedly glyphosate-exposed cases and controls in the North American Pooled Project, as reported by Pahwa et al. (2015), cannot readily be derived from the published numbers from the underlying studies. Due to the lack of transparency on this issue in the documents available to us[7], and our resulting lack of confidence in the results, we did not include the findings from Pahwa et al. (2015) in our primary analysis.

Differences between the analysis of Alavanja et al. (2013) and that of De Roos et al. (2005) include the following:

- Longer follow-up through 2008 (Alavanja et al. 2013) instead of 2001 (De Roos et al. 2005), resulting in the identification of more NHL cases (333 versus 92 in the complete cohort, respectively) and greater statistical power in Alavanja et al. (2013);
- Reporting of "high," "medium," and "low" glyphosate exposure versus none but not ever versus never glyphosate use (Alavanja et al. 2013) rather than tertiles of glyphosate exposure and ever versus never glyphosate use (De Roos et al. 2005);
- Use of a newer histopathological classification of NHL that includes chronic lymphocytic leukemia (CLL) and some other, less common subtypes (but not multiple myeloma) (Alavanja et al. 2013) that were excluded previously (De Roos et al. 2005);
- Adjustment for age, smoking status, number of livestock, driving of a diesel tractor, and state of residence in fully adjusted models (Alavanja et al. 2013) as opposed to

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[6] De Roos et al. (2003) included results from Cantor et al. (1992), Hoar et al. (1986), and Zahm et al. (1990) in their pooled analysis of multiple pesticides and NHL. Due to study overlap, and because Hoar et al. (1986) and Zahm et al. (1990) did not report associations between glyphosate use and NHL risk, we included only the results of De Roos et al. (2003) in our original meta-analysis (Chang and Delzell 2016).

[7] Other documents that we reviewed were an unpublished draft manuscript (Pahwa et al. An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP). September 21, 2015; received by Exponent from Mr. Eric G. Lasker, Hollingsworth LLP; tables, figure, and appendix omitted) and a published abstract from the 2015 International Society for Environmental Epidemiology Conference in Sao Paolo, Brazil (http://ehp.niehs.nih.gov/isee/2015-868/).

adjustment for age, education, smoking pack-years, alcohol consumption, first-degree family history of cancer, state of residence, and use of 2,4-dichlorophenoxyacetic acid (2,4-D), alachlor, atrazine, metolachlor, trifluralin, benomyl, maneb, paraquat, carbaryl, and diazinon (De Roos et al. 2005); and

- Possible revision of the algorithm for estimating intensity of pesticide exposure using questionnaire data on mixing status, application, method, equipment repair, and use of personal protective equipment[8].

Differences between the analysis of Pahwa et al. (2015) and those of Cantor et al. (1992), De Roos et al. (2003), Hoar et al. (1986), McDuffie et al. (2001), and Zahm et al. (1990) include the following:

- Pooling of raw data for a unified analysis (Pahwa et al. 2015) instead of analyzing each contributing study separately (Cantor et al. 1992; De Roos et al. 2003; Hoar et al. 1986; McDuffie et al. 2001; Zahm et al. 1990), thereby resulting in greater statistical power in Pahwa et al. (2015);
- Inclusion of data on glyphosate exposure (Pahwa et al. 2015) that were not published by Hoar et al. (1986) and Zahm et al. (1990);
- Adjustment for age, sex, state/province, first-degree family history of lymphohematopoietic cancer, proxy respondent use, any personal protective equipment use, and use of 2,4-D, dicamba, or malathion in the unified dataset (Pahwa et al. 2015) as opposed to study-specific adjustment for age, state, vital status, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures (Cantor et al. 1992); age, study site, and ten other pesticides (De Roos et al. 2003); age (Hoar et al. 1986; associations with glyphosate use not reported); age and province (McDuffie et al. 2001); or age (Zahm et al. 1990; associations with glyphosate use not reported);
- Inclusion of women (Pahwa et al. 2015), who were excluded from prior analyses (Zahm et al. 1990; De Roos et al. 2003);
- Possible inclusion of subjects who lived or worked on a farm when younger than 18 years of age, but not after age 18 (Pahwa et al. 2015), who were excluded from prior analyses (Zahm et al. 1990; De Roos et al. 2003);
- Use of logistic regression analysis in the unified dataset (Pahwa et al. 2015) versus use of either hierarchical or logistic regression analysis in one of the case-control studies (De Roos et al. 2003).

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[8] Alavanja et al. (2013) cited Coble et al. (An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. Int J Environ Res Public Health 2011;8(12):4608–4622) as the source for this algorithm, whereas De Roos et al. (2005) cited Dosemeci et al. (A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg 2002;46(2):245–260).

We used the same meta-analysis statistical methods as described in our publication (Chang and Delzell 2016). Following those methods, the primary relative risk (RR) estimate that we chose to include based on data from Alavanja et al. (2013) was an estimate calculated by us that compared ever versus never use of glyphosate, using the fully adjusted model and the newer histopathological classification of NHL (from Supplemental Table 2 of Alavanja et al. (2013)). Because Alavanja et al. (2013) did not report RR estimates for ever versus never use of glyphosate, but instead reported RRs for low, medium, and high versus no exposure to glyphosate, we combined the RR estimates for the three different levels of exposure into a single estimate using random-effects meta-analysis. As shown in Table 1 below, the combined RR for ever versus never use of glyphosate in association with NHL risk in Alavanja et al. (2013) was the same after rounding (i.e., combined RR = 0.9, 95% confidence interval (CI) = 0.7–1.1) regardless of whether glyphosate exposure was classified using total days of exposure or intensity-weighted days of exposure, and whether the newer or an older classification of NHL was used.[9]

We conducted sensitivity analyses using four alternative RR estimates from Alavanja et al. (2013), namely, those comparing 1) "high" versus no exposure to glyphosate using intensity-weighted days of exposure, the newer NHL classification, and the fully adjusted model (from Supplemental Table 2 of Alavanja et al. (2013)); 2) "high" versus no exposure to glyphosate using unweighted days of exposure, the newer NHL classification, and the fully adjusted model (from Supplemental Table 2 of Alavanja et al. (2013)); 3) "high" versus no exposure to glyphosate using intensity-weighted days of exposure, the older NHL classification, and the age-adjusted model (from Supplemental Table 7 of Alavanja et al. (2013); results of fully adjusted model not reported); and 4) "high" versus no exposure to glyphosate using unweighted days of exposure, the older NHL classification, and the age-adjusted model (from Supplemental Table 7 of Alavanja et al. (2013); results of fully adjusted model not reported).

In our previously published meta-analysis, we prioritized the results of De Roos et al. (2003) based on a hierarchical regression model over the results from a logistic regression model because, according to the authors, hierarchical models can have "increased precision and accuracy for the ensemble of estimates" when modeling multiple pesticides simultaneously, and the more conservative prior assumptions specified in these models "seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL." However, since 2003, the International Agency for Research on Cancer and the United States Environmental Protection

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[9] De Roos et al. (2005) coded cancers according to the *International Classification of Diseases*, 9th Revision (1975), whereas the older classification used by Alavanja et al. (2013) was the *International Classification of Diseases for Oncology*, 3rd Edition (2000). These two classifications are not equivalent, although they are broadly similar for NHL overall (see http://apps.who.int/iris/bitstream/10665/96612/1/9789241548496_eng.pdf).

Agency have changed their classifications of the probable carcinogenicity of some pesticides, including glyphosate.[10] Because the prior covariates used by De Roos et al. (2003) probably would have changed in light of these revised classifications, we prioritized the results of the logistical regression model in the present meta-analysis.[11]

The RR estimate that we chose to include from Pahwa et al. (2015) was the fully adjusted estimate comparing ever versus never use of glyphosate using both self- and proxy respondents (RR = 1.13, 95% CI = 0.84–1.51).

Alavanja et al. (2013) also reported RRs for associations between glyphosate use (using unweighted days of exposure and the age-adjusted model) and risk of diffuse large B-cell lymphoma (DLBCL), CLL/small lymphocytic lymphoma (SLL)/mantle-cell lymphoma (MCL), and follicular lymphoma (FL) (from Table 3 of Alavanja et al. (2013)). Likewise, Pahwa et al. (2015) reported fully adjusted RRs for associations between ever versus never glyphosate use and risk of DLBCL, SLL, and FL. Therefore, we also calculated new meta-analysis results for these three NHL subtypes, with the results of Pahwa et al. (2015) included in sensitivity analyses but not in our primary analyses due to our concerns about subject inclusion criteria. For the primary analysis of NHL subtypes, we again combined the Alavanja et al. (2013) RR estimates for low, medium, and high versus no exposure (classified based on total days of exposure; results for intensity-weighted days of exposure not reported) into a single RR estimate for ever versus never glyphosate use using random-effects meta-analysis.

As shown in Table 1 and Figure 1, the primary random-effects meta-RR for the association between glyphosate use and risk of overall NHL, based on six independent studies[12], was 1.2 (95% CI = 0.91–1.6). Thus, compared with our originally reported meta-RR, which included the earlier AHS results of De Roos et al. (2005) and the hierarchical regression model results of De Roos et al. (2003) (meta-RR = 1.3, 95% CI = 1.0–1.6), the new meta-RR was attenuated and statistically nonsignificant. The attenuation is the result of the replacement of the results of De Roos et al. (2005) (RR = 1.1, 95% CI = 0.7–1.9 for ever use of glyphosate) with results of our

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[10] International Agency for Research on Cancer (IARC). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112. Some Organophosphate Insecticides and Herbicides. Lyon: IARC, 2017.

[11] The RR for glyphosate use and NHL risk from the hierarchical model used by De Roos et al. (2003) was 1.6 (95% confidence interval (CI): 0.9–2.8) and that from the logistic regression model was 2.1 (95% CI: 1.1–4.0); thus, using the logistic regression results favored a higher estimated meta-RR.

[12] Alavanja et al. (2013); De Roos et al. (2003); Eriksson M et al. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008;123(7):1657–1663; Hardell L et al.. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002;43(5):1043–1049; McDuffie HH et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10(11):1155–1163; Orsi L et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009;66(5):291–298.

analysis of data from Alavanja et al. (2013) (combined RR = 0.9, 95% CI = 0.7–1.1 for ever use of glyphosate).

Table 1 also shows the results of various sensitivity analyses using the alternative RR estimates from Alavanja et al. (2013); results from De Roos et al. (2005) instead of those from Alavanja et al. (2013); results from Hohenadel et al. (2011)[13] instead of those from McDuffie et al. (2001); and results from Pahwa et al. (2015) instead of those from De Roos et al. (2003) and McDuffie et al. (2001). All of the random-effects and fixed-effects meta-RRs for the association between glyphosate use and NHL risk were statistically nonsignificant, with little change in the point estimate and 95% CI (range of meta-RRs = 1.0–1.3, range of 95% confidence limits = 0.86–1.8) based on the inclusion of alternative RRs.

After inclusion of the results of Alavanja et al. (2013), meta-RRs from our primary analyses of the association between glyphosate use and risk of DLBCL, CLL/SLL with or without MCL, or FL also were statistically nonsignificant and attenuated (for DLBCL and CLL/SLL/MCL) or reversed from positive to inverse (for FL), compared with those reported our original meta-analysis (Table 1). In sensitivity analyses, two meta-RRs for SLL with or without CLL or MCL were statistically marginally nonsignificant or statistically significant, namely, models 4 and 5. However, both of these results were obtained using fixed effects models that included data of uncertain validity from Pahwa et al. (2015). In addition, given the presence of substantial and statistically significant heterogeneity among study-specific RRs in both of these analyses, the random-effects meta-analysis model is preferred[14]. In both analyses, the random-effects meta-RR was statistically nonsignificant and attenuated in comparison with the fixed-effects-meta-RR.

In summary, replacement of the results of De Roos et al. (2005) with the more recent results of Alavanja et al. (2013) resulted in weakened, statistically nonsignificant associations between glyphosate use and risk of all outcomes evaluated, including NHL, DLBCL, CLL/SLL/MCL, and FL.

Limitations

This analysis used non-peer-reviewed results from the AHS reported in a draft manuscript by Alavanja et al. dated March 15, 2013, and non-peer-reviewed, publicly presented results from the North American Pooled Project reported in a presentation by Pahwa et al. at the

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[13] Hohenadel K et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. Int J Environ Res Public Health 2011;8(6):2320–2330.

[14] Higgins JPT and Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0. Updated March 2011. Available: http://handbook.cochrane.org/chapter_9/9_5_4_incorporating_heterogeneity_into_random_effects_models.htm.

International Society for Environmental Epidemiology Conference on August 31, 2015. We cannot verify the accuracy of these results or the published results of any of the other studies included in this analysis.

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Figure 1. Forest plot of meta-analysis of glyphosate use and non-Hodgkin lymphoma risk using unpublished results from Alavanja et al. (2013) in place of previously published results from De Roos et al. (2005) based on the Agricultural Health Study cohort. Some confidence limits are slightly different from those reported in original studies due to the recalculation of standard errors by the Comprehensive Meta-Analysis software (Biostat, Inc., Englewood, NJ).

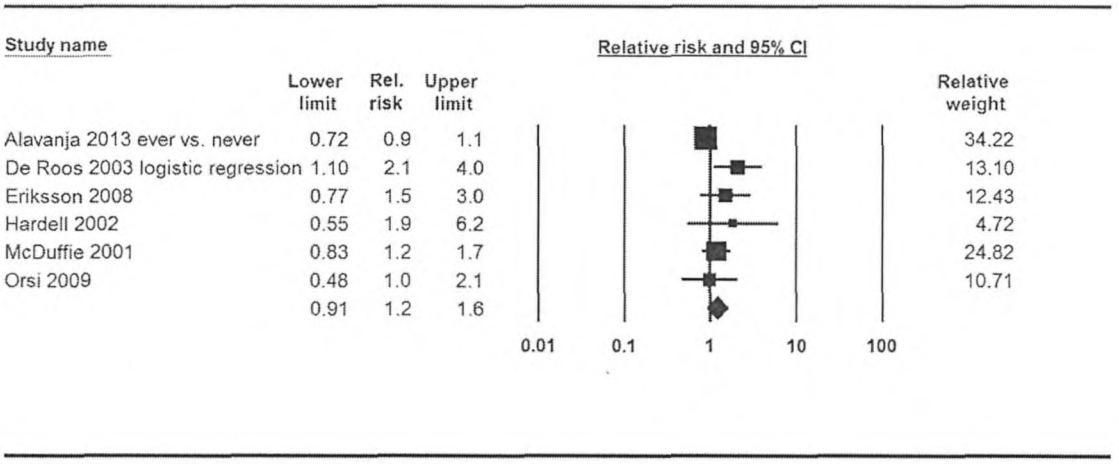

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Table 1. Results of meta-analysis of glyphosate use and non-Hodgkin lymphoma risk including unpublished results from Alavanja et al. (2013) and Pahwa et al. (2015)

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Non-Hodgkin lymphoma	82 cases highly exposed, 249 cases ever exposed based on intensity-weighted exposure, new classification 83 cases highly exposed, 250 cases ever exposed based on total exposure, new classification 60 cases highly exposed, 182 cases ever exposed based on intensity-weighted exposure, old classification 60 cases highly exposed, 183 cases ever exposed based on total exposure, old classification	a. 0.9 (ever vs. never random-effects meta-RR, intensity-weighted exposure, new classification) b. 0.9 (ever vs. never random-effects meta-RR, total exposure, new classification) c. 0.9 (ever vs. never random-effects meta-RR, intensity-weighted exposure, old classification) d. 0.9 (ever vs. never random-effects meta-RR, total exposure, old classification) e. 0.97 (intensity-weighted high exposure, new classification) f. 1.0 (total high exposure, new classification) g. 0.9 (intensity-weighted high exposure, old classification) h. 1.0 (total high exposure, old classification)	a. 0.7–1.1 (ever vs. never random-effects meta-CI, intensity-weighted exposure, new classification) b. 0.7–1.1 (ever vs. never random-effects meta-CI, total exposure, new classification) c. 0.7–1.1 (ever vs. never random-effects meta-CI, intensity-weighted exposure, old classification) d. 0.7–1.1 (ever vs. never random-effects meta-CI, total exposure, old classification) e. 0.7–1.4 (intensity-weighted high exposure, new classification) f. 0.7–1.4 (total high exposure, new classification) g. 0.6–1.4 (intensity-weighted high exposure, old classification) h. 0.7–1.4 (total high exposure, old classification)
2	De Roos et al.	2003	Non-Hodgkin lymphoma	36 cases, 61 controls	a. 2.1 (logistic regression) b. 1.6 (hierarchical regression)	a. 1.1–4.0 (logistic regression) b. 0.9–2.8 (hierarchical regression)
3	De Roos et al.	2005	Non-Hodgkin lymphoma	71 cases (total; not analytic cohort)	1.1	0.7–1.9
4	Eriksson et al.	2008	Non-Hodgkin lymphoma	29 cases, 18 controls	1.51	0.77–2.94
5	Hardell et al.	2002	Non-Hodgkin lymphoma	8 cases, 8 controls	1.85	0.55–6.20
6	Hohenadel et al.	2011	Non-Hodgkin lymphoma	50 cases, 133 controls	1.40 (ever vs. never random-effects meta-RR)	0.62–3.15 (ever vs. never random-effects meta-CI)
7	McDuffie et al.	2001	Non-Hodgkin lymphoma	51 cases, 133 controls	1.20	0.83–1.74
8	Orsi et al.	2009	Non-Hodgkin lymphoma	12 cases, 24 controls	1.0	0.5–2.2

9	Pahwa et al.	2015	Non-Hodgkin lymphoma	113 cases; controls NR	1.13		0.84–1.51			
	Meta-analysis model		**Outcome**	**Studies included**		**Meta-RR**		**95% CI**	I^2	$P_{heterogeneity}$
	***Model 1, random effects**		**Non-Hodgkin lymphoma**	**1a/b/c/d, 2a, 4, 5, 7, 8**	**1.2**		**0.91–1.6**		**42.2%**	**0.12**
	Model 1, fixed effects		"	"	1.1		0.90–1.3		"	"
	Model 2, random effects		"	1e, 2a, 4, 5, 7, 8	1.2		0.97–1.5		9.3%	0.36
	Model 2, fixed effects		"	"	1.2		0.98–1.5		"	"
	Model 3, random effects		"	1f, 2a, 4, 5, 7, 8	1.2		0.99–1.5		2.2%	0.40
	Model 3, fixed effects		"	"	1.2		0.99–1.5		"	"
	Model 4, random effects		"	1g, 2a, 4, 5, 7, 8	1.2		0.96–1.6		14.2%	0.32
	Model 4, fixed effects		"	"	1.2		0.97–1.5		"	"
	Model 5, random effects		"	1h, 2a, 4, 5, 7, 8	1.2		0.99–1.5		2.2%	0.40
	Model 5, fixed effects		"	"	1.2		0.99–1.5		"	"
	Model 6, random effects		"	1a/b/c/d, 2b, 4, 5, 7, 8	1.1		0.90–1.4		21.6%	0.27
	Model 6, fixed effects		"	"	1.1		0.90–1.3		"	"
	Model 7, fixed and random effects		"	1e, 2b, 4, 5, 7, 8	1.2		0.96–1.5		0.0%	0.61
	Model 8, fixed and random effects		"	1f, 2b, 4, 5, 7, 8	1.2		0.97–1.5		0.0%	0.67
	Model 9, fixed and random effects		"	1g, 2b, 4, 5, 7, 8	1.2		0.95–1.5		0.0%	0.56
	Model 10, fixed and random effects		"	1h, 2b, 4, 5, 7, 8	1.2		0.97–1.5		0.0%	0.67
	Model 11, random effects		"	1a/b/c/d, 2a, 4, 5, 6, 8	1.3		0.90–1.8		42.4%	0.12
	Model 11, fixed effects		"	"	1.1		0.88–1.3		"	"
	Model 12, random effects		"	1e, 2a, 4, 5, 6, 8	1.3		0.96–1.6		11.2%	0.34
	Model 12, fixed effects		"	"	1.2		0.96–1.6		"	"
	Model 13, random effects		"	1f, 2a, 4, 5, 6, 8	1.3		0.97–1.6		3.8%	0.39
	Model 13, fixed effects		"	"	1.2		0.97–1.6		"	"
	Model 14, random effects		"	1g, 2a, 4, 5, 6, 8	1.3		0.94–1.7		15.5%	0.31
	Model 14, fixed effects		"	"	1.2		0.95–1.6		"	"
	Model 15, random effects		"	1h, 2a, 4, 5, 6, 8	1.3		0.97–1.6		3.8%	0.39
	Model 15, fixed effects		"	"	1.2		0.97–1.6		"	"
	Model 16, random effects		"	1a/b/c/d, 2b, 4, 5, 6, 8	1.1		0.88–1.5		21.5%	0.27
	Model 16, fixed effects		"	"	1.0		0.87–1.3		"	"
	Model 17, fixed and random effects		"	1e, 2b, 4, 5, 6, 8	1.2		0.94–1.5		0.0%	0.59
	Model 18, fixed and random effects		"	1f, 2b, 4, 5, 6, 8	1.2		0.95–1.5		0.0%	0.64
	Model 19, fixed and random effects		"	1g, 2b, 4, 5, 6, 8	1.2		0.93–1.6		0.0%	0.54
	Model 20, fixed and random effects		"	1h, 2b, 4, 5, 6, 8	1.2		0.95–1.5		0.0%	0.64
	Model 21, fixed and random effects		"	1a/b/c/d, 4, 5, 8, 9	1.0		0.86–1.2		0.0%	0.42
	Model 22, fixed and random effects		"	1e, 4, 5, 8, 9	1.1		0.91–1.4		0.0%	0.71

	Model 23, fixed and random effects		"	1f, 4, 5, 8, 9	1.1	0.91–1.4	0.0%	0.75
	Model 24, fixed and random effects		"	1g, 4, 5, 8, 9	1.1	0.89–1.4	0.0%	0.64
	Model 25, fixed and random effects		"	1h, 4, 5, 8, 9	1.1	0.91–1.4	0.0%	0.75
	Model 26, fixed and random effects		"	3, 4, 5, 8, 9	1.2	0.94–1.5	0.0%	0.85

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Diffuse large B-cell lymphoma	22 cases highly exposed, 68 cases ever exposed based on total exposure	a. 1.0 (ever vs. never random-effects meta-RR, total exposure) b. 0.7 (total high exposure)	a. 0.7–1.4 (ever vs. never random-effects meta-RR, total exposure) b. 0.4–1.3 (total high exposure)
4	Eriksson et al.	2008	Diffuse large B-cell lymphoma	Not reported	1.22	0.44–3.35
8	Orsi et al.	2009	Diffuse large B-cell lymphoma	5 cases, 24 controls	1.0	0.3–2.7
9	Pahwa et al.	2015	Diffuse large B-cell lymphoma	45 cases; controls NR	1.23	0.81–1.88

Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
***Model 1, fixed and random effects**	**Diffuse large B-cell lymphoma**	**1a, 4, 8**	**1.0**	**0.74–1.4**	**0.0%**	**0.94**
Model 2, fixed and random effects	"	1b, 4, 8	0.84	0.53–1.3	0.0%	0.61
Model 3, fixed and random effects	"	1a, 4, 8, 9	1.1	0.85–1.4	0.0%	0.89
Model 4, fixed and random effects	"	1b, 4, 8, 9	1.0	0.76–1.4	0.0%	0.49
Model 5, fixed and random effects	"	4, 8, 9	1.2	0.83–1.7	0.0%	0.94

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	CLL/SLL/MCL	29 cases highly exposed, 90 cases ever exposed based on total exposure	a. 0.9 (ever vs. never random-effects meta-RR, total exposure) b. 1.1 (total high exposure)	a. 0.6–1.3 (ever vs. never random-effects meta-RR, total exposure) b. 0.6–1.8 (total high exposure)
4	Eriksson et al.	2008	CLL/SLL	Not reported	3.35	1.42–7.89
8	Orsi et al.	2009	CLL/SLL	2 cases, 18 controls	0.4	0.1–1.8
9	Pahwa et al.	2015	SLL	15 cases; controls NR	1.79	0.87–3.69

Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
***Model 1, random effects**	**CLL/SLL/MCL**	**1a, 4, 8**	**1.2**	**0.41–3.3**	**78.6%**	**0.009**
Model 1, fixed effects	"	"	1.1	0.75–1.5	"	"
Model 2, random effects	"	1b, 4, 8	1.3	0.47–3.5	73.6%	0.02
Model 2, fixed effects	"	"	1.3	0.87–2.1	"	"
Model 3, random effects	"	1a, 4, 8, 9	1.3	0.64–2.7	72.7%	0.01

	Model 3, fixed effects		"	"	1.2	0.86–1.6	"	"
	Model 4, random effects		"	1b, 4, 8, 9	1.4	0.74–2.8	62.6%	0.05
	Model 4, fixed effects		"	"	1.5	1.0–2.1	"	"
	Model 5, random effects		"	4, 8, 9	1.6	0.59–4.2	67.6%	0.05
	Model 5, fixed effects		"	"	1.9	1.1–3.1	"	"

Study #	Author	Year	Outcome	Number of exposed subjects	RR	95% CI
1	Alavanja et al.	2013	Follicular lymphoma	12 cases highly exposed, 38 cases ever exposed based on total exposure	a. 0.7 (ever vs. never random-effects meta-RR, total exposure) b. 0.7 (total high exposure)	a. 0.4–1.1 (ever vs. never random-effects meta-RR, total exposure) b. 0.4–1.8 (total high exposure)
4	Eriksson et al.	2008	"	Not reported	1.89	0.62–5.79
8	Orsi et al.	2009	"	3 cases, 24 controls	1.4	0.4–5.2
9	Pahwa et al.	2015	Follicular lymphoma	28 cases; controls NR	0.69	0.41–1.15

	Meta-analysis model	Outcome	Studies included	Meta-RR	95% CI	I^2	$P_{heterogeneity}$
	***Model 1, random effects**	**Follicular lymphoma**	**1a, 4, 8**	**1.0**	**0.53–1.9**	**35.2%**	**0.21**
	Model 1, fixed effects	"	"	0.88	0.57–1.4	"	"
	Model 2, random effects	"	1b, 4, 8	1.1	0.60–2.1	75.0%	0.37
	Model 2, fixed effects	"	"	1.1	0.60–2.0	"	"
	Model 3, random effects	"	1a, 4, 8, 9	0.82	0.56–1.2	16.4%	0.31
	Model 3, fixed effects	"	"	0.80	0.57–1.1	"	"
	Model 4, random effects	"	1b, 4, 8, 9	0.86	0.56–1.3	10.5%	0.34
	Model 4, fixed effects	"	"	0.84	0.57–1.2	"	"
	Model 5, random effects	"	4, 8, 9	1.0	0.53–2.0	36.6%	0.21
	Model 5, fixed effects	"	"	0.88	0.57–1.4	"	"

*Primary analysis

CI: confidence interval; CLL: chronic lymphocytic leukemia; MCL: mantle-cell lymphoma; RR: relative risk; SLL: small lymphocytic lymphoma

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Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers

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ABSTRACT

This systematic review and meta-analysis rigorously examines the relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia. Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between any versus no use of glyphosate and risk of NHL (meta-RR = 1.3, 95% confidence interval (CI) = 1.0–1.6, based on six studies) and MM (meta-RR = 1.4, 95% CI = 1.0–1.9; four studies). Associations were statistically null for HL (meta-RR = 1.1, 95% CI = 0.7–1.6; two studies), leukemia (meta-RR = 1.0, 95% CI = 0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). Bias and confounding may account for observed associations. Meta-analysis is constrained by few studies and a crude exposure metric, while the overall body of literature is methodologically limited and findings are not strong or consistent. Thus, a causal relationship has not been established between glyphosate exposure and risk of any type of LHC.

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Introduction

The broad-spectrum herbicide glyphosate (*N*-(phosphonomethyl)glycine), as a constituent of more than 750 products for agricultural, forestry, urban, and residential applications, is the most commonly used herbicide in the world. Therefore, understanding its potential human carcinogenicity has major implications for public health and risk assessment.

In 2014, the German Federal Institute for Risk Assessment (BfR), on behalf of the European Union, reviewed all toxicological studies of glyphosate in laboratory animals, as well as over 30 epidemiological studies in humans, and concluded that "the available data do not show carcinogenic or mutagenic properties of glyphosate" and "there is no validated or significant relationship between exposure to glyphosate and an increased risk of non-Hodgkin lymphoma or other types of cancer."[1,2] This conclusion was consistent with those previously reached by the United States Environmental Protection Agency (U.S. EPA) and the Joint Meeting on Pesticide Residues (JMPR), sponsored by the Food and Agriculture Organization of the United Nations and the World Health Organization (WHO), which concluded that glyphosate was unlikely to be carcinogenic to humans.[3–5]

By contrast, the International Agency for Research on Cancer (IARC) in 2015 classified glyphosate as "probably carcinogenic to humans" (Group 2A). In arriving at this classification, IARC characterized evidence of carcinogenicity in humans as "limited," based on the data available for non-Hodgkin lymphoma (NHL).[6] IARC considered the evidence of carcinogenicity in experimental animals as "sufficient." The latter determination was based on the occurrence of renal tubule carcinoma, hemangiosarcoma, and pancreatic islet-cell adenoma in rodents, as well as mechanistic evidence.

To incorporate the IARC classification into the European Union review of glyphosate, BfR was commissioned by the German government and the European Food Safety Authority (EFSA) to review the IARC assessment.[7] In its subsequent revised assessment report, BfR reached the conclusion that "no carcinogenic risk to humans is to be expected from glyphosate if it is used in the proper manner for the intended purpose."[8] This assessment was supported by all European Union member states except one (Sweden) and by EFSA.[9] The WHO also has established an expert taskforce to re-evaluate the available data on glyphosate and report its findings to JMPR.[10]

In summarizing the epidemiological evidence, IARC stated that "case-control studies in the USA, Canada, and Sweden reported increased risks for NHL associated with exposure to glyphosate. The increased risk persisted in the studies that adjusted for exposure to other pesticides. The [Agricultural Health Study] cohort did not show an excess of NHL. The Working Group noted that there were excesses reported for multiple myeloma in three studies; however, they did not weight this evidence as strongly as that of NHL because of the possibility that chance could not be excluded; none of the risk estimates were statistically significant nor were they adjusted for other pesticide exposures."[6] A recent meta-analysis conducted by investigators from IARC[11] found a statistically significant positive association between glyphosate use and NHL risk (meta-relative risk [RR] = 1.5, 95% confidence interval [CI] = 1.1–2.0), based on six studies.[12–17] The same meta-analysis also found a significant positive association between

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glyphosate use and risk of B-cell NHL, based on two studies.[14,18]

Although Schinasi and Leon[11] stated that in their meta-analysis, "[i]n an effort to use the most unbiased estimate, [they] extracted the most adjusted effect estimate," two or arguably three of the RR estimates that they selected for inclusion were not the most highly adjusted estimates reported by the original authors.[13–15] Instead, in a personal communication (11 August 2015), Dr. Schinasi indicated that other estimates were selected based on considerations of consistency of estimates across meta-analyses of other pesticides, secondary analyses, and statistical modeling approach.

Meta-analyses are not intended to identify, validate, or dispute causal relationships. Although they can be useful in providing a summary measure of association and identifying heterogeneity among research results, they can obscure important differences in methods and results among studies that can be more thoroughly evaluated in a detailed qualitative review. Schinasi and Leon[11] did not assess study quality and did not specifically address the potential impact of study limitations on the findings for glyphosate, nor did they discuss whether the apparent association between glyphosate and NHL risk is likely to be causal. On the other hand, Mink et al.[19] conducted a qualitative systematic review, without a meta-analysis, of epidemiologic studies of glyphosate and various cancers, including NHL. Taking into account potential sources of error, including selection bias, confounding, and especially exposure misclassification, the authors concluded that they "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."

Given the conflicting findings surrounding this issue, we conducted this systematic review and meta-analysis to examine more rigorously the relationship between exposure to glyphosate and risk of NHL, as well as major histopathological subtypes of NHL, in human epidemiologic studies. Because NHL is often considered alongside other lymphohematopoietic cancers (LHC), whose ever-changing classification systems now characterize some leukemias and multiple myeloma (MM) as NHL subtypes,[20] we also included Hodgkin lymphoma (HL), MM, and leukemia in this review. Despite the limitations of quantitative meta-analysis for observational epidemiology,[21,22] we conducted a meta-analysis largely to determine the impact of using RR estimates not used in the meta-analysis by Schinasi and Leon.[11] In addition, we conducted a qualitative evaluation of potential for error and bias. Thus, this article goes beyond previous work by examining all types of LHC, conducting a new meta-analysis, providing a detailed evaluation of study quality and potential for bias, and synthesizing the overall epidemiologic evidence for a causal association between glyphosate and LHC risk.

Methods

Literature search

Sources eligible for inclusion in the meta-analysis were original articles describing epidemiological studies that provided numeric point estimates of the RR (i.e., odds ratio, rate ratio, or prevalence ratio) of LHC, including NHL, HL, MM, leukemia, and any subtypes of these disease entities, associated with individual-level glyphosate exposure, along with corresponding interval estimates (e.g., 95% confidence intervals [CI]) or sufficient raw data to calculate RRs and CIs. Reviews, commentaries, letters to the editor without original data, and non-human studies were excluded, as were articles that did not report quantitative measures of association between glyphosate exposure (e.g., those assessing broadly defined categories of pesticides or herbicides) and risk of LHC (e.g., those assessing other cancers or all malignancies combined).

To identify all potentially relevant articles, we searched MEDLINE via PubMed (Supplementary methods), with additional targeted searches in Web of Science and Google Scholar, along with a review of the bibliographies of recent review articles. Based on a review of titles and abstracts to exclude articles without pertinent information, followed by a review of the full text of relevant articles, 19 articles (as well as one letter to the editor[23] that contained additional results from a study described in another one of the included articles,[24] and one abstract[25] that preceded a full-length article[26]) were ultimately deemed eligible for inclusion (Appendix Fig. A1). Two authors independently reviewed and agreed upon the list of eligible articles.

Of the 19 articles reporting on the association between glyphosate and risk of specific forms of LHC, 12 pertained to NHL or its subtypes (including hairy-cell leukemia, which is a subtype of B-cell NHL),[12–18,24,27–30] 2 pertained to HL,[17,31] 6 pertained to MM,[12,17,26,32–34] and 3 pertained to leukemia.[12,35,36]

Evaluation of study characteristics and quality

From each eligible study, we extracted the following information: first author, publication year, study location, study design, study years, source population, number of subjects, proportion of proxy respondents, exposure assessment method, outcome assessment method, confounders adjusted, number of subjects in each exposure category, and RR estimates with CIs.

In addition to summarizing study characteristics, we qualitatively evaluated the methodological quality of each study in terms of its potential for selection bias, information bias/exposure misclassification, confounding, reporting bias, and other issues affecting validity. Potential for bias was evaluated based on subject identification strategy, participation rates, investigator blinding, assessment methods for exposures, outcomes, and potential confounders, statistical approach, reporting of results, and other considerations.[37–39]

Selection of data for meta-analysis

From each publication, we selected an RR point estimate for inclusion in the meta-analysis based on a set of rules specified *a priori*. First, if unadjusted and adjusted RRs were reported in a publication or across multiple publications from the same study population, the most fully adjusted RR was selected for inclusion. The most fully adjusted RR was defined as the RR estimate that took into consideration, by restriction or statistical adjustment, the most covariates that appeared to be confounders. The rationale for choosing the most fully adjusted RR was

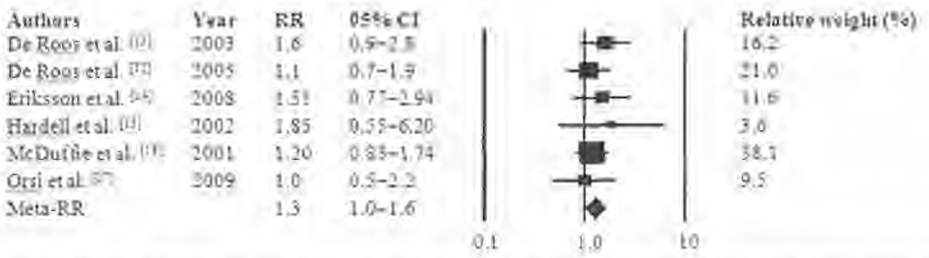

Figure 1. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of non-Hodgkin lymphoma. Meta-RRs were identical in random-effects and fixed-effects models.

based on the assumption that the adjusted covariates were found by the authors to act as confounders by altering the estimate of association (either directly or by acting as a surrogate for another, unmeasured confounder); however, some authors did not explain how confounders were selected, so this assumption may not hold for all studies. If an adjusted RR was not reported, the unadjusted (crude) RR was included as reported by the authors or as calculated from available raw data. Second, if multiple eligible publications were derived from the same study population, the RR from the most recent publication was selected for inclusion unless it was based on a subset of the overall eligible study population, in which case the RR based on the most complete study population was included. Third, subject to the first two rules, the RR for dichotomous exposure with the largest number of exposed cases was selected for inclusion in the meta-analysis. In a few instances where another RR from a given study nearly met these inclusion criteria but was superseded by a more fully adjusted, more recent, or more robust RR, the alternative RR was considered in secondary analyses.

RRs for multiple categories of exposure also were extracted to enable qualitative evaluation of exposure-response trends (based on the assumption, discussed later, that studies were able to distinguish among exposure levels). However, because no two studies used the same set of three or more categories to classify glyphosate exposure, these estimates could not be combined in meta-analysis.

Statistical approach

For associations with at least two independent RR estimates from different study populations, we estimated both fixed-effects and random-effects meta-RRs with 95% CIs. We used comparison of meta-RR estimates from fixed-effects and random-effects models as one approach to the evaluation of the impact of between-study heterogeneity on the meta-RRs. As a quantitative measure of between-study heterogeneity, we calculated I^2, which represents the percentage of between-study variance in RRs that is attributable to study heterogeneity (as opposed to chance).[40] We also tested for statistically significant between-study heterogeneity based on Cochran's Q statistic,[41] although this test has low power to detect modest heterogeneity across a limited number of studies.[42]

In the absence of statistically significant heterogeneity, the presence of at least one statistically significant association, $I^2 <$ 50%, and at least four contributing studies, we evaluated evidence of publication bias (i.e., non-random selection of studies for publication, with a tendency toward submission and publication of studies that report larger, statistically significant associations[43]) by using the linear regression approach of Egger et al.,[44] which measures the degree of funnel plot asymmetry. We also estimated meta-RRs corrected for publication bias by imputing results for missing studies using the trim-and-fill procedure developed by Duval and Tweedie,[45] which iteratively trims asymmetric studies from the overbalanced side of a funnel plot to locate the unbiased effect, and then fills the plot by re-inserting the trimmed studies on the original side of the mean effect, along with their imputed counterparts on the opposite side. Again, we used these approaches with the understanding that they have limited power to detect publication bias based on few studies.[42]

The meta-analysis was conducted using Comprehensive Meta-Analysis Software (Biostat, Inc., Englewood, NJ, USA). All calculated meta-RRs and 95% CIs were confirmed using Episheet (www.krothman.org/episheet.xls).

Sensitivity analysis

To evaluate the robustness of results to various potential sources of heterogeneity, we planned *a priori* to conduct a sensitivity analysis with stratification of studies by study design (case-control vs. cohort), source of controls (population-based vs. hospital-based), gender (males only vs. males and females), geographic region (North America vs. Europe), and time period of cancer diagnosis (1980s, 1990s, or 2000s, with studies contributing to a given stratum if any part of the case diagnosis period was in a given decade).

Overall evaluation

To guide a qualitative assessment of the combined epidemiologic evidence for a causal relationship between glyphosate exposure and risk of LHC, we used Sir Austin Bradford Hill's "viewpoints" as a general framework.[46] Because this review is restricted to the epidemiologic literature, our consideration of the biological plausibility of the association and the coherence of the human, animal, and mechanistic evidence was limited.

Results

Study characteristics and overlap

Studies of NHL and subtypes

Twelve studies from seven independent study populations, including eleven case-control studies and one prospective

cohort study, evaluated the relationship between glyphosate use and risk of NHL and/or its histopathological subtypes.[12–16,24,27–30] Characteristics of these studies are summarized in Table 1. All of the studies considered glyphosate use in agricultural operations or settings, and most evaluated overall NHL as an outcome. The exceptions were Cocco et al.,[18] which analyzed B-cell lymphoma and other NHL subtypes, but not overall NHL, and Nordstrom et al.,[30] which included only hairy-cell leukemia. Eriksson et al.[14] presented results for B-cell lymphoma and other NHL subtypes, as well as for overall NHL, while Orsi et al.[17] included results for overall NHL and several specific NHL subtypes.

De Roos et al.[13] combined data from Cantor et al.[24] with data from two other studies that did not independently report associations between glyphosate use and NHL risk;[47,48] therefore, we did not further consider Cantor et al.[24] as a separate study. Lee et al.[29] was based on Cantor et al.[24] and Hoar Zahm et al.,[48] but not Hoar et al.,[47] and stratified results by asthma status (with no apparent interaction between glyphosate exposure and asthma); therefore, results from De Roos et al.[13] took precedence in our analysis over those from Lee et al.[29] The study by Hardell et al.[15] pooled data from two other studies that reported on glyphosate use and NHL risk.[27,30] Consequently, the latter two studies were not considered further with respect to NHL, although Nordstrom et al.[30] was evaluated separately with respect to hairy-cell leukemia. Based on the same study population as McDuffie et al.[16] (except for four fewer cases excluded after pathology review), Hohenadel et al.[28] reported associations with use of glyphosate with or without malathion, but not glyphosate overall; therefore, the results from McDuffie et al.[16] were prioritized in our analysis.

The seven independent studies ranged markedly in size with respect to the number of NHL cases classified as exposed to glyphosate (based on reported use): Cocco et al.,[18] 4 B-cell lymphoma cases exposed; Hardell et al.,[15] 8 exposed; Orsi et al.,[17] 12 exposed; Eriksson et al.,[14] 29 exposed; De Roos et al.,[13] 36 exposed; McDuffie et al.,[16] 51 exposed; De Roos et al.,[12] 71 exposed in the total eligible cohort. Four studies were based in Europe[14,15,17,18] and three in North America[12,13,16] (Table 1). Four of the case-control studies were population-based,[13–16] one was hospital-based,[17] and one included a mixture of population-based and hospital-based cases and controls.[18] Four studies were restricted to males,[13,15–17] while the rest included males and females. Two studies conducted at least some case ascertainment during the 1980s,[13,15] five during the 1990s,[12,14–16,18] and four during the 2000s[12,14,17,18] (categories are overlapping). For reference, glyphosate entered the U.S. and European commercial markets in 1974.[49]

Studies of HL

Two case-control studies estimated the OR between glyphosate use and risk of HL.[17,31] Characteristics of these studies are summarized in Table 1. The study by Karunanayake et al.[31] used the same methods and source population as McDuffie et al.,[16] but focused on HL rather than NHL.

As described in the section on NHL studies, Orsi et al.[17] was a hospital-based case-control study set in Europe (France), restricted to males, with case ascertainment in the 2000s, participation rates > 90%, and no proxy respondents. This study classified six HL cases as exposed to glyphosate. Karunanayake et al.[31] was a population-based case-control study set in North America (Canada), restricted to males, with case ascertainment in the 1990s, participation rates of 68% for cases and 48% for controls, and an unspecified proportion of proxy respondents. In this study, 38 HL cases were classified as glyphosate-exposed.

Studies of MM

Six studies from four independent study populations, including four case-control studies and two prospective cohort studies, evaluated the association between glyphosate use and risk of MM.[12,17,26,32–34] These studies are described in Table 1. A cross-sectional analysis within a subset of the Agricultural Health Study Cohort examined the association between glyphosate use and risk of monoclonal gammopathy of unknown significance (MGUS), an MM precursor;[50] this study was not included in the present review.

The studies by De Roos et al.[12] and Sorahan[26] were based on virtually identical datasets from the Agricultural Health Study cohort (except that the dataset used by Sorahan was stripped of data on race, state of residence, and applicator type due to privacy concerns; these differences should not have affected the results substantively). Because the Sorahan[26] study included all eligible cohort members, whereas the De Roos et al.[12] study was based on a restricted subset of the cohort with complete data,[51] the Sorahan[26] results were prioritized in our analysis of MM. Brown et al.[32] employed the same methods and source population as Cantor et al.,[24] which was included in the pooled analysis of NHL by De Roos et al.[13] Pahwa et al.[34] and Kachuri et al.[33] conducted overlapping analyses in the same Canadian source population as McDuffie et al.,[16] Hohenadel et al.,[28] and Karunanayake et al.[31] Pahwa et al.[34] included more controls in their analysis, but these controls were excluded from Kachuri et al.[33] because they were younger than any enrolled MM cases (≤29 years) and thus did not contribute meaningfully to the analysis. Kachuri et al.[33] also controlled for more confounders, and therefore was prioritized in our analysis.

With respect to glyphosate use, the four independent studies of MM included, respectively, 5 exposed cases,[17] 11 exposed cases,[32] 24 exposed cases,[26] and 32 exposed cases.[33] All but one study, which was based in France,[17] were conducted in North America, and all except one[26] were restricted to males. One of the two case-control studies was population-based[32] and the other was hospital-based.[17] Case ascertainment took place during the early 1980s in one study,[32] at least partly during the 1990s in two studies,[26,33] and at least partly during the 2000s in two studies.[17,26]

Studies of leukemia

Two case-control studies and one prospective cohort study investigated the relationship between glyphosate use and risk of leukemia.[12,35,36] Key characteristics of these studies are provided in Table 1. The study by Brown et al.[35] used the same methods

Table 1. Design characteristics of studies of glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
Brown et al.[35]	1990	Leukemia (including myelodysplasias)	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa Tumor Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 86% Controls: 77% random digit dialing, 79% Medicare, 77% proxies for deceased Supplemental interview: 93% cases, 96% controls	Cases: 578 Controls: 1,245 Supplemental interview: 86 cases, 203 controls	Cases: 238 (41%) Controls: 425 (34%) Supplemental interview, 63 (73%) cases, 57 (28%) controls
Brown et al.[32]	1993	MM	United States (Iowa)	Population-based case-control	1981–1984	White men aged ≥ 30 years in Iowa	Cases: Iowa Health Registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificates if deceased	Cases: 84% Controls: 78% overall	Cases: 173 Controls: 650	Cases: 72 (42%) Controls: 198 (30%)
Cantor et al.[24]	1992	NHL	United States (Iowa and Minnesota)	Population-based case-control	1980–1983	White men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Iowa State Health Registry and special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 89% Controls: 77% random-digit dialing, 79% Medicare, 77% proxies for deceased	Cases: 622 Controls: 1245	Cases: 184 (30%) Controls: 425 (34%)
Cocco et al.[18]	2013	B-cell NHL	Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain)	Population- and hospital-based case-control	1998–2004	Persons aged ≥ 17 years in Germany and Italy general populations, and in referral areas of participating hospitals in Czech Republic, France, Ireland, and Spain	Cases: NR Controls: random sampling of population registers in Germany and Italy; recruitment from hospital departments for infectious and parasitic (17.6%), mental and nervous (14.6%), circulatory (8.7%), digestive (7.1%), endocrine and metabolic (4.1%), respiratory (3.9%), and several other conditions (33.2%), excluding cancer, in Czech Republic, France, Ireland, and Spain	Cases: 88% overall; 90% Czech Republic, 91% France, 87% Germany, 90% Ireland, 93% Italy, 82% Spain Controls: 69% overall, 81% hospital-based, 52% population-based; 60% Czech Republic, 74% France, 44% Germany, 75% Ireland, 66% Italy, 96% Spain	Cases: 2348 Controls: 2462	None
De Roos et al.[13]	2003	NHL	United States (Nebraska, Iowa, Minnesota, and Kansas)	Population-based case-control (pooled analysis of 3 studies)	1979–1986	White men aged ≥ 21 years in one of the 66 counties of eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester; white men aged ≥ 21 years in Kansas	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records; University of Kansas Cancer Data Service registry Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska (93% living, 89% deceased); 89% Iowa and Minnesota; 96% Kansas Controls: 85% Nebraska; 77% random-digit dialing, 79% Medicare, 77% deceased (proxies) Iowa and Minnesota; 93% Kansas Analysis restricted to subjects who lived or worked on a farm before 18 years of age (% NR); analysis of multiple pesticides restricted to subjects with non-missing data (75% cases, 75% controls)	Cases: 650 (in analyses of multiple pesticides) Controls: 1933 (in analyses of multiple pesticides)	Cases: 201 (30.9%) (in analyses of multiple pesticides) Controls: 767 (39.7%) (in analyses of multiple pesticides)
De Roos et al.[12]	2005	LHC, NHL, MM, leukemia	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort: 36,509–49,211 in analyses adjusted for demographics and lifestyle 30,613–40,719 in analyses additionally adjusted for other pesticides	None
Eriksson et al.[14]	2008	NHL, B-cell NHL, SLL/CLL, FL grades I-III, DLBCL, other specified B-cell NHL, unspecified B-cell NHL, T-cell NHL, unspecified NHL	Europe (Sweden)	Population-based case-control	1999–2002	Adults aged 18–74 years in 4 of 7 health service regions in Sweden associated with university hospitals in Lund, Linköping, Örebro, and Umeå	Cases: contact with treating physicians and pathologists Controls: national population registry	Cases: 81% Controls: 65% (92% of initially enrolled controls with 71% participation)	Cases: 995 Controls: 1016	None

Hardell and Eriksson[27]	1999	NHL	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden	Cases: regional cancer registries Controls: national population registry if living, national registry for causes of death if deceased	Cases: 91% (91% living, 92% deceased) Controls: 84% (83% living, 85% deceased)	Cases: 404 Controls: 741	Cases: 177 (44%) Controls: NR (~44%; matched to cases)
Hardell et al.[15]	2002	NHL including hairy-cell leukemia	Europe (Sweden)	Population-based case-control	1987–1990	Men aged ≥ 25 years in the four northernmost counties of Sweden and three counties in mid-Sweden (for NHL) or in the entire country of Sweden (for hairy-cell leukemia)	Cases: regional cancer registries for NHL, national cancer registry for hairy-cell leukemia Controls: national population registry, national registry for causes of death if deceased	Cases: 91% Controls: 84%	Cases: 515 Controls: 1141	Cases: ~35% (NR) Controls: ~29% (NR)
Hohenadel et al.[28]	2011	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 513 Controls: 1506	Cases: 110 (21%) Controls: 220 (15%)
Kachuri et al.[33]	2013	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years (≥ 30 years in analysis) in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1357	Cases: 103 (30%) Controls: 202 (15%)
Karunanayake et al.[31]	2012	HL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 68% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 316 Controls: 1506	Cases: NR Controls: 220 (15%)
Kaufman et al.[36]	2009	Leukemia	Bangkok, Thailand	Hospital-based case-control	1997–2003	Patients aged ≥ 18 years residing in Bangkok proper and suburbs of Nonthaburi, Nakornpathom, Patumthani, Samutprakarn, and Samusakorn, admitted to Siriraj Hospital or Dhonburi Hospital	Cases: hospital records Controls: hospital records for acute infection or inflammation (33%), trauma (22%), acute abdominal emergencies such as appendicitis (27%), or various other diagnoses with elective admission, such as cataract, hernia repair, or cosmetic surgery (17%), excluding head trauma with loss of consciousness or cancer; controls at Dhonburi Hospital (a nearby private hospital) matched to 21 cases admitted to private wards for wealthy patients	Cases: 100% Controls: 100%	Cases: 180 Controls: 756	None
Lee et al.[29]	2004	NHL	United States (Nebraska, Iowa, and Minnesota)	Population-based case-control (pooled analysis of 2 studies)	1980–1986	White men and women aged ≥ 21 years in one of 45 counties in eastern Nebraska; white men aged ≥ 30 years in Iowa and Minnesota, excluding Minneapolis, St. Paul, Duluth, and Rochester	Cases: Nebraska Lymphoma Study Group and area hospitals; Iowa State Health Registry; special surveillance of Minnesota hospital and pathology laboratory records Controls: random-digit dialing if aged < 65 years, Medicare files if aged ≥ 65 years, state death certificate files if deceased	Cases: 91% Nebraska, 89% Iowa and Minnesota Controls: 85% Nebraska, 78% Iowa and Minnesota	Cases: 872 Controls: 2336	Cases: 266 (31%) Controls: 779 (33%)

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Table 1. (*Continued*)

Authors	Year	Outcomes studied	Study location	Study design	Study years	Source population	Subject identification	Subject participation	Subjects (n)	Proxy respondents
McDuffie et al.[16]	2001	NHL	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 67% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 517 Controls: 1506	Cases: ~21% (NR) Controls: 220 (15%)
Nordström et al.[30]	1998	Hairy-cell leukemia	Europe (Sweden)	Population-based case-control	1987–1992 (1993 for one case)	Men living in Sweden	Cases: national cancer registry Controls: national population registry	Cases: 91% Controls: 83%	Cases: 111 Controls: 400	Cases: 4 (4%) Controls: 5 (1%)
Orsi et al.[17]	2009	LHC, NHL, DLBCL, FL, LPS, CLL, hairy-cell leukemia, HL, MM	Europe (France)	Hospital-based case-control	2000–2004	Men aged 20–75 years living in the catchment areas of the main hospitals in Brest, Caen, Nantes, Lille, Toulouse, and Bordeaux, with no history of immunosuppression or taking *immunosuppressant* drugs	Cases: hospital records Controls: hospital records for orthopedic or rheumatological conditions (89.3%), gastrointestinal or genitourinary tract diseases (4.8%), cardiovascular diseases (1.1%), skin and subcutaneous tissue disease (1.8%), and infections (3.0%), *excluding patients* admitted for cancer or a disease directly related to occupation, smoking, or alcohol abuse	Cases: 95.7% Controls: 91.2%	Cases: 491 LHC, 244 NHL, 104 LPS, 87 HL, 56 MM Controls: 456	None
Pahwa et al.[34]	2012	MM	Canada (Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan)	Population-based case-control	1991–1994	Men aged ≥ 19 years in Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan	Cases: hospital records in Quebec, cancer registries in all other provinces Controls: provincial health insurance records in Alberta, Saskatchewan, Manitoba, and Quebec; computerized telephone listings in Ontario; voter lists in British Columbia	Cases: 58% Controls: 48% Based on postal codes, respondents were not more or less likely than non-respondents to live in a rural area.	Cases: 342 Controls: 1506	Cases: 103 (30%) Controls: 220 (15%)
Sorahan[26]	2015	MM	United States (Iowa and North Carolina)	Prospective cohort	1993–1997 through 2001 Median = 6.7 years	Private and commercial pesticide applicators in Iowa and North Carolina who were licensed to apply restricted-use pesticides	Pesticide applicators identified when seeking a state-issued restricted-use pesticide license; invited to complete the enrollment questionnaire at the licensing facility	298 subjects (0.5%) lost to follow-up or with no person-time contributed > 80% of eligible pesticide applicators enrolled in study by completing on-site questionnaire 44% of applicators completed take-home questionnaire	Eligible cohort (1): 54,315 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, or missing glyphosate use 49,211 also excluding missing education, smoking, or alcohol 40,719 excluding missing other pesticides Eligible cohort (2): 53,656 excluding subjects with cancer before enrollment, loss to follow-up, missing age at enrollment, missing glyphosate use, or missing cumulative exposure days of glyphosateuse 53,304 also excluding missing intensity of glyphosate use Eligible cohort (3): 55,934 excluding subjects with cancer before enrollment, loss to follow-up, or missing age at enrollment	None

Table 1. Continued (additional columns).

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Brown et al.[35]	1990	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, and personal applying/mixing/handling In 1987, supplemental telephone interview to evaluate usual number of days of pesticide use per year among Iowa subjects who had reported agricultural use of specific pesticides	Diagnostic confirmation by regional pathologists; special review of myelodysplasias by one pathologist co-author	No	Adjusted: vital status, age, state, ever used tobacco daily, first-degree family history of LHC, non-farming job related to leukemia risk in this study, exposure to substances (benzene, naphtha, hair dyes) related to leukemia risk in this study	Partial support from National Institute of Environmental Health Sciences	Brown et al.[32]; Cantor et al.[24]; De Roos et al.[13]; Lee et al.[29]
Brown et al.[32]	1993	In-person structured interview, including detailed farming and pesticide use history For each pesticide, evaluated ever use, first and last year of use, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation by an expert pathologist	No	Adjusted: vital status, age Considered: smoking, education, other factors found not to be confounders of agricultural risk factors	Partial support from National Institute of Environmental Health Sciences	Brown et al.[35]; Cantor et al.[24]; De Roos et al.[13]; Lee et al.[29]
Cantor et al.[24]	1992	In-person structured interview, including detailed farming and pesticide use history of all subjects who had worked on a farm for ≥ 6 months since age 18 years For each pesticide, evaluated ever use, first and last year of use, method of application, personal applying/mixing/handling, and use of protective equipment	Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	No	Adjusted: vital status, state, age, cigarette smoking status, first-degree family history of LHC, non-farming job related to NHL risk in this study, exposure to hair dyes, exposure to other substances associated with NHL risk in this study Considered: pesticides belonging to other chemical families	Partial support from National Institute of Environmental Health Sciences	Brown et al.[35]; Brown et al.[32]; De Roos et al.[13]; Lee et al.[29]
Cocco et al.[118]	2013	In-person structured interview, including detailed farming and pesticide use history for all subjects who reported having worked in agriculture For each agricultural job, reported tasks, crops, size of cultivated area, pests treated, pesticides used, crop treatment procedures, use of personal protective equipment, re-entry after treatment, and frequency of treatment in days per year	Histologically or cytologically confirmed cases with central review of slides of ~20% by an international team of pathologists	No	Adjusted: age, gender, education, study center	European Commission, 5th and 6th Framework Programmes; Spanish Ministry of Health; German Federal Office for Radiation Protection; La Fondation de France; Italian Ministry for Education, University and Research; Italian Association for Cancer Research	None
De Roos et al.[13]	2003	Telephone interview in Nebraska and Kansas; in-person structured interview in Iowa and Minnesota Nebraska: Question about use of any pesticide, followed by prompting for specific selected pesticides, including years of use and average days per year Iowa and Minnesota: Direct question about a selected use of specific pesticides, including first and last years of use Kansas: Open-ended question about use of pesticides, followed by questions on duration of use and days per year for groups of pesticides but not individual pesticides (with validation study)	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists Kansas: Diagnostic confirmation and classification by panel of 3 pathologists	Yes in Nebraska; no in Iowa, Minnesota, and Kansas	Adjusted: age, study site, other individual pesticides with ≥ 20 users in full study Considered: first-degree family history of LHC, education, smoking	NR; assume National Cancer Institute	Brown et al.[35]; Brown et al.[32]; Cantor et al.[24]; Lee et al.[29] (also Hoar et al.[47]; Hoar Zahm et al.[48])
De Roos et al.[12]	2005	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors	Linkage to state cancer registry files, state death registries, and National Death Index	None	Adjusted: age at enrollment, education, cigarette smoking pack-years, alcohol consumption in past year, first-degree family history of cancer, state of residence Considered (adjusted for MM only): 5 pesticides for which cumulative exposure-days were most highly associated with those for glyphosate (i.e., 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, trifluralin), 5 pesticides for which ever/never use was most highly associated with that for glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, diazinon)	National Cancer Institute, National Institute of Environmental Health Sciences, Environmental Protection Agency, and National Institute for Occupational Safety and Health	Sorahan[26]
Eriksson et al.[14]	2008	Self-administered mailed questionnaire with additional telephone interview for missing or unclear answers; evaluated occupational exposure to individual pesticides, including number of years, number of days per year, and approximate length of exposure per day	Diagnostic pathological specimens examined and classified by 1 of 5 Swedish expert lymphoma reference pathologists, if not already initially reviewed by one of them; panel review if classification differed from original report	Yes	Adjusted: age, sex, and year of diagnosis or enrollment; other associated agents (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid and/or 2,4,5-trichlorophenoxyacetic acid, mercurial seed dressing, arsenic, creosote, tar) for NHL only	Swedish Council for Working Life and Social Research; Cancer and Allergy Fund; Key Fund; Örebro University Hospital Cancer Fund	None

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Table 1. (*Continued*)

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Hardell and Eriksson[27]	1999	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed use of pesticides within different occupations, wet contact if not handling the sprayer, brand names of pesticides, years of exposure, and cumulative days of exposure Exposure excluded 1 year prior to diagnosis or index year	Histopathological diagnosis of NHL reported to regional cancer registries, confirmed by review of pathology reports	Yes	Adjusted: age, county, vital status, year of death if deceased, use of phenoxyacetic acids	Swedish Work Environment Fund, Swedish Medical Research Council, Örebro County Council Research Committee, Örebro Medical Center Research Foundation	Hardell et al.[75]
Hardell et al.[33]	2002	Self-administered mailed questionnaire with supplemental telephone interview for unclear answers; assessed years and total number of days of occupational exposure to various agents and names of agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Histologically verified NHL; confirmation of hairy-cell leukemia NR	Yes	Adjusted: study, study area, vital status, other associated pesticides (4-chloro-2-methyl phenoxyacetic acid, 2,4-dichlorophenoxyacetic acid + 2,4,5-trichlorophenoxyacetic acid, other herbicides)	Swedish Cancer Research Fund, Swedish Medical Research Council, Örebro County Council Research Committee, Örebro Medical Centre Research Foundation	Hardell and Eriksson[27] Nordström et al.[40]
Hohenadel et al.[28]	2011	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent Considered: diesel exhaust, ultraviolet radiation, farm animals, chemicals such as benzene, first-degree family history of cancer	Health Canada, British Columbia Health Research Foundation, Centre for Agricultural Medicine at University of Saskatchewan	Kachuri et al.[32]; Karunanayake et al.[31]; McDuffie et al.[16]; Pahwa et al.[34]
Kachuri et al.[32]	2013	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, use of a proxy respondent, smoking status, personal history of rheumatoid arthritis, allergies, measles, shingles, or cancer, family history of cancer	Occupational Cancer Research Centre; Cancer Care Ontario; Ontario Workplace Safety and Insurance Board; Canadian Cancer Society, Ontario Division, Mitacs-Accelerate Graduate Research Internship Program	Hohenadel et al.[28]; Karunanayake et al.[31]; McDuffie et al.[16]; Pahwa et al.[34]
Karunanayake et al.[31]	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours/year of cumulative exposure to any combination of herbicides, insecticides, fungicides, fumigants, and algicides Pesticide interview collected information on exposure to individual pesticides, place of pesticide use, year of first use, first year on market, number of years of use, and days per year of use (Note differences from related studies)	Initial diagnosis based on information from cancer registries and hospitals; pathology and tumor tissue slides for 155 of 316 cases reviewed by a reference pathologist who confirmed HL in 150/155 cases, plus 7 cases originally classified as NHL; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, acne, hay fever, or shingles, first-degree family history of cancer	NR; assume same as in related studies	Hohenadel et al.[28]; Kachuri et al.[32]; McDuffie et al.[16]; Pahwa et al.[34]
Kaufman et al.[36]	2009	Interview with nurse to assess occupational and non-occupational exposure to pesticides and other potential risk factors	Histologically confirmed leukemia diagnosed within 6 months before current hospital attendance or admission	No	Considered: age, sex, income, use of cellular telephones, benzene and other solvent exposure, occupational and non-occupational pesticide exposure, pesticides used near home, working with power lines, living near power lines, exposure to X-rays, exposure to certain types of electromagnetic fields, use of hair dyes	Thailand Research Fund and Commission on Higher Education	None
Lee et al.[29]	2004	Telephone interview in Nebraska; in-person structured interview in Iowa and Minnesota Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with years of first and last use	Nebraska: Pathology review with histological confirmation and classification including immunologic phenotyping Iowa and Minnesota: Diagnostic confirmation and morphological classification by panel of 4 experienced regional pathologists	Yes in Nebraska; no in Iowa and Minnesota	Adjusted: age, state, vital status Considered: gender, smoking, first-degree family history of LHC, ever having a job correlated with risk of LHC (e.g., painting or welding), use of protective equipment	NR; assume National Cancer Institute	Brown et al.[35]; Brown et al.[74]; Cantor et al.[24]; De Roos et al.[14] (also Hoar Zahm et al.[48])

McDuffie et al.[16]	2001	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 hours of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 hours (total = 179 cases, 456 controls with telephone interview) Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist; subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, cancer, or allergy desensitization shots, first-degree family history of cancer Considered: pesticide exposure, smoking history	Health Canada, British Columbia Health Research Foundation, Centre for Agricultural Medicine at University of Saskatchewan	Hohenadel et al.[18]; Kachuri et al.[33]; Karunanayake et al.[11]; Pahwa et al.[34]
Nordström et al.[30]	1998	Self-administered mailed questionnaire with supplemental telephone interview for unclear or missing answers; assessed total number of days of occupational exposure to various agents Exposure defined as ≥ 1 working day with induction period of ≥ 1 year	Reported to national cancer registry; further confirmation not described	Yes	Adjusted: age Considered: exposure to animals, herbicides, insecticides, fungicides, impregnating agents, organic solvents, exhausts, or ultraviolet light	Swedish Work Environment Fund, Örebro County Council Research Committee, Örebro Medical Centre Research Foundation.	Hardell et al.[15]
Orsi et al.[17]	2009	Self-administered written questionnaire with lifetime occupational history, followed by in-person structured interview evaluating non-occupational exposure to pesticides and agricultural questionnaire for subjects who had worked as a farmer or gardener for ≥ 6 months during lifetime Agricultural questionnaire collected data on location of all farms where subject had worked for ≥ 6 months, period of occupation and area, farmer's status at each farm, crops and animal husbandry with mean sizes, all pesticides used on each crop during a given period, whether subject had personally prepared, mixed, or sprayed the pesticide, chemical used, brand name, main use, type of spraying equipment used, annual number and duration of applications, and use of pesticides in farm buildings for animals, grain, hay or straw, or to clear lanes and yards All questionnaires reviewed by an occupational hygienist and an agronomist; repeat telephone interviews conducted to clarify information from 95 (56.8%) of 158 subjects who completed the agricultural questionnaire, not completed by 35 (20.8%) who refused (n = 15), died/were in poor health (n = 10), or could not be contacted (n = 15); all chemicals coded using ad hoc system and classified as definite or possible exposure	All diagnoses cytologically or histologically confirmed and reviewed by a panel of pathologists and hematologists	Yes	Adjusted: age, study center, socioeconomic category Considered: all combinations of pesticide families associated with the LHC subtype considered with a p-value ≤ 0.10, rural/urban status, type of housing, educational level, history of mononucleosis, history of influenza immunization, family history of cancer, skin characteristics, smoking status, and alcohol drinking status	Association pour la Recherche contre le Cancer, Fondation de France, AFSSET, Faberge employees (donation)	None
Pahwa et al.[34]	2012	Telephone interview for detailed information on pesticide use in subjects who reported in a self-administered mail questionnaire that they had ≥ 10 h of pesticide use during their lifetime, plus 15% random sample of subjects with < 10 h Pesticide interview (with validation study) included a pre-mailed list of specific pesticides (chemical and trade names) with number of days used and number of hours per day at home or work for each pesticide	Diagnostic confirmation based on information, including pathology reports, from cancer registries and hospitals; pathological material reviewed and classified by a reference pathologist (including pathology and tumor tissue slides for 125 [37%] of 342 cases); subjects with unavailable pathological material retained in study	No	Adjusted: age, province, personal history of measles, mumps, allergies, arthritis, or shingles, first-degree family history of cancer	Occupational Cancer Research Centre; Cancer Care Ontario; Ontario Workplace Safety and Insurance Board; Canadian Cancer Society	Hohenadel et al.[18]; Kachuri et al.[33]; Karunanayake et al.[11]; McDuffie et al.[16]

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Table 1. (*Continued*)

Authors	Year	Exposure assessment	Outcome assessment	Investigator blinding	Confounders considered or adjusted	Funding source	Overlap
Sorahan[26]	2015	Self-administered written questionnaire (with validation study) evaluating detailed use of 22 pesticides for private applicators, 28 pesticides for commercial applicators (ever/never use, frequency, duration, and intensity of use, decade of first use), and ever/never use for additional pesticides up to total of 50, with general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair Additional self-administered take-home questionnaire with further questions on occupational exposures and lifestyle factors Missing data classified into "not known/missing" category, with unknown use of 2,4-dichlorophenoxyacetic acid classified with no use and unknown education classified with no education beyond high school due to lack of MM cases in unknown categories	Linkage to state cancer registry files, state death registries, and National Death Index	None	Fully adjusted: age, gender, smoking pack-years, alcohol use in year before enrollment, first-degree family history of cancer, education, use of 2,4-dichlorophenoxyacetic acid, alachlor, atrazine, metolachlor, or trifluralin, ever use of benomyl, maneb, paraquat, carbaryl, or diazinon Intermediate adjusted: age, gender, smoking, alcohol, family history of cancer, education Adjusted in full cohort: age, gender, family history of cancer, education	Monsanto Europe SA/NV	De Roos et al.[12]

CI: confidence interval; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; LHC: lymphohematopoietic cancer; LPS: lymphoproliferative syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; NR: not reported; OR: odds ratio; SLL: small lymphocytic lymphoma.

and source population as Brown et al.,[32] which was described in the section on MM, and Cantor et al.,[24] which was included as part of De Roos et al.[13] in a pooled analysis of NHL.

As described earlier, De Roos et al.,[12] the only prospective cohort study included, was based in North America (Iowa and North Carolina), enrolled both males and females, ascertained cancer incidence in the 1990s and 2000s, and had a 99.5% follow-up rate through 2001. In the total eligible cohort, 43 leukemia cases occurred among glyphosate users. Brown et al.[55] was a population-based case-control study set in North America (Iowa and Minnesota), restricted to white males, with cases identified in 1980–1983, participation rates of 86% for cases and 77–79% for controls, and proxy respondent rates of 41% for cases and 34% for controls. Fifteen leukemia cases in this study were classified as having used glyphosate. The other case-control study of leukemia, by Kaufman et al.,[56] was a hospital-based study set in Asia (Thailand), with males and females, case ascertainment in the 1990s and 2000s, participation rates of 100%, and no proxy respondents for cases or controls.

Meta-analysis

NHL

All relevant RRs and 95% CIs for the association between reported glyphosate use and risk of overall NHL, including those not used in the meta-analysis, such as estimates within subgroups, minimally adjusted estimates, and estimates of exposure-response patterns, are provided in Table 2. The estimates selected from each independent study population for inclusion in the meta-analysis, according to the rules specified in the methods section, are provided in Table 3.

As shown in Table 3 and Fig. 1, the combined meta-RR for overall NHL in association with any use of glyphosate, based on six studies,[12–17] was 1.3 (95% CI = 1.0–1.6). The results were identical in the random-effects and fixed-effects models, suggesting limited between-study heterogeneity in the association. Little heterogeneity also was indicated by the I^2 value of 0.0% and the highly non-significant P-value of 0.84 for Cochran's Q. Given the lack of heterogeneity and at least one statistically significant association, we tested for publication bias using Egger's linear regression approach to evaluating funnel plot asymmetry, and found no significant asymmetry (one-tailed P-value = 0.20). Using Duval and Tweedie's trim-and-fill approach to adjust for publication bias, the imputed meta-RR for both the random-effects and fixed-effects models was 1.2 (95% CI = 1.0–1.6).

In secondary analyses, we replaced the RR estimated by De Roos et al.[13] using a hierarchical (i.e., multistage) regression model with the RR estimated using a more traditional logistic regression model (Table 3). (The hierarchical regression RR was selected for the primary analysis because, as stated by the authors, hierarchical regression models can yield "increased precision and accuracy for the ensemble of estimates" when modeling multiple pesticides simultaneously, and the more conservative prior assumptions specified in these models "seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL.") Using the logistic regression RR did not appreciably affect the results of the meta-analysis (meta-RR = 1.3, 95% CI = 1.0–1.6; identical for random-effects and fixed-effects models).

In another secondary analysis, we replaced the RR reported by McDuffie et al.[16] with the results reported by Hohenadel et al.[28] in the same study population (minus four previously misclassified NHL cases) (Table 3). Because Hohenadel et al.[28] reported two estimates for glyphosate use—one in the absence of malathion use and one in the presence of malathion use—we combined these two estimates into a single estimate (RR = 1.40, 95% CI = 0.62–3.15) using random-effects meta-analysis. Using this alternative estimate also did not appreciably affect the meta-RR (1.3, 95% CI = 1.0–1.7; identical for random-effects and fixed-effects models). Finally, using both the logistic regression RR instead of the hierarchical regression RR from De Roos et al.[13] and the combined RR from Hohenadel et al.[28] instead of the RR from McDuffie et al.[16] slightly but non-significantly increased the meta-RR to 1.4 (95% CI = 1.0–1.8; identical for random-effects and fixed-effects models) (Table 3).

As noted earlier, in their meta-analysis of the association between glyphosate use and NHL risk, Schinasi and Leon[11] included RR estimates from Eriksson et al.[14] and Hardell et al.[15] that were not the most highly adjusted estimates reported by the authors (shown in Table 2 as univariate odds ratios). They also used the logistic regression estimate from De Roos et al.[13] that arguably was not as highly adjusted as the hierarchical regression estimate. When we included these estimates in the meta-analysis, along with the same estimates from De Roos et al.,[13] McDuffie et al.,[16] and Orsi et al.[17] as included in our main meta-analysis, we obtained the same results as reported by Schinasi and Leon:[11] random-effects meta-RR = 1.5, 95% CI = 1.1–2.0 (I^2 = 32.7%, $p_{heterogeneity}$ = 0.19). The fixed-effects meta-RR based on these estimates (not reported by Schinasi and Leon[11]) was 1.4 (95% CI = 1.1–1.8).

NHL subtypes

All reported RRs and 95% CIs for the association between glyphosate use and risk of various NHL subtypes are shown in Table 2. The estimates included in meta-analyses, which were conducted for B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia (i.e., all NHL subtypes for which at least two estimates from independent studies were available), are shown in Table 3. Too few studies of any given NHL subtype were conducted to justify testing for publication bias.

The meta-RR for the association between any use of glyphosate and risk of B-cell lymphoma, based on two studies,[14,18] was 2.0 (95% CI = 1.1–3.6) according to both the random-effects and the fixed-effects model (I^2 = 0.0%, $p_{heterogeneity}$ = 0.58) (Table 3). These results are the same as reported by Schinasi and Leon.[11] The four B-cell lymphoma cases who were classified by Cocco et al.[18] as having used glyphosate consisted of one patient with diffuse large B-cell lymphoma, one with chronic lymphocytic

Table 2. Estimated associations between glyphosate exposure and risk of lymphohematopoietic cancer (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Authors	Year	Exposure groups and number of subjects	Relative risk	95% CI
Brown et al.[35]	1990	Non-farmers: 243 cases, 547 controls	Leukemia OR = 0.9	Leukemia 95% CI = 0.5–1.6
		Ever mixed, handled, or applied glyphosate: 15 cases, 49 controls		
Brown et al.[32]	1993	Non-farmers: 62 cases, 272 controls	MM OR = 1.7	MM 95% CI = 0.8–3.6
		Ever mixed, handled, or applied glyphosate: 11 cases, 40 controls	Among those who did not use protective equipment, MM OR = 1.9	Among those who did not use protective equipment, MM 95% CI = NR
Cantor et al.[24]	1992	Non-farmers: 226 cases, 547 controls	NHL OR = 1.1	NHL 95% CI = 0.7–1.9
		Ever handled, mixed, or applied glyphosate: 26 cases, 49 controls		
Cocco et al.[18]	2013	Unexposed to any pesticides: NR cases, 2262 controls	B-cell NHL OR = 3.1	B-cell NHL 95% CI = 0.6–17.1
		Occupationally exposed to glyphosate: 4 cases (1 DLBCL, 1 CLL, 1 MM, 1 unspecified B-cell NHL), 2 controls		
De Roos et al.[13]	2003	Unexposed to glyphosate: 614 cases, 1892 controls	Hierarchical regression NHL OR = 1.6	Hierarchical regression NHL 95% CI = 0.9–2.8
		Exposed to glyphosate: 36 cases, 61 controls	Logistic regression NHL OR = 2.1	Logistic regression NHL 95% CI = 1.1–4.0
De Roos et al.[12]	2005	Never used glyphosate: 47 LHC, 21 NHL, 8 MM, 14 leukemia; 13,280 cohort members	Fully adjusted LHC RR = 1.1	Fully adjusted LHC 95% CI = 0.8–1.6
			Age-adjusted LHC RR = 1.1	Age-adjusted LHC 95% CI = 0.8–1.5
		Ever used glyphosate: 143 LHC, 71 NHL, 24 MM, 43 leukemia; 41,035 cohort members	Fully adjusted NHL RR = 1.1	Fully adjusted NHL 95% CI = 0.7–1.9
			Age-adjusted NHL RR = 1.2	Age-adjusted NHL 95% CI = 0.7–1.9
			Fully adjusted MM RR = 2.6 (2.6 in Iowa, 2.7 in North Carolina)	Fully adjusted MM 95% CI = 0.7–9.4
			Age-adjusted MM RR = 1.1	Age-adjusted MM 95% CI = 0.5–2.4
			Fully adjusted leukemia RR = 1.0	Fully adjusted leukemia 95% CI = 0.5–1.9
			Age-adjusted leukemia RR = 1.1	Age-adjusted leukemia 95% CI = 0.6–2.0
		1–20 glyphosate exposure days: 48 LHC, 29 NHL, 8 MM, 9 leukemia	Cumulative exposure days, tertiles 2 and 3 vs. 1	Cumulative exposure days, tertiles 2 and 3 vs. 1
			LHC RRs = 1.2, 1.2; p-trend = 0.69	LHC 95% CIs = 0.8–1.8, 0.8–1.8
		21–56 glyphosate exposure days: 38 LHC, 15 NHL, 5 MM, 14 leukemia	NHL RRs = 0.7, 0.9; p-trend = 0.73	NHL 95% CIs = 0.4–1.4, 0.5–1.6
			MM RRs = 1.1, 1.9; p-trend = 0.27	MM 95% CIs = 0.4–3.5, 0.6–6.3
		57–2,678 glyphosate exposure days: 36 LHC, 17 NHL, 6 MM, 9 leukemia	Leukemia RRs = 1.9, 1.0; p-trend = 0.61	Leukemia 95% CIs = 0.8–4.5, 0.4–2.9
			> 108 vs. > 0–9 exposure days, NHL RR = 0.9	> 108 vs. > 0–9 exposure days, NHL 95% CI = 0.4–2.1
		0.1–79.5 intensity-weighted glyphosate exposure days: 38 LHC, 24 NHL, 5 MM, 7 leukemia	Intensity-weighted exposure days, tertiles 2 and 3 vs. 1	Intensity-weighted exposure days, tertiles 2 and 3 vs. 1
			LHC RRs = 1.0, 1.0; p-trend = 0.90	LHC 95% CIs = 0.6–1.5, 0.7–1.6
		79.6–337.1 intensity-weighted glyphosate exposure days: 40 LHC, 15 NHL, 6 MM, 17 leukemia	NHL RRs = 0.6, 0.8; p-trend = 0.99	NHL 95% CIs = 0.3–1.1, 0.5–1.4
			MM RRs = 1.2, 2.1; p-trend = 0.17	MM 95% CIs = 0.4–3.8, 0.6–7.0
		337.2–18,241 intensity-weighted glyphosate exposure days: 43 LHC, 22 NHL, 8 MM, 8 leukemia	Leukemia RRs = 1.9, 0.7; p-trend = 0.11	Leukemia 95% CIs = 0.8–4.7, 0.2–2.1
			Intensity tertile 3 vs. 1	Intensity tertile 3 vs. 1
			MM RR = 0.6	MM 95% CI = 0.2–1.8
			Cumulative exposure days, tertiles 1, 2, and 3 vs. never	Cumulative exposure days, tertiles 1, 2, and 3 vs. never
			MM RRs = 2.3, 2.6, 4.4; p-trend = 0.09	MM 95% CIs = 0.6–8.9, 0.6–11.5, 1.0–20.2
			Cumulative exposure days, quartile 4 vs. never	Cumulative exposure days, quartile 4 vs. never
			MM RR = 6.6; p-trend = 0.01	MM 95% CI = 1.4–30.6
Eriksson et al.[14]	2008	No pesticide exposure: NR	NHL OR, any glyphosate, multivariate = 1.51	NHL 95% CI, any glyphosate, multivariate = 0.77–2.94
		Glyphosate exposure for ≥ 1 full working day, ≥ 1 calendar year prior to year of diagnosis or enrollment: 29 NHL cases, 18 controls (NHL subtypes NR)	NHL OR, any glyphosate, univariate = 2.02	NHL 95% CI, any glyphosate, univariate = 1.10–3.71
			NHL OR, glyphosate 1 to ≤ 10 days = 1.69	NHL 95% CI, glyphosate 1 to ≤ 10 days = 0.70–4.07
			NHL OR, glyphosate > 10 days = 2.36	NHL 95% CI, glyphosate > 10 days = 1.04–5.37
		Glyphosate exposure for 1 to ≤ 10 days: 12 NHL cases, 9 controls	NHL OR, any glyphosate, latency 1–10 years = 1.11	NHL 95% CI, any glyphosate, latency 1–10 years = 0.24–5.08
			NHL OR, any glyphosate, latency > 10 years = 2.26	NHL 95% CI, any glyphosate, latency > 10 years = 1.16–4.40
		Glyphosate exposure for > 10 days: 17 NHL cases, 9 controls	B-cell NHL OR, any glyphosate = 1.87	B-cell NHL 95% CI, any glyphosate = 0.998–3.51
			SLL/CLL OR, any glyphosate = 3.35	SLL/CLL 95% CI, any glyphosate = 1.42–7.89
			FL grades I–III OR, any glyphosate = 1.89	FL grades I–III 95% CI, any glyphosate = 0.62–5.79
			DLBCL OR, any glyphosate = 1.22	DLBCL 95% CI, any glyphosate = 0.44–3.35
			Other specified B-cell NHL OR, any glyphosate = 1.63	Other specified B-cell NHL 95% CI, any glyphosate = 0.53–4.96
			Unspecified B-cell NHL OR, any glyphosate = 1.47	Unspecified B-cell NHL 95% CI, any glyphosate = 0.33–6.61
			T-cell NHL OR, any glyphosate = 2.29	T-cell NHL 95% CI, any glyphosate = 0.51–10.4
			Unspecified NHL OR, any glyphosate = 5.63	Unspecified NHL 95% CI, any glyphosate = 1.44–22.0
Hardell and Eriksson[22]	1999	No pesticide exposure	NHL OR adjusted for phenoxyacetic acids = 5.8	NHL 95% CI adjusted for phenoxyacetic acids = 0.6–54
		Glyphosate exposure ≥ 1 year prior to diagnosis or control index year: 4 cases, 3 controls	NHL OR unadjusted for phenoxyacetic acids = 2.3	NHL 95% CI unadjusted for phenoxyacetic acids = 0.4–13
Hardell et al.[15]	2002	No pesticide exposure: NR	Multivariate NHL OR = 1.85	Multivariate NHL 95% CI = 0.55–6.20
		Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 8 cases, 8 controls	Univariate NHL OR = 3.04	Univariate NHL 95% CI = 1.08–8.52
Hohenadel et al.[28]	2011	Use of neither glyphosate nor malathion: 422 cases, 1301 controls	NHL OR, glyphosate only = 0.92	NHL 95% CI, glyphosate only = 0.54–1.55
		Use of glyphosate only: 19 cases, 78 controls	NHL OR, malathion only = 1.95	NHL 95% CI, malathion only = 1.29 –2.93
		Use of malathion only: 41 cases, 72 controls	NHL OR, glyphosate and malathion = 2.10	NHL 95% CI, glyphosate and malathion = 1.31–3.37
		Use of glyphosate and malathion: 31 cases, 55 controls	Interaction contrast ratio = 0.23, P-interaction = 0.69	

Kachuri et al.[33]	2013	Never used glyphosate: 310 cases, 1236 controls (216 cases, 1047 controls without proxy) Ever used glyphosate: 32 cases, 121 controls (23 cases, 108 controls without proxy) Used glyphosate for > 0 to ≤ 2 days per year: 15 cases, 88 controls (11 cases, 78 controls without proxy) Used glyphosate for > 2 days per year: 12 cases, 29 controls (10 cases, 26 controls without proxy)	MM OR, ever glyphosate = 1.19 MM OR, ever glyphosate, no proxies = 1.11 MM OR, glyphosate > 0 to ≤ 2 days per year = 0.72 MM OR, glyphosate > 0 to ≤ 2 days per year, no proxies = 0.70 MM OR, glyphosate > 2 days per year = 2.04 MM OR, glyphosate > 2 days per year, no proxies = 2.11	MM 95% CI, ever glyphosate = 0.76–1.87 MM 95% CI, ever glyphosate, no proxies = 0.66–1.86 MM 95% CI, glyphosate > 0 to ≤ 2 days per year = 0.39–1.32 MM 95% CI, glyphosate > 0 to ≤ 2 days per year, no proxies = 0.35–1.40 MM 95% CI, glyphosate > 2 days per year = 0.98–4.23 MM 95% CI, glyphosate > 2 days per year, no proxies = 0.95–4.70
Karunanayake et al.[31]	2012	Never used glyphosate: 278 cases, 1373 controls Ever used glyphosate: 38 cases, 133 controls	Fully adjusted HL OR = 0.99 Minimally adjusted (age, province) HL OR = 1.14 Crude leukemia OR = 1.40	Fully adjusted HL 95% CI = 0.62–1.56 Minimally adjusted (age, province) HL 95% CI = 0.74–1.76 Crude leukemia 95% CI = 0.15–13.56
Kaufman et al.[36]	2009	No glyphosate use: 179 cases, 753 controls Glyphosate: 1 case, 3 controls		
Lee et al.[29]	2004	Non-farmers, non-asthmatics: 259 cases, 684 controls Non-farmers, asthmatics: 9 cases, 37 controls Exposed to glyphosate, non-asthmatics: 53 cases, 91 controls Exposed to glyphosate, asthmatics: 6 cases, 12 controls	NHL OR, non-farmers, asthmatics = 0.6 NHL OR, glyphosate, non-asthmatics = 1.4 NHL OR, glyphosate, asthmatics = 1.2	NHL 95% CI, non-farmers, asthmatics = 0.3–1.4 NHL 95% CI, glyphosate, non-asthmatics = 0.98–2.1 NHL 95% CI, glyphosate, asthmatics = 0.4–3.3
McDuffie et al.[16]	2001	Never used glyphosate: 466 cases, 1373 controls Ever used glyphosate: 51 cases, 1506 controls Glyphosate use for > 0 to ≤ 2 days per year Glyphosate use for > 2 days per year	Fully adjusted NHL OR, ever glyphosate = 1.20 Minimally adjusted (age, province) NHL OR, ever glyphosate = 1.26 Minimally adjusted NHL OR, glyphosate > 0 to ≤ 2 days per year = 1.00 Minimally adjusted NHL OR, glyphosate > 2 days per year = 2.12	Fully adjusted NHL 95% CI, ever glyphosate = 0.83–1.74 Minimally adjusted (age, province) NHL 95% CI, ever glyphosate = 0.87–1.80 Minimally adjusted NHL 95% CI, glyphosate > 0 to ≤ 2 days per year = 0.63–1.57 Minimally adjusted NHL 95% CI, glyphosate > 2 days per year = 1.20–3.73
Nordström et al.[30]	1998	No glyphosate exposure: 107 cases, 395 controls Glyphosate exposure for ≥ 1 working day, ≥ 1 year prior to diagnosis or control index date: 4 cases, 5 controls	Hairy-cell leukemia OR = 3.1	Hairy-cell leukemia 95% CI = 0.8–12
Orsi et al.[17]	2009	Never exposed to glyphosate: 464 LHC, 232 NHL, 102 DLBCL, 47 FL, 100 LPS, 75 CLL, 25 hairy-cell leukemia 81 HL, 51 MM, 432 controls Ever exposed to glyphosate: 27 LHC, 12 NHL, 5 DLBCL, 3 FL, 4 LPS, 2 CLL, 2 hairy-cell leukemia, 6 HL, 5 MM, 24 controls	LHC OR = 1.2 NHL OR = 1.0 DLBCL OR = 1.0 FL OR = 1.4 LPS OR = 0.6 CLL OR = 0.4 Hairy-cell leukemia OR = 1.8 HL OR = 1.7 MM OR = 2.4 MM OR = 1.22	LHC 95% CI = 0.6–2.1 NHL 95% CI = 0.5–2.2 DLBCL 95% CI = 0.3–2.7 FL 95% CI = 0.4–5.2 LPS 95% CI = 0.2–2.1 CLL 95% CI = 0.1–1.8 Hairy-cell leukemia 95% CI = 0.3–9.3 HL 95% CI = 0.6–5.0 MM 95% CI = 0.8–7.3 MM 95% CI = 0.77–1.93
Pahwa et al.[34]	2012	Never used glyphosate: 310 cases, 1373 controls Ever used glyphosate: 32 cases, 133 controls		
Sorahan[26]	2015	Never used glyphosate: 8 cases, 13,280 cohort members (of 54,315); 4 cases, 11,881 cohort members (of 49,211); 3 cases, 9809 cohort members (of 40,719) Ever used glyphosate: 24 cases, 41,035 cohort members (of 54,315); 22 cases, 37,330 cohort members (of 49,211); 19 cases, 30,910 cohort members (of 40,719) 1–20 glyphosate exposure days: 10 cases 21–56 glyphosate exposure days: 8 cases 57–2678 glyphosate exposure days: 6 cases 0.1–79.5 intensity-weighted glyphosate exposure days: 6 cases 79.6–337.1 intensity-weighted glyphosate exposure days: 8 cases 337.2–18,241 intensity-weighted glyphosate exposure days: 10 cases Never used glyphosate: 8 cases Ever used glyphosate: 24 Unknown glyphosate use: 2 cases	Fully adjusted MM RR, cohort of 54,315 = 1.24 Age- and sex-adjusted MM RR, cohort of 54,315 = 1.12 Age-adjusted MM RR, cohort of 54,315 = 1.08 Age-adjusted MM RR, cohort of 49,211 = 1.91 Intermediate adjusted MM RR, cohort of 49,211 = 2.07 Age-adjusted MM RR, cohort of 40,719 = 2.21 Fully adjusted MM RR, cohort of 40,719 = 2.79 Cumulative exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM RRs = 1.14, 1.52, 1.38; p-trend = 0.48 using scores, > 0.50 using means Intermediate adjusted MM RRs = 1.13, 1.50, 1.23; p-trend > 0.50 using scores or means Age- and sex-adjusted MM RRs = 1.06, 1.34, 1.08; p-trend > 0.50 using scores or means Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM RRs = 1.00, 1.27, 1.87; p-trend = 0.22 using scores, 0.18 using means Intermediate adjusted MM RRs = 0.99, 1.22, 1.65; p-trend = 0.27 using scores, 0.24 using means Age- and sex-adjusted MM RRs = 0.91, 1.12, 1.44; p-trend = 0.39 using scores, 0.33 using means MM RR, ever glyphosate = 1.18 MM RR, unknown glyphosate = 1.71 Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never MM RRs = 1.11, 1.45, 1.17, 1.19; p-trend > 0.50 using scores or means, excluding unknown Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never MM RRs = 0.95, 1.19, 1.58, 1.04; p-trend = 0.30 using scores, 0.26 using means, excluding unknown	Fully adjusted MM 95% CI, cohort of 54,315 = 0.52–2.94 Age- and sex-adjusted MM 95% CI, cohort of 54,315 = 0.50–2.49 Age-adjusted MM 95% CI, cohort of 54,315 = 0.48–2.41 Age-adjusted MM 95% CI, cohort of 49,211 = 0.66–5.53 Intermediate adjusted MM 95% CI, cohort of 49,211 = 0.71–6.04 Age-adjusted MM 95% CI, cohort of 40,719 = 0.65–7.48 Fully adjusted MM 95% CI, cohort of 40,719 = 0.78–9.96 Cumulative exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM 95% CIs = 0.43–3.03, 0.54–4.34, 0.42–4.45 Intermediate adjusted MM 95% CIs = 0.44–2.88, 0.56–4.05, 0.42–3.58 Age- and sex-adjusted MM 95% CIs = 0.42–2.70, 0.50–3.58, 0.37–3.11 Intensity-weighted exposure days, tertiles 1, 2, and 3 vs. never Fully adjusted MM 95% CIs = 0.33–3.00, 0.45–3.56, 0.67–5.27 Intermediate adjusted MM 95% CIs = 0.34–2.86, 0.45–3.28, 0.64–4.24 Age- and sex-adjusted MM 95% CIs = 0.31–2.62, 0.42–3.00, 0.57–3.67 MM 95% CI, ever glyphosate = 0.53–2.65 MM 95% CI, unknown glyphosate = 0.36–8.20 Cumulative exposure days, tertiles 1, 2, 3, and unknown vs. never MM 95% CIs = 0.44–2.83, 0.54–3.88, 0.40–3.41, 0.25–5.65 Intensity-weighted exposure days, tertiles 1, 2, 3, and unknown vs. never MM 95% CIs = 0.33–2.75, 0.44–3.19, 0.62–4.05, 0.22–4.92

CI: confidence interval; CLL: chronic lymphocytic leukemia; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; HL: Hodgkin lymphoma; LHC: lymphohematopoietic cancer; LPS: lymphoproliferative syndrome; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; NR: not reported; OR: odds ratio; RR: relative risk; SLL: small lymphocytic lymphoma.

Table 3. Selected estimates included in meta-analyses and calculated meta-analysis relative risks (meta-RRs) of the association between glyphosate exposure and risk of (LHC), including non-Hodgkin lymphoma (NHL), NHL subtypes, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia.

Study *	Authors	Year	Outcome	Number of exposed subjects	RR	95% CI		
1	De Roos et al.[13]	2003	Non-Hodgkin lymphoma	36 cases, 61 controls	a. 1.6 (hierarchical regression) b. 2.1 (logistic regression)	a. 0.9–2.8 (hierarchical regression) b. 1.1–4.0 (logistic regression)		
2	De Roos et al.[12]	2005	Non-Hodgkin lymphoma	71 cases*	1.1	0.7–1.9		
3	Eriksson et al.[14]	2008	Non-Hodgkin lymphoma	29 cases, 18 controls	1.51	0.77–2.94		
4	Hardell et al.[15]	2002	Non-Hodgkin lymphoma	8 cases, 8 controls	1.85	0.55–6.20		
5	Hohenadel et al.[28]	2011	Non-Hodgkin lymphoma	50 cases, 133 controls	1.40 (random effects meta-RR)	0.62–3.15 (random effects meta-CI)		
6	McDuffie et al.[16]	2001	Non-Hodgkin lymphoma	51 cases, 133 controls	1.2	0.83–1.74		
7	Orsi et al.[17]	2009	Non-Hodgkin lymphoma	12 cases, 24 controls	1.0	0.5–2.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Non-Hodgkin lymphoma	1a, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.84
	Model 2		Non-Hodgkin lymphoma	1b, 2, 3, 4, 6, 7	1.3	1.0–1.6	0.0%	0.59
	Model 3		Non-Hodgkin lymphoma	1a, 2, 3, 4, 5, 7	1.3	1.0–1.7	0.0%	0.85
	Model 4		Non-Hodgkin lymphoma	1b, 2, 3, 4, 5, 7	1.4	1.0–1.8	0.0%	0.63
3	Eriksson et al.[14]	2008	B-cell lymphoma	Not reported	1.87	0.998–3.51		
8	Cocco et al.[18]	2013	B-cell lymphoma	4 cases, 2 controls	3.1	0.6–17.1		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		B-cell lymphoma	3, 8	2.0	1.1–3.6	0.0%	0.58
3	Eriksson et al.[14]	2008	Diffuse large B-cell lymphoma	Not reported	1.22	0.44–3.35		
7	Orsi et al.[17]	2009	Diffuse large B-cell lymphoma	5 cases, 24 controls	1.0	0.3–2.7		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Diffuse large B-cell lymphoma	3, 7	1.1	0.5–2.3	0.0%	0.79
3	Eriksson et al.[14]	2008	CLL/SLL	Not reported	3.35	1.42–7.89		
7	Orsi et al.[17]	2009	CLL/SLL	2 cases, 18 controls	0.4	0.1–1.8		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1, random effects		CLL/SLL	3, 7	1.3	0.2–10.0	83.7%	0.01
	Model 1, fixed effects		CLL/SLL	3, 7	1.9	0.9–4.0		
3	Eriksson et al.[14]	2008	Follicular lymphoma	Not reported	1.89	0.62–5.79		
7	Orsi et al.[17]	2009	Follicular lymphoma	3 cases, 24 controls	1.4	0.4–5.2		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Follicular lymphoma	3, 7	1.7	0.7–3.9	0.0%	0.73
7	Orsi et al.[17]	2009	Hairy-cell leukemia	2 cases, 18 controls	1.8	0.3–9.3		
9	Nordström et al.[30]	1998	Hairy-cell leukemia	4 cases, 5 controls	3.1	0.8–12		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Hairy-cell leukemia	7, 9	2.5	0.9–7.3	0.0%	0.63
7	Orsi et al.[17]	2009	Hodgkin lymphoma	6 cases, 24 controls	1.7	0.6–5.0		
10	Karunanayake et al.[31]	2012	Hodgkin lymphoma	38 cases, 133 controls	0.99	0.62–1.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Hodgkin lymphoma	7, 10	1.1	0.7–1.6	0.0%	0.36
2	De Roos et al.[12]	2005	Multiple myeloma	19 cases†	2.6	0.7–9.4		
7	Orsi et al.[17]	2009	Multiple myeloma	5 cases, 24 controls	2.4	0.8–7.3		
11	Brown et al.[32]	1993	Multiple myeloma	11 cases, 40 controls	1.7	0.8–3.6		
12	Kachuri et al.[33]	2013	Multiple myeloma	32 cases, 121 controls	a. 1.19 (with proxies) b. 1.11 (without proxies)	a. 0.76–1.87 (with proxies) b. 0.66–1.86 (without proxies)		
13	Palmwa et al.[34]	2012	Multiple myeloma	32 cases, 133 controls	1.22	0.77–1.93		
14	Sorahan[26]	2015	Multiple myeloma	24 cases	1.24	0.52–2.94		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Multiple myeloma	7, 11, 12a, 14	1.4	1.0–1.9	0.0%	0.63
	Model 2		Multiple myeloma	2, 7, 11, 12a	1.5	1.0–2.1	0.0%	0.48
	Model 3		Multiple myeloma	7, 11, 12b, 14	1.4	0.9–1.9	0.0%	0.58
	Model 4		Multiple myeloma	7, 11, 13, 14	1.4	1.0–2.0	0.0%	0.66
	Model 5		Multiple myeloma	2, 7, 11, 13	1.5	1.0–2.1	0.0%	0.52
2	De Roos et al.[12]	2005	Leukemia	43 cases*	1.0	0.5–1.9		
16	Brown et al.[35]	1990	Leukemia	15 cases, 49 controls	0.9	0.5–1.6		
17	Kaufman et al.[36]	2009	Leukemia	1 case, 3 controls	1.4	0.15–13.56		
	Meta-analysis model		**Outcome**	**Studies included**	**Meta-RR**	**95% CI**	I^2	$P_{heterogeneity}$
	Model 1		Leukemia	2, 16, 17	1.0	0.6–1.5	0.0%	0.92

*Number of exposed cases is provided for the total cohort of 54,315 subjects; the number of exposed cases in the analytic cohort of 49,211 subjects is not stated.
†Number of exposed cases is provided for the analytic cohort of 40,719 subjects, as reported by Sorahan.[26]
CI: confidence interval; CLL: chronic lymphocytic leukemia; RR: relative risk; SLL: small lymphocytic lymphoma.

leukemia, one with unspecified B-cell lymphoma, and one with MM. Eriksson et al.[14] did not report the number of exposed cases, but overall the B-cell lymphomas in their study comprised 29% diffuse large B-cell lymphoma, 24% chronic lymphocytic leukemia/small lymphocytic lymphoma, 20% follicular lymphoma grades I–III, 16% other specified B-cell lymphoma, and 11% unspecified B-cell lymphoma; MM cases were not included.

The meta-RR for the association between any use of glyphosate and risk of diffuse large B-cell lymphoma, based on two studies,[14,17] was 1.1 (95% CI = 0.5–2.3) using both the random-effects and the fixed-effects models (I^2 = 0.0%, $P_{heterogeneity}$ = 0.79) (Table 3).

Based on the same two studies,[14,17] the meta-RR for the association between any use of glyphosate and risk of chronic lymphocytic leukemia/small lymphocytic lymphoma was 1.3 (95% CI = 0.2–10.0) according to the random-effects model and 1.9 (95% CI = 0.9–4.0) according to the fixed-effects model, with significant heterogeneity between the two included estimates (I^2 = 83.7%, $P_{heterogeneity}$ = 0.01) (Table 3).

Results for follicular lymphoma from these two studies,[14,17] by contrast, were not significantly heterogeneous (I^2 = 0.0%, $P_{heterogeneity}$ = 0.73), with a meta-RR of 1.7 (95% CI = 0.7–3.9) in both the random-effects and the fixed-effects models (Table 3).

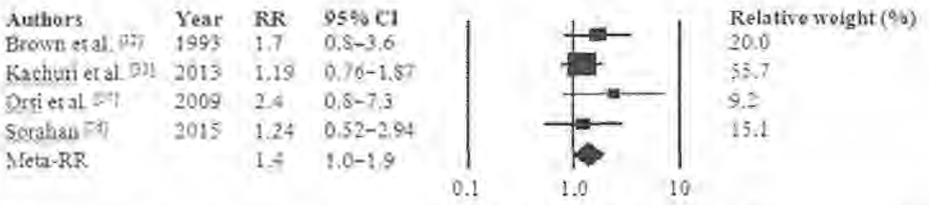

Figure 2. Forest plots of relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between glyphosate exposure and risk of multiple myeloma. Meta-RRs were identical in random-effects and fixed-effects models.

Finally, the two studies that reported associations between any glyphosate use and risk of hairy-cell leukemia[17,30] yielded a meta-RR of 2.5 (95% CI = 0.9–7.3) in the random-effects and fixed-effects models ($I^2 = 0.0\%$, $p_{heterogeneity} = 0.63$) (Table 3).

HL

Both of the published, fully adjusted RRs and 95% CIs for the association between any glyphosate use and HL risk (Table 2) were included in the meta-analysis (Table 3). Based on two studies,[17,31] the meta-RR was 1.1 (95% CI = 0.7–1.6) in both the random-effects and the fixed-effects models, with $I^2 = 0.0\%$ and $p_{heterogeneity} = 0.36$ (Table 3). Publication bias was not evaluated due to the availability of only two studies of HL.

MM

All relevant RRs and 95% CIs for the association between glyphosate use and risk of MM, including estimates that did not contribute to the meta-analysis, are shown in Table 2. The independent estimates selected for inclusion in the meta-analysis are shown in Table 3.

The combined meta-RR for the association between any glyphosate use and risk of MM, based on four studies,[17,26,32,33] was 1.4 (95% CI = 1.0–1.9) according to the random-effects and fixed-effects models (Table 3, Fig. 2). On the basis of the I^2 value of 0.0% and the *P*-value of 0.63 for Cochran's Q statistic, between-study heterogeneity was not evident. Egger's linear regression approach yielded no significant evidence of publication bias (one-tailed *P*-value for asymmetry = 0.10), while the imputed meta-RR using the trim-and-fill procedure to adjust for publication bias was 1.3 (95% CI = 0.9–1.8).

Several secondary analyses were conducted for MM by replacing RRs in the primary meta-analysis with alternative estimates (Table 3). When the RR reported by De Roos et al.,[12] who excluded cohort members with missing data from their analysis, was substituted for the one reported by Sorahan,[26] who included such subjects by creating a separate category for missing or unknown data, the meta-RR was slightly increased to 1.5 (95% CI = 1.0–2.1) and was the same for random-effects and fixed-effects models. When the main RR from Kachuri et al.[33] was replaced with the RR from the same study after exclusion of data reported by proxy respondents, the meta-RR was not appreciably different from the original estimate (alternative meta-RR = 1.4, 95% CI = 0.9–1.9 in random-effects and fixed-effects models). Another secondary analysis included the RR reported by Pahwa et al.,[34] who adjusted for a slightly different (and smaller) set of confounders than Kachuri et al.[33] and also retained controls who were too young to have any age-matched MM cases in this Canadian study. This change had minimal impact on the meta-RR (1.4, 95% CI = 1.0–2.0; same for random-effects and fixed-effects models). When both the De Roos et al.[12] and the Pahwa et al.[34] substitutions were made, the resultant meta-RR was the same as that when only De Roos et al.[12] was used (meta-RR = 1.5, 95% CI = 1.0–1.2 in random-effects and fixed-effects models).

Leukemia

Of the four published RRs and 95% CIs for the association between any use of glyphosate and risk of leukemia (Table 2), three (excluding one age-adjusted RR in favor of a more fully adjusted RR from De Roos et al.[12]) were included in the meta-analysis (Table 3). The meta-RR based on three studies[12,35,36] was 1.0 (95% CI = 0.6–1.5) using the random-effects model and the fixed-effects model ($I^2 = 0.0\%$, $p_{heterogeneity} = 0.92$) (Table 3). Publication bias was not assessed because only three studies of leukemia were available.

Sensitivity analysis

A sensitivity analysis was conducted for overall NHL only (Table 4), because other outcomes had an insufficient number of studies for stratification. In all strata, the random-effects and fixed-effects meta-RRs were identical and I^2 was 0.0%. Results did not differ substantially from the main meta-RR (1.3, 95% CI = 1.0–1.6) when the analysis was restricted to case-control studies (meta-RR = 1.3, 95% CI = 1.0–1.7) or those with population-based controls (meta-RR = 1.4, 95% CI = 1.0–1.8). Meta-analysis could not be conducted for cohort studies or studies with hospital-based

Table 4. Sensitivity analysis of the association between glyphosate exposure and risk of non-Hodgkin lymphoma (NHL).

Stratum	Number of studies	Meta-RR*	95% CI
All	6	1.3	1.0–1.6
Case-control	5	1.3	1.0–1.7
Cohort	1	NR	
Population controls	4	1.4	1.0–1.8
Hospital controls	1	NR	
Males only	4	1.3	1.0–1.7
Males and females	2	1.2	0.8–1.8
North America	3	1.2	1.0–1.6
Europe	3	1.3	0.8–2.1
Sweden	2	1.6	0.9–2.8
Cases in 1980s	2	1.6	1.0–2.7
Cases in 1990s	4	1.2	1.0–1.6
Cases in 2000s	3	1.2	0.8–1.7

*All meta-RRs were identical in random-effects and fixed-effects models.
CI: confidence interval; meta-RR: meta-analysis relative risk; NR: not reported, when only one study was available.

controls because only one of each of these study types was available. No major differences were detected between studies restricted to males (meta-RR = 1.3, 95% CI = 1.0–1.7) and those that included males and females (meta-RR = 1.2, 95% CI = 0.8–1.8) or between those conducted in North America (meta-RR = 1.2, 95% CI = 1.0–1.6) and those conducted in Europe (meta-RR = 1.3, 95% CI = 0.8–2.1). Prompted by Schinasi and Leon,[11] we also conducted a stratified meta-analysis of the two studies conducted in Sweden[14,15] and found a stronger, albeit statistically non-significant, association in these particular studies (meta-RR = 1.6, 95% CI = 0.9–2.8). The estimated meta-RR declined somewhat from studies that ascertained cases in the 1980s (meta-RR = 1.6, 95% CI = 1.0–2.7) to those conducted in the 1990s (meta-RR = 1.2, 95% CI = 1.0–1.6) to those conducted in the 2000s (meta-RR = 1.2, 95% CI = 0.8–1.7).

Exposure-response trends

NHL and subtypes. Three studies evaluated exposure-response trends between glyphosate use and NHL risk, with exposure classified as cumulative lifetime[12,14] or annual[16] days of glyphosate use (Table 2). Two studies detected some evidence of a positive exposure-response trend (statistical significance not reported),[14,16] whereas the other did not.[12] All of these studies relied wholly or in part on evaluating days of glyphosate use in an attempt to quantify exposure; however, this metric has been shown to be a poor indicator of actual glyphosate dose received.[52]

In a model adjusted for age, sex, and year of diagnosis or enrollment, Eriksson et al.[14] found that the RR of NHL was higher with > 10 days of lifetime glyphosate use (RR = 2.36, 95% CI = 1.04–5.37) than with ≤ 10 days (RR = 1.69, 95% CI = 0.70–4.07), compared with no pesticide use. Also, the RR of NHL was higher after more than 10 years since first use of glyphosate (RR = 2.26, 95% CI = 1.16–4.40) than after 1–10 years (RR = 1.11, 95% CI = 0.24–5.08). Statistical tests for trend were not performed, and exposure-response analyses adjusted for other potential confounders (i.e., 2-methyl-4-chlorophenoxyacetic acid (MCPA), 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and/or 2,4-dichlorophenoxyacetic acid (2,4-D), mercurial seed dressing, arsenic, creosote, and tar) were not presented, even though adjustment for these characteristics attenuated the RR for overall glyphosate use from 2.02 to 1.51.

McDuffie et al.[16] reported that the RR for more than two days of glyphosate use per year (RR = 2.12, 95% CI = 1.20–3.73) was higher than that for up to two days per year (RR = 1.00, 95% CI = 0.63–1.57), compared with never use, adjusting for age and province of residence. Tests for a significant exposure-response trend were not performed, and results were not reported after adjustment for other potential confounders (i.e., personal medical history and family history of cancer; adjustment for these characteristics attenuated the RR for overall glyphosate use from 1.26 to 1.20) or significantly associated pesticides (i.e., aldrin, dicamba, and mecoprop) in this study population.

The most detailed analysis of glyphosate-NHL exposure-response trends was performed by De Roos et al.,[12] who examined tertiles of cumulative lifetime days of glyphosate use (1–20, 21–56, or 57–2,678 days) and tertiles of intensity-weighted cumulative days of use (i.e., years of use × days per year × intensity level, where intensity was defined as (mixing status + application method + equipment repair status) × personal protective equipment use). In analyses adjusted for age, education, smoking, alcohol, family history of cancer, and state of residence, no significant trend was detected for NHL risk in association with increasing cumulative days of glyphosate use (RRs for tertiles 1, 2, and 3, respectively = 1.0 (referent), 0.7 (95% CI = 0.4–1.4), and 0.9 (95% CI = 0.5–1.6); $p_{trend} = 0.73$) or intensity-weighted cumulative exposure days (RRs = 1.0 (referent), 0.6 (95% CI = 0.3–1.1), and 0.8 (95% CI = 0.5–1.4); $p_{trend} = 0.99$).

Exposure-response trends between glyphosate use and risk of specific NHL subtypes were not evaluated in any of the included studies.

HL. No studies assessed exposure-response trends between glyphosate use and risk of HL.

MM. Three studies reported exposure-response trends between glyphosate use and MM risk, including the two analyses based on the same Agricultural Health Study cohort dataset[12,26] and the Canadian case-control study[33] (Table 2). The case-control study found mixed evidence of a positive trend (statistical significance not reported), while a positive trend was detected in one analysis of the cohort data[12] but not the other.[25]

The Canadian case-control study found a lower risk of MM among those who used glyphosate for up to two days per year than those who had never used glyphosate (RR = 0.72, 95% CI = 0.39–1.32).[33] However, risk was higher in those with more than two days of glyphosate use per year (RR = 2.04, 95% CI = 0.98–4.23), adjusting for age, province of residence, proxy status, smoking, personal medical history, and family history of cancer. Results were similar after exclusion of data reported by proxy subjects. The authors did not conduct statistical tests for exposure-response trends.

Based on the 55% of Agricultural Health Study cohort members who had available exposure and covariate data, De Roos et al.[12] reported a positive, albeit statistically non-significant, trend between MM risk and increasing tertiles of cumulative days of glyphosate use (RRs for tertiles 1, 2, and 3, respectively = 1.0 (referent), 1.1 (95% CI = 0.4–3.5), and 1.9 (95% CI = 0.6–6.3); $p_{trend} = 0.27$) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.2 (95% CI = 0.4–3.8), and 2.1 (95% CI = 0.6–7.0); $p_{trend} = 0.17$). These estimates were adjusted for age, education, smoking, alcohol, family history of cancer, state of residence, the five pesticides for which cumulative-use variables were most highly associated with glyphosate cumulative use days (i.e., 2,4-D, alachlor, atrazine, metolachlor, and trifluralin), and the five pesticides that were most highly associated with ever use of glyphosate (i.e., benomyl, maneb, paraquat, carbaryl, and diazinon). When intensity alone was analyzed in association with MM risk, the RR for the highest versus the lowest tertile was 0.6 (95% CI = 0.2–1.8), indicating that the suggested trend was due only to total days of use. When subjects who never used glyphosate were set as the reference group, the RRs for tertiles 1, 2, and 3 of cumulative days

of use were 2.3 (95% CI = 0.6–8.9), 2.6 (95% CI = 0.6–11.5), and 4.4 (95% CI = 1.0–20.2); $p_{trend} = 0.09$. When cumulative use was categorized into quartiles, the RR for the highest quartile versus never use was 6.6 (95% CI = 1.4–30.6); $p_{trend} = 0.01$.

In contrast to De Roos et al.,[12] Sorahan[26] included more than 53,000 eligible cohort members in the analysis (excluding only those with a history of cancer before enrollment, loss to follow-up, missing data on age at enrollment, or missing data on glyphosate use) by creating separate categories for missing or unknown exposure and covariate data. Adjusting for age, sex, education, smoking, alcohol, family history of cancer, and the same 10 pesticides as De Roos et al.,[12] the RRs for each tertile of cumulative days of glyphosate use, compared with never use, were 1.14 (95% CI = 0.43–3.03), 1.52 (95% CI = 0.54–4.34), and 1.38 (95% CI = 0.42–4.45); $p_{trend} = 0.48$ using category scores of 1–4, $p_{trend} > 0.50$ using mean exposures within categories. RRs for increasing tertiles of intensity-weighted days of use versus never use were 1.00 (95% CI = 0.33–3.00), 1.27 (95% CI = 0.45–3.56), and 1.87 (95% CI = 0.67–5.27); $p_{trend} = 0.22$ using scores, $p_{trend} = 0.18$ using means. When Sorahan[26] expanded the eligible cohort to 55,934 subjects to include those with unknown use of glyphosate, he again detected no significant exposure-response trends with respect to either cumulative days of use (for tertiles 1, 2, and 3 and unknown use versus never use, respectively, RRs = 1.11 (95% CI = 0.44–2.83), 1.45 (95% CI = 0.54–3.88), 1.17 (95% CI = 0.40–3.41), and 1.19 (95% CI = 0.25–5.65); $p_{trend} > 0.50$ across categories of known use using scores or means, excluding unknown) or intensity-weighted cumulative days of use (RRs = 0.95 (95% CI = 0.33–2.75), 1.19 (95% CI = 0.44–3.19), 1.58 (95% CI = 0.62–4.05), and 1.04 (95% CI = 0.22–4.92); $p_{trend} = 0.30$ using scores, $p_{trend} = 0.26$ using means, excluding unknown).

Leukemia. The De Roos et al.[12] study based on the Agricultural Health Study cohort was the only study that reported exposure-response trends between glyphosate use and risk of leukemia (Table 2). No significant trend was observed between increasing tertiles of cumulative days of glyphosate use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.5), and 1.0 (95% CI = 0.4–2.9) for tertiles 1, 2, and 3, respectively; $p_{trend} = 0.61$) or intensity-weighted cumulative days of use (RRs = 1.0 (referent), 1.9 (95% CI = 0.8–4.7), and 0.7 (95% CI = 0.2–2.1); $p_{trend} = 0.11$), adjusting for demographic and lifestyle factors as well as other pesticides.

Evaluation of bias

Selection bias

All studies of the association between glyphosate exposure and risk of LHC were case-control studies except for the Agricultural Health Study, the prospective cohort study that served as the basis for the studies by De Roos et al.[12] and Sorahan.[26] In case-control studies, differences in participation patterns between cases and controls can result in selection bias if participation is related to the exposure of interest. In cohort studies, selection bias can occur if loss to follow-up is related to the exposure and outcome of interest or, less commonly, if baseline participation differs by exposure status and risk of developing the outcome of interest in the future (e.g., based on having a positive family history of an outcome with a genetic susceptibility component). Selection bias in any study also can occur if inclusion in the data analysis, e.g., predicated on data completeness, differs by exposure and outcome status. In general, lower participation, follow-up, or data completeness and large differences in participation between groups increase the potential magnitude of selection bias.

Table 1 shows the reported participation and follow-up proportions in all reviewed studies. Most studies did not report data completeness. The substantial differences in participation between cases and controls in the European multi-center study,[18] the most recent Swedish study,[14] and the Canadian study, which also had relatively low absolute participation proportions of <70% for cases and <50% for controls,[10,28,31,33,34] are of particular concern. However, the smaller discrepancies between case and control participation in other studies also could have produced selection bias. Moreover, even identical participation by cases and controls can obscure differences in reasons for study participation that could result in bias.

Given that several case-control studies were originally designed to evaluate associations between pesticides and risk of LHC,[13–16,28,31–35] it is plausible that cases with a history of agricultural pesticide use were more likely than controls to participate, thereby biasing results toward a positive association for glyphosate as well as other pesticides. It is also possible that certain sources of controls in some of these studies (e.g., residential telephone calls and voter lists) were more likely to identify individuals who were not farmers, again biasing results toward a positive association. Investigators from the Canadian study[10,28,31,33,34] reported that an analysis of postal codes showed that respondents and non-respondents did not differ significantly in terms of rural versus urban residence, but they could not examine differences in occupation or pesticide use.

Although the initial follow-up completion of >99% in the Agricultural Health Study was high,[12,25] the sizeable proportions of subjects with missing data raise concerns about selection bias. Specifically, 88% of the eligible cohort (excluding those who were diagnosed with cancer before enrollment or were lost to follow-up) provided usable data on ever use of glyphosate and key demographic and lifestyle covariates, 73% additionally provided data on use of other pesticides, 65–66% contributed to analyses of cumulative days of glyphosate use (with or without intensity weighting), and 55% contributed to analyses of cumulative use additionally adjusted for other pesticides. Questionnaire completion could conceivably have varied by demographic and lifestyle factors that are associated with LHC risk, thereby producing bias. Neither analysis accounted for missing data using methods such as multiple imputation or inverse probability weighting.

Differential data completeness by disease status is more likely to occur in case-control studies, such as the pooled Midwestern U.S. study conducted by De Roos et al.[13] In this study, the analysis of multiple pesticides excluded 25% of cases and 25% of controls who lacked complete data. Although the overall frequency of missing data was the same between cases and controls, this exclusion could have led to selection bias if subjects'

reasons for providing complete data, and thus being included in the analysis, differed by disease status and were related to glyphosate exposure status. The authors also excluded subjects who had lived or worked on a farm before age 18 years. If glyphosate use was more common in such subjects, then RR estimates would have been biased upward if a childhood farm environment was inversely associated with NHL risk[53] and biased downward if the association was positive.[54]

Exposure misclassification

All of the included studies assessed use of glyphosate and other pesticides based on self-reported information (Table 1), which is prone to various types of error, such as better recall by cases than controls and by subjects than proxies, inaccurate recall of specific pesticides and amounts used, and a lack of the best measure of biological dose received.[55] Thus, probable exposure misclassification is a key limitation of all of these studies. The degree of misclassification may vary by mode of data collection, for example, by written questionnaire, telephone interview, or in-person interview.[56] The extent of misclassification also may depend on questionnaire structure, for example, whether subjects were asked in an open-ended manner to report use of any pesticides or whether they were prompted to report use of specific pesticides based on a prepared list.[57] Some authors did not clearly describe the structure of their study's questions on pesticide use.

Of the eight independent study populations included in this review (seven studies of NHL with or without other types of LHC and one study of leukemia), three provided information on validation of their exposure assessment methods: the Canadian case-control study,[16,28,31,33,34] the Agricultural Health Study,[12,26] and the Kansas case-control study[47] that contributed to the pooled Midwestern U.S. study by De Roos et al.[13] Overall, these studies do not establish the validity of self-reported information on glyphosate use; rather, the limited results suggest considerable error and inconsistency in such data.

Specifically, in the Canadian study, Dosman et al.[58] reported on the results of a validation pilot study of 21 volunteer farmers whose self-reported pesticide use was compared with written records of pesticide purchases through their local agrochemical supplier. Of the 21 farmers, 17 (81%) had a supplier who had retained written records; the remaining four transactions were conducted with cash. Based on the written records, 146 (65%) of 226 chemicals reported by farmers were verified; 50 of the unverified reports were potentially explained by aerial applications, home and garden use, use more than five years in the past (i.e., during 1958–1984), or use outside of Canada. In 32 instances (for 25 chemicals) the suppliers' records indicated a purchase of chemicals that was unreported by the farmer; 2 of these were for glyphosate. Detailed self-reported exposure (e.g., frequency, intensity, and duration of use of specific pesticides) could not be validated in this pilot study.

Likewise, Hoar et al.[47] reported that suppliers for 110 subjects in the Kansas study (out of 130 sought) were located and provided information on the subjects' crops and herbicide and insecticide purchases as "corroborative evidence" of self-reported pesticide use. The authors observed that suppliers usually reported less pesticide use than subjects; that agreement on specific years of use was better for insecticide use than herbicide use; that the differences between agreement for cases and controls were not consistent; and that agreement between suppliers and subjects was better for pesticide use within the last 10 years than for earlier use. Quantitative results on concordance were not provided by Hoar et al.,[47] but in a summary of this study shared with Dosman et al.[58] the authors stated that reports on herbicide use agreed 59% of the time, with little variation by crop type, and that reports on insecticide use also agreed 59% of the time, but differed by crop type.

In the Agricultural Health Study, the reliability of the question on ever having mixed or applied glyphosate was evaluated by comparing responses to two questionnaires completed one year apart by 3,763 pesticide applicators.[59] Agreement on a positive response to the question was 82%, and the kappa statistic value for inter-rater agreement was moderate (0.54, 95% CI = 0.52–0.58). For more detailed questions about glyphosate use, including years mixed or applied, days per year mixed or applied, and decade first applied, the percentage with exact agreement ranged from 52% to 62% and kappa ranged from 0.37 to 0.71. These metrics evaluated only the reliability (i.e., reproducibility) of self-reported glyphosate use, not its accuracy.

Subsequent exposure validation studies for other pesticides in the Agricultural Health Study, based on comparisons between exposure intensity estimated from an expert-derived algorithm using self-reported or directly observed exposure data and pesticide biomarker levels measured in urine, yielded Spearman correlation coefficients between 0.4 and 0.8, depending on the type of pesticide.[60,61] Correlations with urinary biomarker levels were poorer for self-reported determinants of pesticide exposure such as kilograms of active ingredient, hours spent mixing and applying, and number of acres treated, with correlation coefficients of −0.4 to 0.2, but application method and use of personal protective equipment were found to be important determinants of exposure intensity. However, the latter factors were evaluated in the study questionnaire only for pesticides or pesticide classes in general, not for glyphosate or other individual pesticides;[62] thus, limitations remain in the assessment of specific pesticide exposures.

Several studies included a sizeable proportion of surveys that were completed by proxy respondents for deceased or otherwise unavailable cases and controls (Table 1). The use of exposure data reported by surrogates most likely resulted in even poorer accuracy of exposure information in these studies. Although some exposure misclassification may have been nondifferential by disease status, such error does not inevitably result in underestimated exposure-disease associations unless additional strict conditions are met, such as independence from other classification errors.[63,64]

Furthermore, differential exposure misclassification in case-control studies can readily result in overestimated associations. Reasonable scenarios include more accurate and/or detailed recollection of past exposures by cases, who are more motivated than controls to try to understand the potential causes of their disease; false recollection by cases, who are more aware of scientific hypotheses or media reports that a certain exposure has been linked to their disease; and unconscious influence by study investigators who are aware of causal hypotheses and subjects' case-control status. Only the authors of the Swedish

studies,[14,15] the French study,[17] and the Nebraska component of the pooled Midwestern U.S. study[48] specifically stated that investigators were blinded to case-control status. In reality, such blinding is often difficult to achieve in studies that collect interview data.

Others have discussed in detail the problems of estimating individual subjects' exposure to glyphosate from responses to interviews and questionnaires asking about days of use, mixing and application procedures, use of personal protective equipment, and other work practices.[19,52] Acquavella et al.[52] reported that any given day of pesticide use can entail highly variable amounts of pesticides used and numbers of mixing operations, and that urine concentrations of glyphosate were poorly correlated with lifetime average exposure intensity scores derived from data self-reported by farmers using this agent. Although recall bias between cases and controls generally might be anticipated to affect all specific pesticides (including glyphosate) equally, variation in the degree of misclassification due to these and other factors affecting usage and exposure could result in different pesticide-specific associations.

Most of the case-control studies did not use procedures to exclude glyphosate exposure that might have occurred after disease onset. The Swedish studies omitted glyphosate use within one year prior to diagnosis or the index date in controls,[15,30] or within the same calendar year or the year before.[14] In some cases, however, these restrictions may not have been sufficient to exclude exposure that occurred during the latency period between disease onset and diagnosis. Inclusion of any such post-disease exposure would have led to misclassification.

Finally, exposure misclassification resulting from the crude dichotomization of glyphosate use as ever versus never is an important limitation of most of the included studies. This classification conflates individuals with considerably different frequencies, intensities, and durations of glyphosate use, and precludes potentially informative analyses of any gradient in LHC risk with increasing glyphosate exposure. As described earlier in the section on exposure-response trends, only three independent studies reported on glyphosate use in more than two (ever vs. never) categories, and only the Agricultural Health Study evaluated more than three exposure categories.

Confounding

As shown in Table 1, the degree of control for confounding varied widely among the reviewed studies. Although several studies considered potential confounding by other pesticides or pesticide families, only a minority[12–15,26,28] reported RR estimates for the association between glyphosate use and LHC risk adjusted for use of other pesticides. Given that Schinasi and Leon[11] found significant associations between NHL risk and several other types of pesticides, including carbamate insecticides, organophosphorus insecticides, lindane, and MCPA, and numerous other associations of specific pesticides with LHC risk have been reported in the literature (e.g.,[65,66])—and because most people who use pesticides occupationally are exposed to multiple pesticides—it is important to control for confounding, whether direct or indirect (if pesticides are surrogates for other risk factors), by these agents.

None of the studies controlled for potential confounding by agricultural exposures other than pesticides, such as other agricultural chemicals, farm animals, allergens, and infectious agents. These exposures have been hypothesized, and in some studies shown, to be associated with risk of NHL, HL, MM, or leukemia,[67–73] and they are probably correlated with glyphosate use, making them potential confounders of associations between glyphosate and LHC risk. Medical history, certain infections, diet, alcohol consumption, and obesity also may be associated with risk of these malignancies[74–77] and could vary by glyphosate use, again making them possible confounders. Even in studies where numerous confounders were included in multivariable regression models, crude categorization or other misclassification of confounders could have enabled residual confounding of observed associations. The direction and magnitude of confounding depend on the relationships of each factor with glyphosate use and LHC risk, and are therefore difficult to predict.

Other issues

Additional issues related to the design, conduct, and reporting of the included studies also could have affected study results and their interpretation. For instance, Hardell et al.[15] enrolled some prevalent rather than incident cases, since eligible NHL cases were diagnosed in 1987–1990 but interviewed in 1993–1995.[27] The relatively long time interval between diagnosis and interview may have hampered recollection of past exposures, thereby undermining the accuracy of self-reported exposure data in this study. The delay between diagnosis and interview also almost certainly increased the proportion of cases and matched controls who were deceased (43%) and had proxy interviews, leading to further exposure misclassification.

In the studies by De Roos et al.[13] and Brown et al.,[32,33] LHC cases were diagnosed in 1979–1986, 1980–1983, and 1980–1984, respectively. With glyphosate having come to market in 1974, the cases in these studies would have had a relatively short potential induction time since first use of glyphosate. However, few studies to date have considered the issue of induction time. The Agricultural Health Study collected information on decade of first use of glyphosate in the baseline questionnaire for private pesticide applicators,[62] but did not use this information in the published analysis.[12] If glyphosate is a cause of LHC, the actual induction time is unknown because the mechanism of carcinogenesis is not established.

Orsi et al.,[17] Kaufman et al.,[36] and four of the six study centers included in Cocco et al.[18] enrolled hospital-based rather than population-based cases and controls. Given that farmers have lower hospitalization rates than non-farmers,[78] hospital-based controls may be less likely than population-based controls to report agricultural occupational exposures, including pesticides, thereby resulting in overestimated RRs for pesticide use. On the other hand, occupational injuries are more common in agriculture than in general private industry,[79] possibly leading to oversampling of farmers from hospital trauma/emergency and orthopedics departments, which might result in underestimated RRs. We did not observe any meaningful change in the meta-RR after restriction to population-based case-control studies.

As noted in Table 1, many possible analyses were not conducted or not reported by authors. De Roos et al.[13] specifically acknowledged that they did not report results for pesticide combinations that were analyzed but yielded statistically null

associations for joint effects, and Hohenadel et al.[28] likewise did not show results for pesticide combinations without evidence of joint effects. Most other authors did not explicitly state when null results were not reported, but the Methods sections of several papers suggested that certain analyses were performed, yet not shown. Given the widespread predilection for emphasizing statistically significant associations in published research articles,[80] unreported results probably are usually statistically null. The omission of null results is a form of reporting bias that favors positive associations.

Other evidence suggests that statistically null associations between glyphosate and LHC risk have been underreported in the epidemiologic literature. For example, two of the studies that contributed to the pooled analysis conducted by De Roos et al.[13] apparently collected information on glyphosate use, yet associations between glyphosate and NHL risk were not reported in the original publications.[47,48] In an analysis of interactions between pesticide use and asthma, allergies, or hay fever diagnosis in relation to NHL risk in the Canadian case-control study,[81] results were reported for several specific pesticides, but not glyphosate, even though information was available for glyphosate use. The most probable scenario in each of these cases is that no significant association was detected between glyphosate use and NHL risk. The omission of such results from the published literature represents a distortion of the body of epidemiologic evidence.

The largest number of studies included in any of the meta-analyses described here was six (in the analysis of NHL), and the majority of meta-analyses (of HL, B-cell lymphoma, diffuse large B-cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and hairy-cell leukemia) included only two studies. The small number of available studies limits the robustness of the estimated meta-RRs, as well as the ability to perform informative sensitivity analysis and evaluation of heterogeneity and publication bias. Even with 10 contributing studies (which we lacked), the statistical power to detect modest heterogeneity using Cochran's Q statistic is "low."[42] The small number of studies also provides little opportunity to qualitatively investigate possible sources of heterogeneity by subject characteristics or study design. Thus, the results of the meta-analyses and related statistical tests reported here should be interpreted cautiously in light of the sparse and possibly selectively published literature, as well as the high potential for bias and confounding in most of the available studies.

Overall evaluation

The validity of the meta-RRs for glyphosate use and LHC risk reported here and by others[11] is uncertain because systematic error due to bias and confounding cannot reasonably be ruled out as explanations for the observed associations (including both positive and null associations). In addition, an evaluation of the association between glyphosate exposure and risk of LHC based on the Bradford Hill viewpoints[46] does not favor a causal relationship with NHL, any NHL subtype, HL, MM, or leukemia. These nine viewpoints are strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.

To evaluate the strength of the association between glyphosate use and risk of each type of LHC, we considered the magnitude of study-specific RRs and the corresponding meta-RRs. In individual studies, estimates of the association between glyphosate use and risk of NHL ranged between 1.0 and 2.1, and estimates of the association with NHL subtypes ranged between 0.4 and 3.35 (Table 3). For HL, the two estimates of association were 0.99 and 1.7. For MM, RRs ranged between 1.0 and 2.4, and those for leukemia ranged between 0.9 and 1.40. Most study-specific estimates were between 1.0 and 1.5. The estimated meta-RRs for all LHC outcomes, including those calculated in secondary and sensitivity analyses, ranged between 1.0 (for leukemia) and 2.5 (for hairy-cell leukemia). The meta-RRs calculated based on at least four studies ranged between 1.3 and 1.4. These associations are not of sufficient magnitude to exclude modest bias or confounding as reasonable explanations for the observed results.

Results were not consistent between case-control studies of NHL and the one prospective cohort study of NHL, which reported no association.[12] Even among the six studies that contributed to the meta-analysis of NHL, RR point estimates varied by more than two-fold, only one statistically significant positive association was observed, and results from some studies were internally inconsistent (Table 3). Another, arguably more appropriately adjusted RR (from a hierarchical regression model) that was 24% lower and statistically non-significant was reported in the same study that found a significant association.[13] The lack of statistically significant heterogeneity among studies of NHL, based on an underpowered statistical test, does not indicate consistency of results. For NHL subtypes, RR estimates also were variable, except for diffuse large B-cell lymphoma, for which both estimates were close to 1.0. Only one statistically significant positive association was detected (for chronic lymphocytic leukemia/small lymphocytic lymphoma),[14] and this result was contradicted by a non-significant inverse association in the other study of this outcome.[17] No significant associations with ever use of glyphosate were detected for HL, MM, or leukemia, and for MM the RR point estimates varied by more than two-fold. Results for MM in the Agricultural Health Study were internally inconsistent;[12,26] and the positive association with cumulative glyphosate exposure probably was due largely to selection bias.

Numerous associations have been hypothesized between glyphosate exposure and diverse health outcomes, and between various exposures and risk of NHL, NHL subtypes, HL, MM, or leukemia. Thus, the putative associations are not specific to either the exposure or any of the outcomes. As noted by Bradford Hill,[46] "diseases may have more than one cause" and "one-to-one relationships are not frequent"; therefore, a lack of specificity does not detract from a causal hypothesis.

In case-control studies, where exposure assessment was retrospective, a temporal sequence was not definitively established with glyphosate use preceding the time of disease onset. Although some studies attempted to exclude use close to the time of case diagnosis (or enrollment, for controls),[14,15,30] in practice individuals may not accurately recall the timing of use. Only the prospective Agricultural Health Study[12,20] was designed to collect information on glyphosate use prior to cancer ascertainment. However, the authors did not exclude malignancies diagnosed close to

(e.g., within one year of) study enrollment, nor did they report the distribution of diagnoses with respect to time since first use of glyphosate. Thus, some preclinical cancers may have existed prior to study entry and, possibly, prior to at least some reported glyphosate use.

As discussed in detail earlier, in the three studies of NHL with information on frequency, intensity, and/or duration of glyphosate use,[12,14,16] a positive biological gradient was not consistently demonstrated and was notably lacking in the Agricultural Health Study,[12] which had the most detailed exposure information (Table 2). One case-control study[33] and one prospective cohort study[12] of MM reported results suggesting a positive biological gradient with glyphosate use, but the alternative analysis of the Agricultural Health Study data[20] did not demonstrate such a trend. No data were available to evaluate exposure-response trends between glyphosate and risk of NHL subtypes or HL, and the single study with such data for leukemia found no apparent trend.[12]

Inhalation exposure to glyphosate from agricultural or residential uses is likely to be slight due to glyphosate's extremely low vapor pressure.[82] Although dermal contact can be considerable, the very low skin penetrability of glyphosate[83] should result in minimal, if any, biologically absorbed dose. A study of farm families with a lower limit of detection of 0.001 μg/mL (1 ppb) found that 40% of glyphosate applicators had undetectable urinary glyphosate, which reflects all routes of exposure (dermal, inhalation, and oral).[84] Among those with detectable urinary glyphosate, the distribution of concentrations was right skewed, with a peak geometric mean concentration of 0.0032 μg/mL (3.2 ppb) on the day of application and declining thereafter. A review of seven human biomonitoring studies of glyphosate (including[84]) yielded the conclusion that "no health concern was revealed because the resulting exposure estimates were by magnitudes lower" than the science-based acceptable daily intake and the acceptable operator exposure level proposed by EFSA.[85] Glyphosate is usually applied in agricultural operations only a few days per year. Given the low biological dose of glyphosate that is expected to be sustained, along with the lack of information on the mechanism of carcinogenesis that may exist in humans, the biological plausibility of LHC development due to typical glyphosate exposure has not been established.

IARC recently determined based on their process that there is "sufficient" evidence of carcinogenicity of glyphosate in experimental animals and mechanistic evidence of genotoxicity and oxidative stress.[6] By contrast, U.S. EPA,[86] JMPR,[5] BfR,[11] EFSA,[9] and others[87,88] concluded that glyphosate does not have genotoxic, mutagenic, or carcinogenic effects in *in vivo* animal and *in vitro* studies, and that the negative findings constitute evidence against carcinogenicity. Given these widely divergent opinions, one cannot unambiguously conclude whether the scientific evidence is coherent with the hypothesis that glyphosate causes any or all LHC.

No true experimental evidence exists regarding the association between glyphosate exposure and risk of LHC in humans. However, positive associations between farming and risk of LHC were detected prior to 1974, when glyphosate was first commercially marketed.[89,90] Thus, if the apparent associations between farming and risk of LHC are due to causal agricultural exposures, they cannot be explained only by glyphosate exposure. Likewise, the recent worldwide increase (followed by a plateau or decline) in NHL incidence began before the 1970s[91,92]—although any impact of glyphosate on NHL incidence trends might be obscured by stronger risk factors. No marked increase in the incidence of HL, MM, or leukemia has been observed in parallel with the introduction and expansion of glyphosate use.[93–96]

Finally, numerous analogies exist to support or oppose the hypothesis of a causal link between glyphosate exposure and risk of LHC. On balance, such analogies do not strengthen or weaken a conclusion of causality.

In summary, although none of the Bradford Hill viewpoints can establish or disprove causality, we did not find compelling evidence in support of causality based on any of the nine viewpoints. Thus, on balance, the existing epidemiologic evidence does not favor a causal effect of glyphosate on NHL, HL, MM, leukemia, or any subtype of these malignancies.

Discussion

Our meta-analysis yielded borderline significant RRs of 1.3 and 1.4 between glyphosate use and risk of NHL and MM, respectively, and no significant association with risk of HL or leukemia. Based on more fully adjusted RRs, our NHL meta-RR of 1.3 (95% CI = 1.0–1.6) was weaker than that reported by Schinasi and Leon[11] (RR = 1.5, 95% CI = 1.1–2.0). The largest meta-RR of 2.5 (for hairy-cell leukemia) and the only meta-RR with a lower 95% confidence limit that excluded 1.0 (for B-cell lymphoma) were based on only two studies each, and the maximum number of studies contributing to any meta-analysis was six. The few studies with available data did not consistently detect positive exposure-response trends between quantitative measures of glyphosate use and risk of any LHC.

Consideration of the available epidemiologic evidence in light of the Bradford Hill viewpoints does not substantiate a causal relationship between glyphosate exposure and risk of any type of LHC. A conclusion in favor of causality also is undermined by the studies' methodological limitations, which could reasonably account for at least part of the observed associations. These limitations include exposure misclassification (which may differ by outcome status especially in case-control studies, which constitute nearly all available studies), selection bias (due to differential enrollment, follow-up, or data completeness), poor adjustment for confounding (by other agricultural exposures, for instance), small numbers (which lead to low statistical power as well as a higher probability that a statistically significant finding is false[97]), and potential reporting and publication bias. Although underpowered statistical tests did not formally detect publication bias, we identified several examples of studies with available data that did not report associations between glyphosate use and LHC risk, and these unreported associations were most likely null.

Underpowered statistical tests also generally did not detect heterogeneity of results among studies, except for chronic lymphocytic leukemia/small lymphocytic lymphoma and MM. Nevertheless, our sensitivity analysis revealed some evidence of stronger associations with NHL risk in studies based in Sweden and those that ascertained cases in the 1980s, whereas the meta-RRs for studies that ascertained cases in the 2000s were

close to the null and statistically non-significant The stronger association with NHL diagnosed in the 1980s raises questions about whether glyphosate, an agent first introduced in 1974 in the United States and Europe, could plausibly cause lymphoma less than a decade later. However, deliberation on the potential induction time requires an understanding of the presumed mechanism of carcinogenesis, which is unknown for glyphosate. The classification system for lymphoid tumors underwent major changes in 1994 and 2001,[20] such that the definition of NHL as a disease entity is not entirely comparable between recent studies and those conducted in the 1980s. Study quality also may have improved over time, for example, due to refinements in survey design, interviewing techniques, data management, and other methods to augment data integrity.

The stronger association in Swedish studies probably is not explained by geographical differences in glyphosate use or effect modifiers related to NHL risk. One possible explanation is that of the six NHL studies, only the two Swedish studies[14,15] compared subjects who used glyphosate with those who did not use any pesticides as the reference group, whereas the other studies defined the reference group as those who did not use glyphosate in particular. Comparisons with subjects who do not use any pesticides are more likely to be confounded by other pesticides and agricultural exposures.

Meta-analysis can be problematic when applied to observational epidemiology.[21,22] Meta-analysis increases statistical precision by combining results from studies that may differ substantially in terms of source population, exposure and outcome assessment and classification, control for confounding, and other key characteristics. In the presence of such heterogeneity, even if not detectable using formal statistical tests, a single summary estimate may not be scientifically meaningful. Additionally, even when studies are statistically homogeneous, meta-analysis may not yield valid results, since this technique cannot overcome problems in the design and conduct of the underlying studies. Instead, given that bias can seldom be ruled out and unmeasured and uncontrolled confounding can never be eliminated from observational epidemiologic studies, modest meta-RRs detected across multiple studies may simply be due to shared biases, rather than a true association.[21] As stated earlier, the purpose of meta-analysis is not to evaluate whether associations are causal. We conducted a meta-analysis primarily for comparison with published findings.

Considering the shortcomings of the existing literature, what can be done to shed further light on whether glyphosate causes LHC in humans? Perhaps the foremost need is better exposure assessment. Self-reported information on use of specific pesticides, unless validated by comparison with sales records (which most likely would need to be collected prospectively, and might not be closely correlated with pesticide use) or other objective documentation, is not sufficiently accurate and reliable to yield credible estimates of association, especially exposure-response trends. Urinary glyphosate levels would provide more accurate and quantitatively detailed information on biological dose of glyphosate received, but would probably have to be measured repeatedly to reflect long-term exposure.

Information about temporal aspects of glyphosate exposure, such as the putative induction time since first use of glyphosate, duration of use, and time since last use, could help to shed light on the exposure-outcome relationship. Results from additional prospective cohort studies are necessary to alleviate concerns about selection and reporting bias in case-control studies.

More specific outcome classification also is needed. Only two studies[14,17] examined associations between glyphosate use and more than one histological subtype of NHL, despite growing evidence of important etiologic heterogeneity among NHL subtypes.[74] Information on NHL subtypes also is available in the Agricultural Health Study,[66] and publication of risk associations with glyphosate is anticipated. Risk factors for HL and leukemia also are known to differ by subtype,[76,77] yet no studies estimated associations with glyphosate separately for subtypes of these tumors. (Chronic lymphocytic leukemia and hairy-cell leukemia, which were analyzed as distinct outcomes, are classified as NHL subtypes.[20]) Large, probably pooled studies with histopathological data can determine whether associations with specific tumor subtypes might be obscured by analyzing overall NHL, HL, MM, or leukemia as a single disease entity.

Conclusion

In conclusion, we found marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL and MM, and statistically null associations with HL and leukemia. A statistically significant positive meta-RR for B-cell lymphoma, but not other NHL subtypes, was calculated based on only two studies. Combining these results with recognition of the methodological weaknesses of the small number of existing studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient, we determined that no causal relationship has been established between glyphosate exposure and risk of NHL, HL, MM, leukemia, or any subtype of LHC.

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References

[1] BfR. The BfR has finalised its draft report for the re-evaluation of glyphosate. Press release. Bundesinstitut für Risikobewertung (BfR): Berlin. 2014. Available at http://www.bfr.bund.de/en/the_bfr_has_finalised_its_draft_report_for_the_re_evaluation_of_glyphosate-188632.html (accessed Nov 2015).

[2] BfR. Does glyphosate cause cancer? BfR Communication No 007/2015, 23 March 2015. Bundesinstitut für Risikobewertung (BfR): Berlin, 2015. Available at http://www.bfr.bund.de/cm/349/does-glyphosate-cause-cancer.pdf (accessed Nov 2015).

[3] JMPR. Pesticide residues in food - 2004. Joint FAO/WHO Meeting on Pesticide Residues. Evaluations 2004. Part II - Toxicological. World Health Organization: Geneva, 2006.

[4] U.S. EPA. Reregistration Eligibility Decision (RED): Glyphosate. United States Environmental Protection Agency (U.S. EPA), Office of Prevention, Pesticides and Toxic Substances: Washington, DC, 1993.

[5] U.S. EPA. Glyphosate; Pesticide Tolerances. 40 CFR Part 180 [EPA-HQ-OPP-2012-0132; FRL-9384-3]. Final Rule. Federal Register, 2013, *78*, 25396–25401.

[6] IARC. Glyphosate. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 112. Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos*; International Agency for Research on Cancer (IARC): Lyon, France, 2015.

[7] BfR. Frequently asked questions on the procedure for the re-assessment of glyphosate within the framework of the EU active substance review. Available at http://www.bfr.bund.de/en/frequently_asked_questions_on_the_procedure_for_the_re_assessment_of_glyphosate_within_the_framework_of_the_eu_active_substance_review-195637.html (accessed Nov 2015). Bundesinstitut für Risikobewertung (BfR): Berlin, 2015.

[8] BfR. Frequently asked questions on the assessment of the health risk of glyphosate. Available at http://www.bfr.bund.de/en/frequently_asked_questions_on_the_assessment_of_the_health_risk_of_glyphosate-127871.html#topic_195669 (accessed Nov 2015). Bundesinstitut für Risikobewertung (BfR): Berlin, 2015.

[9] EFSA. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA (European Food Safety Authority) Journal. **2015**, *13*, 4302.

[10] JMPR. World Health Organization. Food safety. Joint FAO/WHO Meeting on Pesticide Residues (JMPR). Expert Taskforce on Diazinon, Glyphosate and Malathion. Available at http://www.who.int/foodsafety/areas_work/chemical-risks/jmpr/en/ (accessed Nov 2015,).

[11] Schinasi, L.; Leon, M.E. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. Int. J. Environ. Res. Public Health. **2014**, *11*, 4449–4527.

[12] De Roos, A.J.; Blair, A.; Rusiecki, J.A.; Hoppin, J.A.; Svec, M.; Dosemeci, M.; Sandler, D.P.; Alavanja, M.C. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ. Health Perspect. **2005**, *113*, 49–54.

[13] De Roos, A.J.; Zahm, S.H.; Cantor, K.P.; Weisenburger, D.D.; Holmes, F.F.; Burmeister, L.F.; Blair, A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup. Environ. Med. **2003**, *60*, E11.

[14] Eriksson, M.; Hardell, L.; Carlberg, M.; Akerman, M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int. J. Cancer. **2008**, *123*, 1657–1663.

[15] Hardell, L.; Eriksson, M.; Nordstrom, M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk. Lymphoma. **2002**, *43*, 1043–1049.

[16] McDuffie, H.H.; Pahwa, P.; McLaughlin, J.R.; Spinelli, J.J.; Fincham, S.; Dosman, J.A.; Robson, D.; Skinnider, L.F.; Choi, N.W. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol. Biomarkers Prev. **2001**, *10*, 1155–1163.

[17] Orsi, L.; Delabre, L.; Monnereau, A.; Delval, P.; Berthou, C.; Fenaux, P.; Marit, G.; Soubeyran, P.; Huguet, F.; Milpied, N.; Leporrier, M.; Hemon, D.; Troussard, X.; Clavel, J. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup. Environ. Med. **2009**, *66*, 291–298.

[18] Cocco, P.; Satta, G.; Dubois, S.; Pili, C.; Pilleri, M.; Zucca, M.; t Mannetje, A.M.; Becker, N.; Benavente, Y.; de Sanjose, S.; Foretova, L.; Staines, A.; Maynadie, M.; Nieters, A.; Brennan, P.; Miligi, L.; Ennas, M.G.; Boffetta, P. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup. Environ. Med. **2013**, *70*, 91–98.

[19] Mink, P.J.; Mandel, J.S.; Sceurman, B.K.; Lundin, J.I. Epidemiologic studies of glyphosate and cancer: a review. Regul. Toxicol. Pharmacol. **2012**, *63*, 440–452.

[20] Swerdlow, S.H.; Campo, E.H., N.L.; Jaffe, E.S.; Pileri, S.A.; Stein, H.; Thiele, J.; Vardiman, J.W. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th Ed. World Health Organization (WHO): Geneva, 2008.

[21] Shapiro, S. Meta-analysis/Shmeta-analysis. Am. J. Epidemiol. **1994**, *140*, 771–778.

[22] Weed, D.L. Meta-analysis and causal inference: a case study of benzene and non-Hodgkin lymphoma. Ann. Epidemiol. **2010**, *20*, 347–355.

[23] Cantor, K.P.; Blair, A.; Brown, L.M.; Burmeister, L.F.; Everett, G. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res. **1992**, *52*, 2447–2455.

[24] Cantor, K.P.; Blair, A.; Everett, G.; Gibson, R.; Burmeister, L.F.; Brown, L.M.; Schuman, L.; Dick, F.R. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res. **1992**, *52*, 2447–2455.

[25] Sorahan, T. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study data. Toxicol. Lett. **2012**, *211*, S169–S169.

[26] Sorahan, T. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data. Int. J. Environ. Res. Public Health. **2015**, *12*, 1548–1559.

[27] Hardell, L.; Eriksson, M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer. **1999**, *85*, 1353–1360.

[28] Hohenadel, K.; Harris, S.A.; McLaughlin, J.R.; Spinelli, J.J.; Pahwa, P.; Dosman, J.A.; Demers, P.A.; Blair, A. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. Int. J. Environ. Res. Public Health. **2011**, *8*, 2320–2330.

[29] Lee, W.J.; Cantor, K.P.; Berzofsky, J.A.; Zahm, S.H.; Blair, A. Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. Int. J. Cancer. **2004**, *111*, 298–302.

[30] Nordström, M.; Hardell, L.; Magnuson, A.; Hagberg, H.; Rask-Andersen, A. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. Br. J. Cancer. **1998**, *77*, 2048–2052.

[31] Karunanayake, C.P.; Spinelli, J.J.; McLaughlin, J.R.; Dosman, J.A.; Pahwa, P.; McDuffie, H.H. Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study. J. Agromedicine. **2012**, *17*, 30–39.

[32] Brown, L.M.; Burmeister, L.F.; Everett, G.D.; Blair, A. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control. **1993**, *4*, 153–156.

[33] Kachuri, L.; Demers, P.A.; Blair, A.; Spinelli, J.J.; Pahwa, M.; McLaughlin, J.R.; Pahwa, P.; Dosman, J.A.; Harris, S.A. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. Int. J. Cancer. **2013**, *133*, 1846–1858.

[34] Pahwa, P.; Karunanayake, C.P.; Dosman, J.A.; Spinelli, J.J.; McDuffie, H.H.; McLaughlin, J.R. Multiple myeloma and exposure to pesticides: a Canadian case-control study. J Agromedicine. **2012**, *17*, 40–50.

[35] Brown, L.M.; Blair, A.; Gibson, R.; Everett, G.D.; Cantor, K.P.; Schuman, L.M.; Burmeister, L.F.; Van Lier, S.F.; Dick, F. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. **1990**, *50*, 6585–6591.

[36] Kaufman, D.W.; Anderson, T.E.; Issaragrisil, S. Risk factors for leukemia in Thailand. Ann. Hematol. **2009**, *88*, 1079–1088.

[37] Woodruff, T.J.; Sutton, P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ. Health Perspect. **2014**, *122*, 1007–1014.

[38] Higgins, J.P.T.; Altman, D.G.; Sterne, J.A.C. Chapter 8: Assessing risk of bias in included studies. In *Cochrane Handbook for Systematic Reviews of Interventions*; Higgins, J.P.T.; Green, S. Eds.; The Cochrane Collaboration, 2011. Version 5.1.0 [updated March 2011]. Available at http://handbook.cochrane.org/ (accessed Nov 2015).

[39] Guyatt, G.H.; Oxman, A.D.; Vist, G.; Kunz, R.; Brozek, J.; Alonso-Coello, P.; Montori, V.; Akl, E.A.; Djulbegovic, B.; Falck-Ytter, Y.; Norris, S.L.; Williams, J.W., Jr.; Atkins, D.; Meerpohl, J.; Schunemann, H.J. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J. Clin. Epidemiol. **2011**, *64*, 407–415.

[40] Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. BMJ. **2003**, *327*, 557–560.

[41] Cochran, W.G. The combination of estimates from different experiments. Biometrics. **1954**, *10*, 101–129.

[42] Ioannidis, J.P. Interpretation of tests of heterogeneity and bias in meta-analysis. J. Eval. Clin. Pract. **2008**, *14*, 951–957.

[43] Dickersin, K.; Min, Y.I. Publication bias: the problem that won't go away. Ann. N. Y. Acad. Sci. **1993**, *703*, 135–146; discussion 146–138.

[44] Egger, M.; Davey Smith, G.; Schneider, M.; Minder, C. Bias in meta-analysis detected by a simple, graphical test. BMJ. **1997**, *315*, 629–634.

[45] Duval, S.; Tweedie, R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. **2000**, *56*, 455–463.

[46] Hill, A.B. The Environment and Disease: Association or Causation? Proc. R. Soc. Med. **1965**, *58*, 295–300.

[47] Hoar, S.K.; Blair, A.; Holmes, F.F.; Boysen, C.D.; Robel, R.J.; Hoover, R.; Fraumeni, J.F., Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA. **1986**, *256*, 1141–1147.

[48] Hoar Zahm, S.; Weisenburger, D.D.; Babbitt, P.A.; Saal, R.C.; Vaught, J.B.; Cantor, K.P.; Blair, A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiol. **1990**, *1*, 349–356.

[49] Glyphosate Task Force. History of glyphosate. 2013. Available at http://www.glyphosate.eu/glyphosate-basics/history-glyphosate. (accessed Nov 2015).

[50] Landgren, O.; Kyle, R.A.; Hoppin, J.A.; Beane Freeman, L.E.; Cerhan, J.R.; Katzmann, J.A.; Rajkumar, S.V.; Alavanja, M.C. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. **2009**, *113*, 6386–6391.

[51] Lash, T.L. Bias analysis applied to Agricultural Health Study publications to estimate non-random sources of uncertainty. J. Occup. Med. Toxicol. **2007**, *2*, 15.

[52] Acquavella, J.F.; Alexander, B.H.; Mandel, J.S.; Burns, C.J.; Gustin, C. Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring. Epidemiol. **2006**, *17*, 69–74.

[53] Rudant, J.; Orsi, L.; Monnereau, A.; Patte, C.; Pacquement, H.; Landman-Parker, J.; Bergeron, C.; Robert, A.; Michel, G.; Lambilliotte, A.; Aladjidi, N.; Gandemer, V.; Lutz, P.; Marguerite, G.; Plantaz, D.; Mechinaud, F.; Hemon, D.; Clavel, J. Childhood Hodgkin's lymphoma, non-Hodgkin's lymphoma and factors related to the immune system: the Escale Study (SFCE). Int. J. Cancer. **2011**, *129*, 2236–2247.

[54] Hofmann, J.N.; Hoppin, J.A.; Lynch, C.F.; Poole, J.A.; Purdue, M.P.; Blair, A.; Alavanja, M.C.; Beane Freeman, L.E. Farm characteristics, allergy symptoms, and risk of non-Hodgkin lymphoid neoplasms in the agricultural health study. Cancer Epidemiol. Biomarkers Prev. **2015**, *24*, 587–594.

[55] Blair, A.; Zahm, S.H. Methodologic issues in exposure assessment for case-control studies of cancer and herbicides. Am. J. Ind. Med. **1990**, *18*, 285–293.

[56] Bowling, A. Mode of questionnaire administration can have serious effects on data quality. J. Public Health (Oxf). **2005**, *27*, 281–291.

[57] Griffith, L.E.; Cook, D.J.; Guyatt, G.H.; Charles, C.A. Comparison of open and closed questionnaire formats in obtaining demographic information from Canadian general internists. J. Clin. Epidemiol. **1999**, *52*, 997–1005.

[58] Dosman, J.A.; McDuffie, H.H.; Pahwa, P.; Fincham, S.; McLaughlin, J.R.; Robson, D.; Theriault, G. Pesticides, Soft Tissue Sarcoma, Lymphoma, and Multiple Myeloma. A Case Control Study in Three Regions of Canada. Report to Health and Welfare Canada on Project 6008–1223; University of Saskatchewan: Saskatoon, Canada, 1990.

[59] Blair, A.; Tarone, R.; Sandler, D.; Lynch, C.F.; Rowland, A.; Wintersteen, W.; Steen, W.C.; Samanic, C.; Dosemeci, M.; Alavanja, M.C. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiol. **2002**, *13*, 94–99.

[60] Blair, A.; Thomas, K.; Coble, J.; Sandler, D.P.; Hines, C.J.; Lynch, C. F.; Knott, C.; Purdue, M.P.; Zahm, S.H.; Alavanja, M.C.; Dosemeci, M.; Kamel, F.; Hoppin, J.A.; Freeman, L.B.; Lubin, J.H. Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study. Occup. Environ. Med. **2011**, *68*, 537–541.

[61] Coble, J.; Thomas, K.W.; Hines, C.J.; Hoppin, J.A.; Dosemeci, M.; Curwin, B.; Lubin, J.H.; Beane Freeman, L.E.; Blair, A.; Sandler, D.P.; Alavanja, M.C. An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. Int. J. Environ. Res. Public Health. **2011**, *8*, 4608–4622.

[62] Agricultural Health Study. Agricultural Health Study Questionnaires & Study Data. Available at http://aghealth.nih.gov/collaboration/questionnaires.html (accessed 28 November 2015). 1996.

[63] Jurek, A.M.; Greenland, S.; Maldonado, G. How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null? Int. J. Epidemiol. **2008**, *37*, 382–385.

[64] Jurek, A.M.; Greenland, S.; Maldonado, G.; Church, T.R. Proper interpretation of non-differential misclassification effects: expectations vs observations. Int. J. Epidemiol. **2005**, *34*, 680–687.

[65] Weichenthal, S.; Moase, C.; Chan, P. A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. Environ. Health Perspect. **2010**, *118*, 1117–1125.

[66] Alavanja, M.C.; Hofmann, J.N.; Lynch, C.F.; Hines, C.J.; Barry, K.H.; Barker, J.; Buckman, D.W.; Thomas, K.; Sandler, D.P.; Hoppin, J.A.; Koutros, S.; Andreotti, G.; Lubin, J.H.; Blair, A.; Beane Freeman, L.E. Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the Agricultural Health Study. PLoS One. **2014**, *9*, e109332.

[67] Pearce, N.; McLean, D. Agricultural exposures and non-Hodgkin's lymphoma. Scand. J. Work Environ. Health. **2005**, *31*(Suppl 1), 18–25; discussion 15–17.

[68] McDuffie, H.H.; Pahwa, P.; Spinelli, J.J.; McLaughlin, J.R.; Fincham, S.; Robson, D.; Dosman, J.A.; Hu, J. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). Am. J. Ind. Med. **2002**, *Suppl 2*, 54–61.

[69] Fritschi, L.; Johnson, K.C.; Kliewer, E.V.; Fry, R.; Canadian Cancer Registries Epidemiology Research, G. Animal-related occupations and the risk of leukemia, myeloma, and non-Hodgkin's lymphoma in Canada. Cancer Causes Control. **2002**, *13*, 563–571.

[70] Khuder, S.A.; Mutgi, A.B.; Schaub, E.A.; Tano, B.D. Meta-analysis of Hodgkin's disease among farmers. Scand. J. Work Environ. Health. **1999**, *25*, 436–441.

[71] Pahwa, P.; McDuffie, H.H.; Dosman, J.A.; Robson, D.; McLaughlin, J.R.; Spinelli, J.J.; Fincham, S. Exposure to animals and selected risk factors among Canadian farm residents with Hodgkin's disease, multiple myeloma, or soft tissue sarcoma. J. Occup. Environ. Med. **2003**, *45*, 857–868.

[72] Perrotta, C.; Staines, A.; Cocco, P. Multiple myeloma and farming. A systematic review of 30 years of research. Where next? J. Occup. Med. Toxicol. **2008**, *3*, 27.

[73] Keller-Byrne, J.E.; Khuder, S.A.; Schaub, E.A. Meta-analysis of leukemia and farming. Environ. Res. **1995**, *71*, 1–10.

[74] Morton, L.M.; Slager, S.L.; Cerhan, J.R.; Wang, S.S.; Vajdic, C.M.; Skibola, C.F.; Bracci, P.M.; de Sanjose, S.; Smedby, K.E.; Chiu, B.C.; Zhang, Y.; Mbulaiteye, S.M.; Monnereau, A.; Turner, J.J.; Clavel, J.; Adami, H.O.; Chang, E.T.; Glimelius, B.; Hjalgrim, H.; Melbye, M.; Crosignani, P.; di Lollo, S.; Miligi, L.; Nanni, O.; Ramazzotti, V.; Rodella, S.; Costantini, A.S.; Stagnaro, E.; Tumino, R.; Vindigni, C.; Vineis, P.; Becker, N.; Benavente, Y.; Boffetta, P.; Brennan, P.; Cocco,

P.; Foretova, L.; Maynadie, M.; Nieters, A.; Staines, A.; Colt, J.S.; Cozen, W.; Davis, S.; de Roos, A.J.; Hartge, P.; Rothman, N.; Severson, R.K.; Holly, E.A.; Call, T.G.; Feldman, A.L.; Habermann, T.M.; Liebow, M.; Blair, A.; Cantor, K.P.; Kane, E.V.; Lightfoot, T.; Roman, E.; Smith, A.; Brooks-Wilson, A.; Connors, J.M.; Gascoyne, R.D.; Spinelli, J.J.; Armstrong, B.K.; Kricker, A.; Holford, T.R.; Lan, Q.; Zheng, T.; Orsi, L.; Dal Maso, L.; Franceschi, S.; La Vecchia, C.; Negri, E.; Serraino, D.; Bernstein, L.; Levine, A.; Friedberg, J.W.; Kelly, J.L.; Berndt, S.I.; Birmann, B.M.; Clarke, C.A.; Flowers, C.R.; Foran, J.M.; Kadin, M.E.; Pal-tiel, O.; Weisenburger, D.D.; Linet, M.S.; Sampson, J.N. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J. Natl. Cancer Inst. Monogr. **2014**, *2014*, 130–144.

[75] Becker, N. Epidemiology of multiple myeloma. Recent Results Cancer Res. **2011**, *183*, 25–35.

[76] Glaser, S.L.; Chang, E.T.; Clarke, C.A.K., T.H. Chapter 1. Epidemiology. In *Hodgkin Lymphoma. A Comprehensive Overview*. 2nd ed.; Engert, A., Younes, A. Eds.; Springer: New York, 2015; 3–26.

[77] Linet, M.S.; Devesa, S.S.; Morgan, G.J. Chapter 44. The Leukemias. In *Cancer Epidemiology and Prevention*. 3rd Ed.; Schottenfeld, D.; Fraumeni, J.F., Jr. Eds.; Oxford University Press: New York, 2006; 841–871.

[78] Stiernstrom, E.L.; Holmberg, S.; Thelin, A.; Svardsudd, K. A prospective study of morbidity and mortality rates among farmers and rural and urban nonfarmers. J. Clin. Epidemiol. **2001**, *54*, 121–126.

[79] McCurdy, S.A.; Carroll, D.J. Agricultural injury. Am. J. Ind. Med. **2000**, *38*, 463–480.

[80] Kavvoura, F.K.; Liberopoulos, G.; Ioannidis, J.P. Selection in reported epidemiological risks: an empirical assessment. PLoS Med. **2007**, *4*, e79.

[81] Pahwa, M.; Harris, S.A.; Hohenadel, K.; McLaughlin, J.R.; Spinelli, J. J.; Pahwa, P.; Dosman, J.A.; Blair, A. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. Int. J. Cancer. **2012**, *131*, 2650–2659.

[82] Acquavella, J.; Farmer, D.; Cullen, M.R. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer. **1999**, *86*, 729–731.

[83] Wester, R.C.; Melendres, J.; Sarason, R.; McMaster, J.; Maibach, H.I. Glyphosate skin binding, absorption, residual tissue distribution, and skin decontamination. Fundam. Appl. Toxicol. **1991**, *16*, 725–732.

[84] Acquavella, J.F.; Alexander, B.H.; Mandel, J.S.; Gustin, C.; Baker, B.; Chapman, P.; Bleeke, M. Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. Environ. Health Perspect. **2004**, *112*, 321–326.

[85] Niemann, L.; Sieke, C.; Pfeil, R.; Solecki, R. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. J. Verbr. Lebensm. **2015**, *10*, 3–12.

[86] U.S. EPA. Glyphosate (CASRN 1071-83-6). Integrated Risk Information System. Carcinogenicity Assessment for Lifetime Exposure, 1993. Available at http://www.epa.gov/iris/subst/0057.htm. (accessed Nov 2015).

[87] Kier, L.D.; Kirkland, D.J. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit. Rev. Toxicol. **2013**, *43*, 283–315.

[88] Greim, H.; Saltmiras, D.; Mostert, V.; Strupp, C. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit. Rev. Toxicol. **2015**, *45*, 185–208.

[89] Fasal, E.; Jackson, E.W.; Klauber, M.R. Leukemia and lymphoma mortality and farm residence. Am. J. Epidemiol. **1968**, *87*, 267–274.

[90] Milham, S., Jr. Leukemia and multiple myeloma in farmers. Am. J. Epidemiol. **1971**, *94*, 507–510.

[91] Sandin, S.; Hjalgrim, H.; Glimelius, B.; Rostgaard, K.; Pukkala, E.; Askling, J. Incidence of non-Hodgkin's lymphoma in Sweden, Denmark, and Finland from 1960 through 2003: an epidemic that was. Cancer Epidemiol. Biomarkers Prev. **2006**, *15*, 1295–1300.

[92] Holford, T.R.; Zheng, T.; Mayne, S.T.; McKay, L.A. Time trends of non-Hodgkin's lymphoma: are they real? What do they mean? Cancer Res. **1992**, *52*, 5443s–5446s.

[93] Thygesen, L.C.; Nielsen, O.J.; Johansen, C. Trends in adult leukemia incidence and survival in Denmark, 1943–2003. Cancer Causes Control. **2009**, *20*, 1671–1680.

[94] Hjalgrim, H. On the aetiology of Hodgkin lymphoma. Dan. Med. J. **2012**, *59*, B4485.

[95] Hirabayashi, Y.; Katanoda, K. Comparison of time trends in multiple myeloma incidence (1973–1997) in East Asia, Europe and United States, from Cancer Incidence in Five Continents, Vols IV-VIII. Jpn. J. Clin. Oncol. **2008**, *38*, 720–721.

[96] Morton, L.M.; Wang, S.S.; Devesa, S.S.; Hartge, P.; Weisenburger, D.D.; Linet, M.S. Lymphoma incidence patterns by WHO subtype in the United States, 1992–2001. Blood. **2006**, *107*, 265–276.

[97] Button, K.S.; Ioannidis, J.P.; Mokrysz, C.; Nosek, B.A.; Flint, J.; Robinson, E.S.; Munafo, M.R. Power failure: why small sample size undermines the reliability of neuroscience. Nat. Rev. Neurosci. **2013**, *14*, 365–376.

Appendix

Literature search methods

The authors conducted a search of MEDLINE via PubMed using the following search string, which includes Chemical Abstracts Service (CAS) Registry Numbers for glyphosate and its salts:

(glyphosat OR glifosat* OR glyfosat* OR gliphosat* OR Roundup OR Round-up OR 1071-83-6 OR 38641-94-0 OR 70901-12-1 OR 39600-42-5 OR 69200-57-3 OR 34494-04-7 OR 114370-14-8 OR 40465-66-5 OR 69254-40-6 OR (aminomethyl w phosphonic*) OR 1066-51-9 OR pesticid* OR herbicid* OR organophosphorus compounds [MeSH] OR pesticides [MeSH] OR herbicides [MeSH]) AND (leukemi* OR leukaemi* OR lymphoma* OR NHL OR lymphopoietic OR hemato* OR hematopoie* or hematolog* OR lymphoid OR myeloid OR myeloma OR leukemia [MeSH] OR lymphoma [MeSH] OR multiple myeloma [MeSH]) AND (cases OR controls OR case-control OR cohort).*

As of June 23, 2015, this search string identified a total of 11,755 articles in PubMed. We conducted additional targeted searches in PubMed, Web of Science, and Google Scholar using simpler keyword combinations such as *(glyphosate AND lymphoma)*, *(pesticides AND lymphoma)*, and *(herbicides AND lymphoma)*. References also were identified from the bibliographies of recent review articles.

Altogether, a total of 12,709 articles were identified from these combined sources (Fig. A1). Based on a review of titles and abstracts, 321 articles were identified as potentially containing estimates of the association between glyphosate exposure and LHC risk, and were obtained for further evaluation. Forty-seven of these articles contained the word "glyphosate" or "Roundup" (or alternative spellings of these terms) in the text; as specified earlier, articles that did not mention glyphosate were ineligible for inclusion. Following a review of the full text of each of the 47 articles mentioning glyphosate, 19 articles were ultimately deemed eligible for inclusion.

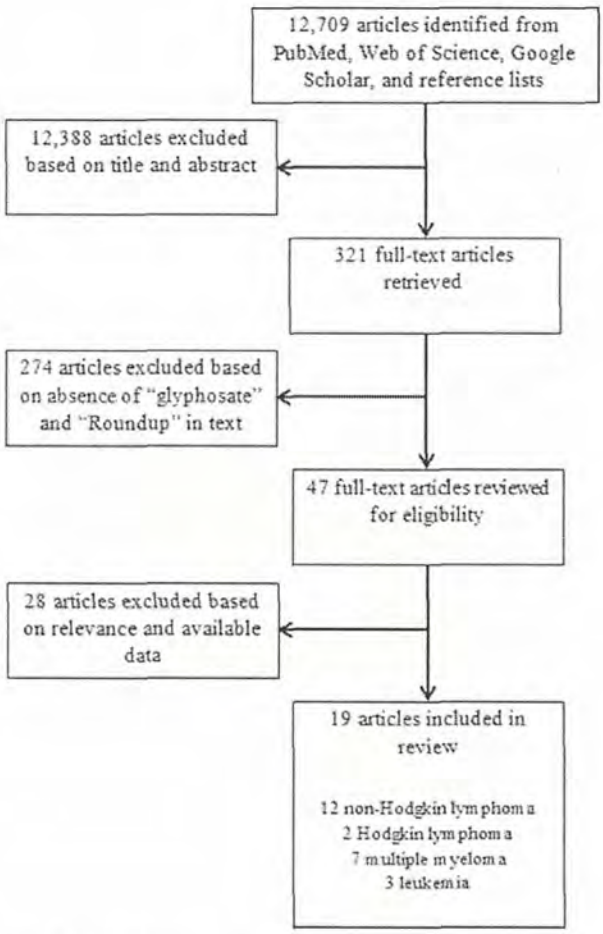

Figure A1. Flow chart of literature identification and selection process.

Message

From: John Acquavella [redacted]
Sent: 6/2/2015 2:06:19 PM
To: Thomas Sorahan [redacted]
Subject: Re: IARC updates

EXHIBIT 24-4
WIT: Nucci
DATE: 9/22/17
Maureen Pollard, RMR

Got it. Thanks. john On 6/2/15, 6:32 AM, "Thomas Sorahan" wrote: >Hi John > >John Mc is one of the 125 Pearce IARC insiders. I thought he was very >careful at IARC not to gainsay anything said by Aaron or Francesco >Forastiere. > >Tom > > >-----Original Message----- >From: John Acquavella [redacted] >Sent: 02 June 2015 14:20 >To: Thomas Sorahan >Subject: Re: IARC updates > >Tom: > >I have the highest regard for Elizabeth. She is as expert as any >occupational epidemiologist. Plus, she is a personal friend. The major >con with Elizabeth is that she works for Exponent and would not be >perceived as an academic with no direct conflict of interest. She would >be a top choice if we only considered merit in putting together the >investigator group. > >My sense is that you are right that it may be impossible to find a >prominent EU epidemiologist that will want to get in the middle of this. >Based on your IARC experience, what did you think of John McLaughlin? >Might he be a possibility? > > >Regards, > >John > > >> On Jun 2, 2015, at 5:41 AM, Thomas Sorahan >>wrote: >> >> Hi John >> >> I can't think of anyone suitable over here. Yes there are some very >>clever people here, but they will take the initiative to be anti-IARC >>(which it isn't), and therefore not for them. Personally, I would go for >>Elizabeth Delzell. >> >> Tom >> >> >> -----Original Message----- >> From: John Acquavella [redacted] >> Sent: 02 June 2015 13:26 >> To: Thomas Sorahan >> Cc: Donna >> Subject: Re: IARC updates >> >> Hi Tom. That's too bad, but perhaps not unexpected. >> >> The probability of the AHS agreeing to the collaboration route is >>probably less than 50/50 and likely depends on our getting the agreement >>of people like David and Tim. Do you have another EU epidemiologist in >>mind? >> >> It is nice that David might be willing to comment on the protocol, but >>that will not really carry any weight in the big scheme of things. >>Nonetheless, worth getting his comments. >> >> Regards, >> >> John >> >> >>> On Jun 2, 2015, at 4:53 AM, Thomas Sorahan >>>wrote: >>> >>> Donna/John >>> >>> I have had a reply from David Coggon. Because of his work on govt >>>advisory committees, he does not want to be involved with industry >>>funded work or work funded by campaign groups. However, if the work >>>proceeded in collaboration with AHS researchers, I think he would be >>>open to commenting on the protocol. >>> >>> Tom >>> >>> >>> -----Original Message----- >>> From: Thomas Sorahan >>> Sent: 01 June 2015 11:23 >>> To: 'John Acquavella'; FARMER, DONNA R [AG/1000] >>> Subject: RE: IARC updates >>> >>> Donna/John >>> >>> I have asked David Coggon, whether he might be interested, in >>>principle, in being part of a small team to work on updated findings >>>for NHL and multiple myeloma from the AHS. I will let you know his >>>response. Some practical issues arise. >>> >>> Are we aiming for one paper on NHL and one on multiple myeloma, or a >>>single paper that deals with both outcomes. NHL is so important that it >>>might help to have a single paper on it. If monies are going to central >>>University funds there will need to be a research contract between >>>Monsanto and the University. The University has a standard contract >>>that can be amended or the University will be happy to work on a >>>Monsanto document. But I should warn you in advance that getting all >>>the paperwork in place is tedious and time-consuming. The next issue is >>>whether Monsanto has a separate contract with Southampton or whether >>>Southampton has a sub-contract with B'ham. >>> >>> A bigger question is whether we are hoping to collaborate on the work >>>itself with AHS researchers or just get their agreement for access to >>>the data. >>> >>> Tom >>> >>> >>> -----Original Message----- >>> From: John Acquavella [redacted] >>> Sent: 30 May 2015 20:16 >>> To: Thomas Sorahan; FARMER, DONNA R [AG/1000] >>> Subject: ?spam? Re: IARC updates >>> >>> Donna/Tom: >>> >>> Donna, assuming you approve, I will contact Tim Lash on Monday. >>> >>> Tom: just so we tell them the same thing, I assume there will be a >>>time lag before we get data from the AHS. So, it seems they don't need >>>to be available immediately - perhaps 4Q earliest. Also, we discussed >>>setting this up so there is no direct conflict. As such, we are not >>>going to pay them per se, but instead offer a contribution to their >>>school in some shape or form? Did we say $10K each (assuming a >>>cumulative 5 days at $2,000/day)? >>> >>> Their efforts will include consulting on the study

protocol (Tom as >>>lead author), reviewing the analyses (Tom to implement), and being >>>co-authors on a report/publication (Tom as lead author). They will ask >>>about the right to publish, so my suggestion is to say the author group >>>has last say (Tom, David, Tim) after considering any suggestions from >>>the sponsor. I will also see whether Michael will agree to collaborate >>>after we know our academic collaborators. >>> >>> Comments? >>> >>> Regards, >>> >>> John >>> >>> On 5/30/15, 12:15 AM, "Thomas Sorahan" wrote: >>> >>>> Dear Donna >>>> >>>> I will contact David C on Monday. >>>> >>>> Tom >>>> _____ >>>> From: FARMER, DONNA R [AG/1000] [redacted] >>>> Sent: Friday, May 29, 2015 8:07 PM >>>> To: John Acquavella; Thomas Sorahan >>>> Subject: RE: IARC updates >>>> >>>> Yes we just got the approval for Elizabeth's work as well today. >>>> >>>> -----Original Message----- >>>> From: John Acquavella [redacted] >>>> Sent: Friday, May 29, 2015 2:07 PM >>>> To: FARMER, DONNA R [AG/1000]; Thomas Sorahan >>>> Subject: Re: IARC updates >>>> >>>> >>>> Donna: >>>> >>>> I suggest Tom reach out to David Coggin. I will reach out to Tim Lash. >>>> Then, we'll know if we have our preferred academic collaborators. If >>>> not, regroup and try to recruit two other prominent academics. >>>> >>>> Once we have the academic team settled, suggest I contact Michael >>>> Alavanja to test the waters on going the AHS collaboration route. >>>> Otherwise, I guess the route is FOIA. >>>> >>>> Assume Elizabeth's work is in progress. >>>> >>>> Regards, >>>> >>>> John >>>> >>>> >>>> >>>> On 5/29/15, 12:01 PM, "FARMER, DONNA R [AG/1000]" >>>> wrote: >>>> >>>>> John and Tom, >>>>> >>>>> We have gotten approval to move forward on the AHS collaboration. >>>>> >>>>> How do you recommend we proceed? >>>>> >>>>> Regards, >>>>> >>>>> Donna >>>>> >>>>> -----Original Message----- >>>>> From: John Acquavella [redacted] >>>>> Sent: Monday, April 20, 2015 11:34 AM >>>>> To: Thomas Sorahan; FARMER, DONNA R [AG/1000] >>>>> Subject: Re: IARC updates >>>>> >>>>> It would be great if David would participate. >>>>> >>>>> On 4/20/15, 9:06 AM, "Thomas Sorahan" wrote: >>>>> >>>>>> Hi John >>>>>> >>>>>> I would have thought David Coggan would be interested in an AHS >>>>>> collaboration. Not sure if he is involved in any UK national >>>>>> pesticide committees at the moment. >>>>>> >>>>>> Tom >>>>>> >>>>>> _____ >>>>>> From: John Acquavella [redacted] >>>>>> Sent: Monday, April 20, 2015 2:38 PM >>>>>> To: Donna >>>>>> Cc: Thomas Sorahan >>>>>> Subject: Re: IARC updates >>>>>> >>>>>> Thank you Donna. Doesn't reflect well on IARC to be so out of >>>>>> touch on glyphosate. Interesting roster for the upcoming IARC >>>>>> meeting. >>>>>> >>>>>> Did the 2,4-D taskforce really get 3 observer spots? I see that >>>>>> Coggin was quoted. Wonder if that increases the odds that he will >>>>>> participate in an AHS collaboration. Perhaps Tom has an opinion. >>>>>> >>>>>> Regards, >>>>>> >>>>>> John >>>>>> >>>>>> >>>>>> On Apr 20, 2015, at 6:18 AM, FARMER, DONNA R [AG/1000] >>>>>> wrote: >>>>>> >>>>>> >>>>>> This e-mail message may contain privileged and/or confidential >>>>>> information, and is intended to be received only by persons >>>>>> entitled to receive such information. If you have received this >>>>>> e-mail in error, please notify the sender immediately. Please >>>>>> delete it and all attachments from any servers, hard drives or any >>>>>> other media. Other use of this e-mail by you is strictly prohibited. >>>>>> All e-mails and attachments sent and received are subject to >>>>>> monitoring, reading and archival by Monsanto, including its >>>>>> subsidiaries. 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If you have received this >>>> e-mail in error, please notify the sender immediately. Please >>>> delete it and all attachments from any servers, hard drives or any >>>> other media. Other use of this e-mail by you is strictly prohibited. >>>> >>>> All e-mails and attachments sent and received are subject to >>>> monitoring, reading and archival by Monsanto, including its >>>> subsidiaries. The recipient of this e-

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Message

From: FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=180070]
Sent: 8/25/2015 8:04:03 PM
To: Elizabeth Delzell [redacted]
CC: Ellen Chang [redacted]
Subject: RE: Revised ms and signed contract
Attachments: Glyphosate ms draft 081715 trackedDRF.docx; niemann_2015.pdf; US EPA Federal Register 2013.pdf

Elizabeth and Ellen,

While I do not understand a lot about epidemiology I can see that you have done a lot of work and appreciate your efforts.

Thank you for the opportunity to review the draft of the paper and please see our suggested comments in the attachment.

Also attached is the Neimann reference that I mentioned for your consideration regarding the paragraph on page 24 and a more recent document from EPA regarding their opinion on glyphosate and carcinogenicity in the Introduction on page 1.

Regards,

Donna

From: Elizabeth Delzell [redacted]
Sent: Monday, August 24, 2015 5:48 PM
To: FARMER, DONNA R [AG/1000]
Cc: Ellen Chang
Subject: FW: Revised ms and signed contract

Dear Donna,

John Acquavella has indicated that the epidemiology expert panel conferring later this week would like to have the most recent version of our review/meta-analysis paper. If Monsanto approves distributing that version of the draft paper to the panel, would you please do so or send a reply email approving our doing it. Also, please let us know if/when we are going to receive comments from Monsanto.

Of course, let us know if you have any questions.

With best regards, Elizabeth

From: Ellen Chang
Sent: Monday, August 17, 2015 12:05 PM
To: FARMER, DONNA R [AG/1000] ([redacted])
Cc: Elizabeth Delzell
Subject: Revised ms and signed contract

Dear Donna,

Attached please find the current version of our manuscript, which has been revised in accordance with comments from Tom Sorahan and John Acquavella. All changes are marked. We do not plan to send this draft to Tom and John until we have received and responded to any comments that Monsanto might have.

Could we please schedule a conference call to discuss next steps and the timeline for journal submission? We'd also like to follow up on the outstanding invoice from March 6, 2015.

Please let us know if you have any questions.

Best wishes,

Ellen

~~~~~~

Ellen T. Chang, Sc.D.

Senior Managing Scientist

Exponent

Health Sciences Practice | 149 Commonwealth Drive | Menlo Park, CA 94025

Office: [redacted] | Mobile: [redacted] | Fax: [redacted] | [redacted]
~~~~~~

Message

From: FARMER, DONNA R [AG/1000] [redacted]
Sent: 10/26/2015 6:01:10 PM
To: HEYDENS, WILLIAM F [AG/1000] [redacted]; John Acquavella [redacted]
Subject: FW: Manuscript decision
Attachments: image001.gif; Reviewer 2 comments.pdf; Reviewer 1 comments.pdf

See below.

From: Ellen Chang [redacted]
Sent: Monday, October 26, 2015 12:04 PM
To: FARMER, DONNA R [AG/1000]
Cc: Elizabeth Delzell
Subject: RE: Manuscript decision

Dear Donna,

They didn't explicitly state why, and one of the reviews was reasonably favorable. I suspect that the editors had concerns about bias and conflict of interest, because they asked me a question about this issue prior to sending the paper out for review. The second reviewer was clearly concerned about this. The reviewers' comments are attached.

Best wishes,
Ellen

~~~~~~

Ellen T. Chang, Sc.D.
Senior Managing Scientist
[redacted]
Health Sciences Practice | 149 Commonwealth Drive | Menlo Park, CA 94025
Office: [redacted] | Mobile: [redacted] | Fax: [redacted] | [redacted]

From: FARMER, DONNA R [AG/1000] [redacted]
Sent: Monday, October 26, 2015 10:00 AM
To: Ellen Chang
Cc: Elizabeth Delzell
Subject: RE: Manuscript decision

Ellen,

Did they give the reason (s) why?

I forwarded to John for his thoughts.
~~~~~~

Donna

From: Ellen Chang [redacted]
Sent: Sunday, October 25, 2015 11:05 PM
To: FARMER, DONNA R [AG/1000]
Cc: Elizabeth Delzell
Subject: Manuscript decision

Dear Donna,

Unfortunately, our manuscript on the meta-analysis and review of glyphosate and lymphohematopoietic cancers was rejected by the International Journal of Environmental Research and Public Health. Elizabeth and I will discuss where we should submit it next, but please let us know if you have any suggestions.

Best wishes,
Ellen

~~~~~~

Ellen T. Chang, Sc.D.
Senior Managing Scientist
[redacted]
Health Sciences Practice | 149 Commonwealth Drive | Menlo Park, CA 94025
Office: [redacted] | Mobile: [redacted] | Fax: [redacted] | [redacted]
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Journal IJERPH (ISSN 1660-4601)
http://www.mdpi.com/journal/ijerph
Manuscript ID ijerph-100633
Journal International Journal of Environmental Research and Public Health
Type Review
Title Systematic Review and Meta-Analysis of Glyphosate Exposure and Risk of Lymphohematopoietic Cancers
Number of Pages 69
Download Manuscript
Authors Ellen T. Chang * , Elizabeth Delzell
Abstract The carcinogenic potential of glyphosate was recently reviewed by health and regulatory agencies. One study considered in these reviews, a meta-analysis of epidemiologic data on pesticides including glyphosate and NHL risk, did not present an in-depth assessment of research quality or a weight-of-evidence evaluation of causality. Therefore, this systematic review and meta-analysis examines more rigorously the relationship between glyphosate and lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia. Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between glyphosate use and risk of NHL (meta-RR=1.3, 95% confidence interval (CI)=1.0–1.6, based on six independent studies) and MM (meta-RR=1.4, 95% CI=1.0–1.9; four studies). Associations were statistically null for HL (meta-RR=1.1, 95% CI=0.7–1.6; two studies), leukemia (meta-RR=1.0, 95% CI=0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). These meta-RRs have uncertain validity because bias and confounding cannot be excluded. Methodological weaknesses include the small number of available studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient. Thus, no valid association, much less a causal relationship, has been established between glyphosate exposure and risk of any LHC.

Review Report Form

English Language and Style
(x) English language and style are fine
( ) Minor spell check required
( ) Extensive editing of English language and style required
( ) I don't feel qualified to judge about the English Language and Style

Comments and Su[redacted] Feedback & Support for Authors

This paper seems like it is agenda-driven from the outset. The authors set out to re-do the meta-analysis of Schinasi and Leon (2014) using specific selection criteria for studies and by presenting multiple meta estimates for various combinations of risk estimates from the studies. They have a similar result as Schinasi and Leon (meta RR of 1.3 [1.0-1.6] vs. meta RR of 1.5 [1.1-2.0]) for the risk of NHL associated with ever vs. never used glyphosate (similar result given the crude exposure metric). In addition, the authors find a meta RR of 1.4 (1.0-1.9) for the association between multiple myeloma (MM) and use of glyphosate (an cancer type that had not been examined Schinasi & Leon) and a significantly increased meta RR for B-cell lymphoma. Then, despite the fact that the authors deemed the meta-analysis worth conducting, the discussion devolves into a laundry list of every possible cause of bias or imprecision of estimates in epidemiologic studies, as well as a review of the Bradford Hill criteria to evaluate the weight-of-evidence for the association, from which the authors conclude that there is no basis for a causal association. My question is – if that is the conclusion from a review of the studies, why even conduct the meta analysis in the first place? Why was the meta analysis deemed worthy of conducting if based on the review, the studies had so many methodological weaknesses as to

conclude that there is 'no valid association'.

Furthermore, despite criticizing the IARC classification of glyphosate as a probable carcinogen throughout the paper, the paper's conclusion about the epidemiologic studies of NHL is essentially the same as IARC's. IARC deemed the evidence for carcinogenicity of glyphosate from human studies to be limited, based on studies of NHL; this 'limited' categorization means that there is some evidence of an association, but biases such as confounding and selection bias cannot be ruled out (the same conclusion as these authors). If the authors set out to debunk the IARC classification of glyphosate as a probable carcinogen, they would have better spent their time on review of the animal studies and mechanistic data, as these data contributed much more importantly to the IARC classification than the epidemiologic data.

The authors should clearly state (in the text) which of the studies they cite were funded (or partially funded) by Monsanto – such as Mink et al. 2012 and Sorahan 2015.

The analysis by Tier 1 vs. Tier 2 based on 'study quality' is so limited as to make it not worthwhile. It is based on participation rates and the percentage of proxy respondents. However, other factors such as the amount of missing data are not included. For example, even though the Ag Health Study has >80% participation, a smaller percentage than this provided useful reporting on glyphosate use. Therefore, this >80% does not have uncontended importance as to what it represents about study quality. Another factor that can importantly cause selection bias is identification of controls from a hospital setting rather than a general population-based setting. Nevertheless, one of the studies that ends up as Tier 1 has hospital-based controls (Orsi et al.). Given that there are only 2 studies that end up as Tier 1 vs. Tier 2 in the NHL analysis (only the Ag Health Study prospective cohort and the Orsi et al. hospital-based study), the classification of these as having higher study quality compared to the others is tenuous, at best. It would be more appropriate and fair to simply discuss the quality of the different studies and admit that the small number of studies precludes cohesive stratification by study quality. For example, it's fair to point out that the only prospective cohort study (AHS) didn't find an association between glyphosate & NHL.

Table 1 is a bit hard to look at – if Table 1a and 1b could both fit on one page, that would be optimal.

Does the 'Results not shown' column only include results that the investigators said they ran but didn't show, or does it also include other analyses that would have been possible but were not mentioned? The former seems fine, but the latter would be an open-ended, hypothetical set of results.

Table 2 should include the disease corresponding to the specific RRs.

Page 42. Do some of the Sorahan trend tests include the category for unknown glyphosate use? (such as at the bottom of page 42). Including this group as a category in the trend tests is not appropriate as there is no reason to expect the magnitude of association for this group to be more or less than any of the glyphosate exposure categories. If this group is NOT included as a category in the trend test, then remove these RRs from the table and text when describing the trend test for glyphosate categories. If the trend test DOES include this category, then I would argue that the test is not meaningful and shouldn't be presented.

The results in Table 3 are nicely presented. However, it would be easier to compare results between the different models if only one study is switched out at a time.

Page 52. A change in the RR from 1.26 to 1.20 can hardly be described as an attenuation.

The estimates for MGUS should not be combined with those for MM. MGUS is a precancerous condition that occurs in approximately 1% of the population – therefore the vast majority of these cases do not progress to MM. It is completely inappropriate to combine the study of MGUS with the studies that focused on MM. Would recommend to remove this study entirely.

The authors use the results from the Sorahan (2015) analysis of the Agricultural Health Study dataset in some analyses and also compare these results to De Roos et al. (2005), an earlier analysis from the same dataset. The two authors used different methods for dealing with missing data in the AHS; De Roos et al. excluded subjects with missing values and Sorahan retained these subjects in the analysis by creating a not known/missing category for each variable. These are two approaches to dealing with missing data that are both inferior to methods such as multiple imputation or inverse probability weighting. The Sorahan and De Roos analyses produce different results, but it is impossible to say which is closer to the truth (e.g., the result if there were no missing data); this depends on (unknown) relationships between the exposures and disease among those with missing data, and whether or not those relationships differ from those subjects with complete data. As the Sorahan analysis uses simply another, inadequate approach to analyzing missing data, the authors of the current meta-analysis should be clear about this and also not use qualifiers such as 'more complete analysis' (page 61) when comparing Sorahan to De Roos et al. For example, on page 52, the authors point out that the results of De Roos et al. in the AHS were based on 55% of the data with both exposure & covariates info. However, the Sorahan results are also based on the same number of people with meaningful data, but with a different reference category given the inclusion of categorical variables for missing data.

The scientific review based on Bradford Hill guidelines is sparse, incomplete, and comes off as biased. The mention of this review in the abstract is particularly misleading and one-sided. I would not characterize the literature as temporally ambiguous (as is implied in the abstract) – even though subjects were interviewed in case-control studies after diagnosis, people can generally remember whether their pesticide use was before diagnosis or not. The RRs are not strong, as indicated by the authors, but they would not be expected to be strong since they are looking at an ever/never exposed metric....summary RRs of 1.3 or 1.4 are about what you would expect for this general categorization. The authors argue that the results are not consistent, but all of their tests indicate little heterogeneity in the results for NHL or MM (but then the authors argue that these tests are underpowered and so they proceed to interpret non-statistical significance in the individual studies as lack of consistency across the studies – when this is a separate issue). They also argue against evidence of a positive biological gradient, whereas there is some evidence for dose-response from studies of NHL and especially MM; it is true that these data are sparse and not entirely convincing, however, they cannot be interpreted as evidence AGAINST a biological gradient. They argue against specificity because numerous associations have been hypothesized between glyphosate exposure and diverse health outcomes; however, hypotheses do not equal associations, so hypotheses can't inform specificity (in addition, lack of specificity does not detract from causality). The information on time trends for lymphohematopoietic cancer diagnoses is not at all relevant for experimental evidence.

The final sentence of the abstract – "Thus, no valid association, much less a causal relationship, has been established between glyphosate exposure and risk of any LHC." Again, if this was the authors' conclusion based on the literature review, why did they even bother to conduct the meta-analysis?

"The small number of available studies limits the robustness of the estimated meta-RRs, as well as the ability to perform informative

sensitivity analysis and evaluation of heterogeneity and publication bias." This statement argues against conducting these tests at all....yet the authors do conduct them. This statement also suggests that the meta-estimates that include only 2 studies at a time are particularly problematic. The majority of analyses in this paper are summaries of 2 studies. Are these analyses really worthwhile?

Page 59. "an evaluation of the association between glyphosate exposure and risk of LHC based on the Bradford Hill viewpoints shows that a causal relationship has not been established with NHL..." The use of the word 'show' here is presumptuous.

Page 63. It's unlikely (or at best unproven) that urinary biomarker data will be a better method for exposure assessment of glyphosate than questionnaire data. Surely, self-reported use of pesticides needs more detailed assessment and validation. It's also unlikely that either urinary measurement or sales records will be useful for this purpose.

Page 63, bottom. The text states that there were no studies that presented results by leukemia subtype, but what about the studies for hairy cell leukemia and CLL?

Date & Signature

Date of manuscript submission	09 Sep 2015 20:34:21
Date of this review	13 Oct 2015 16:05:57

Journal	IJERPH (ISSN 1660-4601)
	http://www.mdpi.com/journal/ijerph
Manuscript ID	ijerph-100533
Journal	International Journal of Environmental Research and Public Health
Type	Review
Title	Systematic Review and Meta-Analysis of Glyphosate Exposure and Risk of Lymphohematopoietic Cancers
Number of Pages	69
	Download Manuscript
Authors	Ellen T. Chang *, Elizabeth Delzell

Abstract The carcinogenic potential of glyphosate was recently reviewed by health and regulatory agencies. One study considered in these reviews, a meta-analysis of epidemiologic data on pesticides including glyphosate and NHL risk, did not present an in-depth assessment of research quality or a weight-of-evidence evaluation of causality. Therefore, this systematic review and meta-analysis examines more rigorously the relationship between glyphosate and lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM), and leukemia. Meta-relative risks (meta-RRs) were positive and marginally statistically significant for the association between glyphosate use and risk of NHL (meta-RR=1.3, 95% confidence interval (CI)=1.0–1.6, based on six independent studies) and MM (meta-RR=1.4, 95% CI=1.0–1.9; four studies). Associations were statistically null for HL (meta-RR=1.1, 95% CI=0.7–1.6; two studies), leukemia (meta-RR=1.0, 95% CI=0.6–1.5; three studies), and NHL subtypes except B-cell lymphoma (two studies each). These meta-RRs have uncertain validity because bias and confounding cannot be excluded. Methodological weaknesses include the small number of available studies and an overall body of literature that is not strong, consistent, temporally unambiguous, or indicative of a positive biological gradient. Thus, no valid association, much less a causal relationship, has been established between glyphosate exposure and risk of any LHC.

Review Report Form

English Language and Style

(x) English language and style are fine
( ) Minor spell check required
( ) Extensive editing of English language and style required
( ) I don't feel qualified to judge about the English Language and Style

Comments and Suggestions for Authors

International Journal of Environmental Research and Public Health - 2015
Systematic Review and Meta-Analysis of Glyphosate Exposure and Risk of Lymphohematopoietic Cancers Ellen T. Chang and Elizabeth Delzell
This is a detailed and well-written manuscript that is very topical and of great interest to the journals readership and the scientific community. The meta-analysis the authors present uses sound research methodology, shows great attention to detail, and a large investment of effort to evaluate study quality, limitations and how these affect the interpretation of summary risk estimates for glyphosate and lymphohematopoietic cancers. Major comments for the authors to address: - Meta-analyses are not intended to identify, validate, or dispute causal relationships and this needs to be made clear in the introduction and discussion sections. Furthermore, in the abstract (and conclusions), the authors conclude that no valid association, much less a causal relationship, has been established between glyphosate exposure and risk of any LHC. This is not supported by the results of the meta-analyses, and the weight-of-evidence evaluation was not sufficient to make conclusions about causality. These statements should be removed. - The framing of the research question in the introduction is partly based on outdated evaluations of glyphosate carcinogenicity (e.g. 1991 U.S. EPA assessment). The German and IARC evaluations include recent epidemiological evidence and illustrate the controversy, so it would suffice to only reference these. - The objective "a synthesis of the overall weight of epidemiologic evidence for a causal association between glyphosate

and LLHC risk" should be removed from the objectives and not reported in the results. The use of Bradford Hill criteria augments the meta-analysis and provides what is basically a crude checklist for evaluation of human epidemiologic evidence. However, the authors take this approach out of context throughout the document and describe it as a weight-of-evidence approach, which is it not. This should be briefly summarized in the discussion, and does not represent an appropriate methodological objective of the paper. - The qualitative evaluation of error and bias is very lengthy and reads almost like a text book. It should be more succinctly included in the discussion, and be used to interpret the results of this meta-analysis. The authors frame their work as an attempt to establish causality, and possibly refute the recent IARC evaluation of a causal relationship. However, establishing or refuting a causal relationship is not generally something that can be accomplished by a single meta-analysis. - Overall, the manuscript is very lengthy and could be shortened in several ways; o Page 4: put the search terms in a supplementary file o Page 5: put the figure in a supplementary file o Page 7: shorten the description of the statistical approach by deleting the background explanatory text (e.g. difference between fixed- and random-effects models) o Pages 54-64: reduce the amount of text describing the limitations of epidemiological studies and instead, focus on the interpretation of the results from the meta-analysis Minor comments: - The establishment of different tiers of study quality could be strengthened by using a standard tool (e.g. STROBE). Formal guidelines for the assessment of study quality are also provided by the Cochorane collaboration. The subjective determination of study quality can be a source of bias. LHCs are relatively rare compared to other cancers and case-control studies are appropriate for studying very rare outcomes - thus, only considering cohort studies as Tier 1 does not seem appropriate. - There was a preference to include more highly adjusted relative risks compared to less adjusted relative risks. Controlling for multiple confounders does not necessarily provide the most valid risk estimates, especially when those confounders are not strongly associated with disease or exposure outcomes, or if they are variables that may be on the causal pathway. I appreciate the authors' choice to use these adjusted estimates, but this limitation should be acknowledged. - The authors extensively discuss numerous flaws with the included epidemiological studies. Are there any other the studies of glyphosate which are worthwhile? If these limitations were perceived to be so great, then this might discount the need for a meta-analysis in the first place. Given that the authors have carried out this meta-analysis, it is more appropriate to shift the focus towards interpreting their findings, rather than a discussion of the findings of the individual studies. - The authors should clarify what this new analysis adds to the epidemiologic literature? Especially since the "weight of evidence" is a part of the discussion, and is not in itself a methodological improvement. Perhaps the authors should comment how the studies included in their analysis differ from other recently conducted analysis on LHC and glyphosate - There are some parts of the text that are wordy and convoluted, e.g. page 55, second paragraph ("The authors also excluded subjects who had lived or worked on a farm before age 18 years...")

Date & Signature

Date of manuscript submission	09 Sep 2015 20:34:21
Date of this review	05 Oct 2015 23:09:59