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TITLE

An evaluation of glyphosate use and the risk of non-Hodgkin lymphoma major histological sub-types in the North American Pooled Project (NAPP)

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WHAT THIS PAPER ADDS

- Exposure to glyphosate, a broad-spectrum and frequently used herbicide, may be associated with non-Hodgkin lymphoma (NHL). Little is known about how risks may differ by glyphosate exposure levels and NHL sub-types.
- To address this research gap, this analysis integrated detailed, self-reported glyphosate use information with assessments of NHL risk overall and by major histological sub-type using pooled data from 1690 NHL cases and 5131 controls from the U.S. Midwest and Canada.
- Subjects who ever used glyphosate had elevated odds ratios for NHL overall and for all subtypes except follicular lymphoma. Significant or nearly significant risks of NHL overall were observed for >2 days per year (OR=2.42, 95% CI: 1.48, 3.96) and >7 lifetime days (OR=1.55, 95% CI: 0.99, 2.44) of glyphosate use, with some differences in risk by sub-type.
- Glyphosate use may be associated with elevated NHL risk. Although the pattern of risks was not clear across exposure categories, these findings from a large dataset offer more precision than results from previous studies.

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ABSTRACT (249)

Objectives: Glyphosate is the most frequently used herbicide worldwide. Some epidemiological studies have found positive associations between glyphosate exposure and non-Hodgkin lymphoma (NHL). This study aimed to evaluate NHL risk overall and by major histological sub-type using detailed glyphosate use metrics.

Methods: The NAPP, composed of pooled case-control studies from the U.S. and Canada, includes NHL cases (N=1690) and controls (N=5131) who provided information on pesticide use. Cases (follicular lymphoma [FL], diffuse large B-cell lymphoma [DLBCL], small lymphocytic lymphoma [SLL], other) from cancer registries and hospitals were frequency-matched to population-based controls. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) by ever/never, duration, frequency, and lifetime days of glyphosate use. Models were adjusted for age, sex, location, proxy respondent, family history of lymphohematopoietic cancer, and personal protective equipment.

Results: Cases who ever used glyphosate (N=133) had a significantly elevated risk of NHL overall (OR=1.43, 95% CI: 1.11, 1.83). Subjects who used glyphosate for >3.5 years had increased SLL risk (OR=1.98, 95% CI: 0.89, 4.39) and those who handled glyphosate for >2 days/year had significantly elevated odds of NHL overall (OR=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR=2.83, 95% CI: 1.48, 5.41). There were suggestive increases (p-trend ≤0.02) in risk of NHL overall, FL, and SLL with more days/year of glyphosate use.

Conclusions: Glyphosate use may be associated with increased NHL risk. Although risk differences by histological sub-type were not consistent across glyphosate use metrics, the NAPP's large sample size yielded more precise results than possible in previous studies.

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INTRODUCTION

Glyphosate [N-(phosphonomethyl)glycine] is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. First developed commercially for agricultural use in the early 1970s, glyphosate quickly became a popular chemical; as of 2012, it was used in more than 750 products with an annual global production volume exceeding 600,000 tonnes (1). In the U.S., the highest levels of agricultural use occur in the mid-west on crops such as corn, soybeans, and wheat (2). These crops are also examples of the many different types of plants that have been genetically engineered to be resistant to glyphosate.

Commented [AB1]: Check to make sure all these crops have genetically modified seed on the market. I do not think that is the case for wheat yet. I think rice was to be available this year.

Glyphosate has been examined as a potential risk factor for lymphatic and hematopoietic cancers including non-Hodgkin lymphoma (NHL). In Canada, NHL ranks as the fifth most incident cancer in males following neoplasms of the prostate, colorectum, lung, and bladder (3). In the American mid-west NHL accounts for an unusually large number of cancers in agricultural areas where populations tend to have lower cancer rates overall (4). The causes of NHL are largely unknown (Hartge P, Wang SS, Bracci PM, Devesa SS, Holly EA. Non-Hodgkin Lymphoma. In Cancer epidemiology and Prevention, 3rd Edition. Shottenfeld D, Fraumeni JF, Jr. (Eds.). Oxford University Press, NY, Ny, 2006), pp. 898-918.). ~~Male~~ NHL has been associated with farming (Blair et al., 1992)~~gender, advanced age, and immune suppression are the best known risk factors. Agricultural exposures are hypothesized to be involved in the development of NHL~~ and this has prompted studies focused on pesticides.

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In the 1980s and 1990s Four~~four~~ population-based case-control studies were conducted in the U.S. mid-west and six Canadian provinces to examine putative associations between agricultural exposures and pesticides and the risk of NHL. Individual study results showed positive associations between self-reported glyphosate use and NHL risk, although there was variation in the magnitude and statistical significance of risks between studies. In an analysis of the Canadian study the odds ratio [OR] for NHL was 1.26 (95% confidence interval [CI]: 0.87, 1.80) for the use of glyphosate with adjustment for age and province (N=51 exposed cases) (5). The OR was slightly higher from~~A similar risk estimate was found in a separate analysis of men who reportedly ever handled glyphosate in Iowa and Minnesota (6) and higher odds were calculated in~~ a pooled analysis that included 36 exposed male cases from Iowa, Minnesota, Kansas, and Nebraska (logistic regression OR=2.1, 95% CI: 1.1, 4.0 adjusted for age, study site, and other pesticides) (7).

Other studies involving glyphosate exposure and NHL risk have been conducted and many were included in a systematic literature review and meta-analysis of epidemiological studies of pesticide exposure and NHL risk (8). This meta-analysis found~~demonstrated~~ that glyphosate exposure was significantly associated with ~~elevated risks of~~ NHL ~~overall~~ (meta risk ratio [mRR]=1.5, 95% CI: 1.1-2.0, 6 papers). The OR for ~~and~~ B cell lymphoma, ~~(mRR=2.0, 95% CI: 1.1-3.6, 2 papers),~~ a commonly diagnosed NHL sub-type in the regions from which included studies were drawn, was (mRR=2.0, 95% CI: 1.1-3.6, 2 papers). ~~However, meta-analyses were based on a small number of included papers and each study contained low numbers of exposed subjects. Only one included study (9) reported risks by NHL sub-type and only three (5, 9, 10) reported risks by glyphosate exposure level.~~

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A comprehensive evaluation of glyphosate carcinogenicity was recently undertaken by the International Agency for Research on Cancer (IARC) (11). This review of mechanistic, animal, and epidemiological evidence classifiedled to the evaluation of glyphosate as a "probable" (group 2A) carcinogen for NHL based on limited evidence in humans and sufficient evidence in experimental animals. The assessment of limited evidence from epidemiological studies was based on case-control studiesprimarily focused on evidence from case-control studies of occupational glyphosate exposure in the U.S., Canada, and Sweden that reported increased risks of NHL that persisted after adjustment for other pesticides. No association between NHL and use of glyphosate was seend in the Agricultural Health Study (AHS), a large prospective study of farmers and commercial pesticide applicators in the U.S.(11). In bioassays, gGlyphosate was was associated with renal tubule carcinoma, pancreatic islet-cell adenoma, and skin tumors (11). able to cause different cancers in mice, postulated to occur through initiation and promotion. Mechanistic and other data supported the "probable" carcinogen conclusion by providing strong evidence for genotoxicity and oxidative stress, both of which are mechanisms of action that can take place in humans (11).

There are several research gaps that need to be addressed in order to better understand the role and impact of glyphosate exposure on the development ofcancer risk, specifically NHL. Individual studies often have limited power for glyphosate exposure, lack evaluation of NHL by sub-type, and do not adjust risk estimates for other pesticides and other exposures (8, 11). MAdditionally, most studies do not have quantitative exposure data needed to perform more sensitive epidemiological analyses and few have addressed potential effect modifiers to identify if glyphosate exposure has a different impact on NHL risk under certain circumstances. Schinasi and Leon (8) have suggested pooling studies as an attempt to overcome some of these limitations. ; AGRICOH, a consortium of agricultural cohorts, is a global effort of this kind (12). Other existing studies can be similarly leveraged for enhancing our knowledge and understanding about glyphosate exposure and NHL risk.

The North American Pooled Project (NAPP) is a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. The primary objective of this effortstudy was to provide larger numbers for more detailed analyses of possible relationships between NHL and pesticide use. In this paper we evaluate the association between glyphosate use and the risk of NHL among men and women in the NAPP. in the North American Pooled Project (NAPP), a pooled resource of population-based case-control studies previously conducted in the U.S. and Canada. NHL risk was assessed overall and by histological sub-type using detailed self-reported glyphosate use information and adjustment for other pesticides and possible risk factors. The secondary aim of this study was to examine the effects of personal protective equipment (PPE) on the association between glyphosate use and NHL risk overall.

METHODS

Study population

The NAPP is a large and newly established resource of pooling ofed data from four previously conducted case-control studies of men and women who were diagnosed with soft tissue sarcoma and lymphatic

and hematopoietic cancers, including NHL, in the U.S. and Canada. NHL cases were recruited from cancer registries and hospitals during the 1980s in four states (Iowa, Minnesota, Kansas, and Nebraska) and between 1991 and 1994 in six provinces (Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia). Cases were 19 years of age or older in all jurisdictions (I think the 19 age cut is correct, just check each study to make sure). Controls were selected from the general population in each state or province. Selection procedures varied by study but included ~~by~~ random digit dialing, voters' lists, health insurance records, Medicare listings for those older than 65 years, and from state mortality files for deceased cases. Controls were matched to NHL cases in each state/province on the basis of age (±2 or 5 years). In some states, cases and controls were matched on the additional variables of sex (Nebraska), race (Nebraska), and vital status and year of death for deceased cases (Iowa, Minnesota, Nebraska, Kansas). All states and provinces included men; women were only included in Nebraska. Deceased cases and controls were eligible for inclusion in the U.S. ~~case-control~~ studies. The Canadian study only considered alive cases and controls. The present analysis used data from both men and women and from alive and deceased NHL cases (N=1690) and controls (N=5131).

Data collection

Participants, or surrogates, provided detailed information about demographic characteristics, pesticide use, agricultural exposures, and exposure to other known or suspected NHL risk factors including lifestyle, medical and occupational history. Interviewer-administered questionnaires were conducted by telephone (Kansas and Nebraska) or in person (Iowa and Minnesota) with cases and controls or their surrogates if subjects were deceased or too ill to respond themselves. In Canada, all cases and controls were mailed a questionnaire to complete themselves (or by their surrogates). Participants who indicated that they had used pesticides were subsequently interviewed over the telephone for details about their pesticide exposure. The Canadian questionnaire was modified from the telephone interview questionnaires that were used in Kansas and Nebraska. The questionnaires from all case-control studies were very similar since they shared a common research objective, involved overlapping groups of principal investigators, and were developed during the same time period. This made the data highly amenable to pooling ~~at present~~. The complete methodologies of each case-control study have been described by Cantor et al., 1992 (Iowa and Minnesota) (6), Hoar et al., 1986 (Kansas) (13), Zahm et al., 1990 (Nebraska) (14), and McDuffie et al., 2001 (Canada) (5).

The NAPP contains extensive information about pesticide use and agricultural exposures reported by cases and controls. In general, pesticide classifications are available from ~~data were collected beginning with the~~ broadest categories (e.g. occupations with potential pesticide exposure), to ~~followed by~~ major chemical classes (e.g. herbicides), to chemical groups (e.g. phenoxy herbicides), and finally individual compounds (e.g. 2,4-D). For each individual compound reported, information was collected for dichotomous use (ever/never), duration of use (number of years), and frequency of personal handling (number of days/year). Duration data were not collected in Kansas and frequency information was not collected in Iowa, Minnesota, and Kansas ~~and Kansas~~. In Kansas participants were asked to open-endedly recall the details of their pesticide use whereas in all other jurisdictions subjects were prompted by a list of chemicals and their trade names. Participants were also asked to report if they had used any

type of PPE in general (Nebraska and Canada) and with herbicides (Iowa, Minnesota, and Kansas) and specific individual pesticides (Iowa and Minnesota).

Assessment of glyphosate use

Self-reported glyphosate use was examined using several different metrics: dichotomous, duration, frequency, and lifetime days (derived by multiplying number of years used with number of days/year handled). Ordinal categories were created for duration, frequency, and lifetime days analyses based on the median of glyphosate used/handled in controls. Since information about duration of glyphosate use was not collected in Kansas, cases and controls from Kansas were omitted from duration analyses. Similarly, cases and controls from Iowa, Minnesota, and Kansas were excluded from frequency and lifetime days analyses owing to the lack of frequency data collected in these states. Participants who had missing or unknown glyphosate use information, but who were from jurisdictions where glyphosate use information was collected, were coded as "never used" in dichotomous analyses. ~~;~~ ~~F~~For duration and frequency analyses, missing values were assigned based on the median duration or frequency by state/province, age, and NHL sub-type (simple imputation, rounded to the nearest whole number). Subjects who reported that they used glyphosate were coded as "ever used" or used/handled for the number of years and days/year that they had reported. Continuous analyses were also conducted in order to determine possible trends and changes in risk for every 5 years, 5 days/year, and 10 lifetime days of glyphosate use.

NHL classification

NHL cases in these s tudies were diagnosed ~~at different time periods~~ during the 1980s and 1990s. NHL cases were classified in Iowa, Minnesota, and Nebraska according to the Working Formulation (15, 16); in Kansas and Quebec by the International Classification of Diseases for Oncology First Edition (ICD-O-1) (1976) (17); and in Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia by ICD-O-2 (1990) (18). The original histology codes used in each study were revisited to classify NHL cases using a single or similar scheme for the NAPP. We used ICD-O-1 to code NHL overall and sub-types in the NAPP since histological sub-types were classified in all jurisdictions according to ICD-O-1. These sub-types were follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), small lymphocytic lymphoma (SLL), and other. The "other" sub-type included all cases whose histologies were unknown or not FL, DLBCL, or SLL. Pathology reviews were conducted on 84% of Canadian cases (5), 87% of Kansas cases (13), and for all interviewed cases in Iowa and Minnesota (6) and Nebraska (14) in order to validate NHL diagnoses.

Power and sample size

A power and sample size analysis was conducted using the U.S. National Cancer Institute's (NCI) Power Version 3.0 program (19, 20) by inputting the following parameters: number of controls = 5131; number of cases = 1690; control:case ratio = 3; type I error (two-sided) = 0.05; type II error = 0.2; probability of NHL at baseline = 0.04 (21).

Of all 5131 controls available in the NAPP, 244 (4.76%) reported that they ever used glyphosate. A 5% prevalence of pesticide exposure in controls corresponds to ~~a~~perfect power of ~~(~~1.00~~)~~ to detect ORs of

2.00 or higher and a ~~, but lower~~ power of (0.46) to detect an OR of 1.25. Given that approximately 5% of controls reported ever being exposed to glyphosate, at a power level of 0.80, a total of 1103 NHL cases would be required to detect an OR of 1.50 (Appendix 1). The numbers of NHL cases and controls in the NAPP appear to be suitable to ~~for~~ detecting low to moderate relative risks associated with glyphosate exposure in this population.

Statistical analyses

Descriptive statistics were used to characterize the study population and identify potentially confounding variables. Based on previously published literature, a priori possible confounders included age, sex, state/province, use of a proxy respondent (5, 6, 22), lymphatic or hematopoietic cancer in a first-degree relative (23), and diagnosis with select medical conditions related to immune suppression (any allergies, food allergies, drug allergies, asthma, hay fever, mononucleosis, arthritis, or tuberculosis; ever received chemotherapy or radiation) (24-26). History of living or working on a farm or ranch was also evaluated as a potential confounder.

It was possible that the use of other pesticides in the NAPP may confound the relationship between glyphosate use and NHL risk. A two-pronged approach was used to identify potentially confounding by other pesticides. First, a correlation matrix of pooled data was produced to determine the presence and extent of correlation between glyphosate and each individual herbicide, insecticide, and fungicide reportedly used by NAPP subjects. Second, previously published articles based on the individual case-control studies comprising the NAPP were searched to identify any positive or significant relationships between individual pesticides and NHL risk, as would be required for confounding to occur. Pesticides that were most strongly correlated with glyphosate (defined in this study as Spearman coefficients ≥0.35 and Cohen's Kappa value ≥0.30) and that were significantly or strongly associated with NHL in previous studies were evaluated as confounders. These were the herbicides 2,4-D (2,4-dichlorophenoxyacetic acid) (5, 6) and dicamba (5, 7), as well as the insecticide malathion (5, 7).

The use of PPE with glyphosate could theoretically modify NHL risk by reducing subjects' exposure to glyphosate. Although such information was sought in some studies, data were on a sizable ~~There was a large~~ proportion of the study subjects ~~missing data for the more specific variables of PPE used for herbicides and glyphosate~~ and. ~~Therefore,~~ effect modification analyses could only be conducted using ~~involving any lifetime PPE use were conducted using data reported by~~ cases and controls from ~~in~~ Nebraska and Canada. Any lifetime PPE usage was also included as a confounding variable in models where it was not evaluated as a possible effect modifier.

Unconditional multiple logistic regression was performed using the LOGISTIC procedure of ~~on~~ the SAS 9.2 statistical software package (SAS Institute, Cary, North Carolina) to calculate pooled ORs and 95% CIs for associations between glyphosate exposure (dichotomous, duration, frequency, lifetime days, and as a continuous variable) and the risk of NHL overall and by histological sub-type (FL, DLBCL, SLL, and other). Primary logistic regression models (OR^a) contained the following variables as confounders: age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, and use of any PPE. Secondary logistic regression models (OR^b) contained the covariates in the primary

model plus reported use of the pesticides 2,4-D, dicamba, and malathion. Medical conditions and history of living or working on a farm or ranch were found not to~~did not appear to play a role in~~ confound~~ing~~ the relationship between glyphosate use and NHL risk and were not included in the models. Use-response trends for duration, frequency, and lifetime days analyses were deemed to be statistically significant if the two-sided p-value for the ordinal glyphosate use category was ≤0.05. The reference group for all analyses was subjects who never used glyphosate. There was a small proportion of subjects (N=175, 2.57% of all participants) with missing age values; these were imputed based on state/province- and case/control-specific means rounded to the nearest whole number.

Sensitivity tests were conducted by excluding proxy respondents from the main analyses. Proxy respondents were excluded from the analyses of PPE as a potential effect modifier in order to minimize the possibility of bias. For the effect modification analyses, glyphosate use was classified dichotomously and by duration, frequency, and lifetime days and overall NHL risks were calculated using logistic regression models adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, and use of 2,4-D, dicamba, and malathion.

Ethics approval

Approval to conduct this analysis was obtained from the University of Toronto Health Sciences Research Ethics Board (#25166) and an ethics exemption was obtained from the U.S. NCI Office of Human Subjects Research (#11351). Individual studies had obtained human subjects approval prior to collection of the data and aAll participants provided informed consent before taking part in the studies included in the NAPP analyses.

RESULTS

Characteristics of NHL cases and controls

A total of 1690 NHL cases and 5131 controls were available in the NAPP for analysis. All participants were included in analyses that encompassed proxy respondents. For assessments involving the duration of glyphosate use, 1520 cases and 4183 controls were available; in frequency and lifetime days analyses, 898 cases and 2938 controls were included. The numbers of cases and controls available for the sensitivity analyses excluding proxy respondents were smaller~~lower~~ (Figure 1).

The most frequently diagnosed histological sub-type was DLBCL (38.28%), followed by FL (27.69%), other (23.91%), and SLL (10.12%) (Table 1). Nebraska yielded the highest proportion of cases (22.78%) and controls (27.91%) compared to other states and provinces. The average ages of cases and controls were 62.72 and 61.66 years, respectively. The majority of subjects were male. A similar proportion of proxy respondents were used by cases and controls. Cases were more than twice as likely to report that a first-degree relative was diagnosed with lymphatic or hematopoietic cancer compared to controls (OR=2.13, 95% CI: 1.69, 2.67). Medical history variables were evaluated as potential confounders but they did not have an appreciable impact on adjusted ORs in the main analyses (OR[a] and OR[b]) and were thus excluded from logistic regression models.

Missing glyphosate use data

There were 7 cases with missing values for the number of years of glyphosate used and 13 cases with missing values for the number of days/year of glyphosate handled in the jurisdictions where duration and frequency of glyphosate use data were collected. The median values for the number of years of glyphosate use in cases all subjects with missing values ranged from 0-2 based on jurisdiction, NHL sub-type, and age. The median value for days/year for subjects with missing information was 0 (zero).

Glyphosate use and NHL risks overall and by major histological sub-type

Overall, 113/1690 cases (6.69%) and 244/5131 (4.76%) controls reported that they had used glyphosate at any point in their lifetime. There was a significant association between glyphosate use and the risk of NHL overall (OR^a=1.43, 95% CI: 1.11, 1.83) (Table 2). Risks were elevated for most NHL sub-types but the magnitude of risk differed by sub-type. The greatest risk was observed in SLL cases (OR^a=1.77, 95% CI: 0.98, 3.22) and the lowest risk was found for FL (OR^a=1.00, 95% CI: 0.65, 1.54). Similar and significant excesses were observed for DLBCL (OR^a=1.60, 95% CI: 1.12, 2.29) and other (OR^a=1.66, 95% CI: 1.04, 2.63) sub-types. Associations were attenuated and no longer statistically significant when the model represented by OR^a was further adjusted for ever use of 2,4-D, dicamba, and malathion (OR^b). The odds of SLL did not change even after adjusting risk estimates for these three pesticides.

When glyphosate use was examined by duration (Table 2), there was a general inverse trend in risks except for cases of SLL, where the odds increased with longer duration of glyphosate use (OR^a=1.98, 95% CI: 0.89, 4.39 for >3.5 years versus OR^a=1.49, 95% CI: 0.63, 3.58 for >0 and ≤3.5 years) and this trend was of borderline statistical significance (p-trend for OR^a=0.08). Additional adjustment for the chemicals 2,4-D, dicamba, and malathion generally resulted in attenuated risk estimates (OR^b) compared to models unadjusted for these pesticides (OR^a) except for SLL, for which the addition of these agents in logistic regression models had no substantial effect on risk (e.g. for >3.5 years of glyphosate use, OR^b=1.94, 95% CI: 0.79, 4.80).

In contrast to duration of glyphosate use, a more consistent pattern of NHL risk emerged in association with frequency of glyphosate personally handled (Table 2). Subjects who handled glyphosate for >2 days/year had NHL risks that were approximately two times the odds observed in participants who handled glyphosate for >0 and ≤2 days/year. This finding was consistent for NHL overall and all sub-types. Elevated risks in the highest category (>2 days/year) were significant for NHL overall (OR^a=2.42, 95% CI: 1.48, 3.96) and DLBCL (OR^a=2.83, 95% CI: 1.48, 5.41) compared to subjects who did not handle glyphosate at all. Significant trends in risk were also found for NHL overall (p-trend for OR^a=0.02) and DLBCL (p-trend for OR^a=0.04). For NHL overall and DLBCL, ORs associated with handling glyphosate for >2 days/year were attenuated but remained statistically significant even after adjusting for the use of 2,4-D, dicamba, and malathion. The pattern of increased risks with more frequent glyphosate handling was still apparent for NHL overall and all sub-types although trends were no longer statistically significant upon adjusting for these three pesticides.

The analysis of lifetime days, derived from the product of number of years used and days/year handled, generally showed risk increases for NHL overall and most sub-types (except "other") in association with

a greater number of lifetime days of glyphosate use (Table 2). These trends were significant for NHL overall (p-trend for OR[a]=0.02), FL (p-trend for OR[a]=0.02), and SLL (p-trend for OR[a]=0.01). There were elevated risks of NHL among participants who had used glyphosate for >7 lifetime days; this was most pronounced for SLL (OR[a]=2.13, 95% CI: 0.76, 5.96). Adjusting for 2,4-D, dicamba, and malathion attenuated risks compared to odds that were unadjusted for these chemicals; however, the general pattern of increased risks remained intact and in some cases (i.e. SLL), was still statistically significant (p-trend for OR[b]=0.03).

Sensitivity analysis

Proxy respondents were used for deceased cases and controls and for alive cases who were too ill to respond to the case-control study questionnaires themselves. The use of proxy respondents might have introduced misclassification of glyphosate use. To account for this possibility, glyphosate use data provided by proxy respondents were excluded from the main analysis presented in Table 2. This generally resulted in reduced ORs compared to risks that included data provided by both self- and proxy respondents, with little effect on the width of confidence intervals and the same general patterns of risks for dichotomous, duration, frequency, and lifetime days analyses (Table 3). For instance, there were significant trends for lifetime days of glyphosate use and the risks of NHL overall (p-trend for OR[a]=0.04), FL (p-trend for OR[a]=0.03), and SLL (p-trend for OR[a]=0.01) (Table 3) that paralleled the trends found in the analysis of data provided by both self- and proxy respondents (Table 2).

However, there were some exceptions to this overall observation. Odds ratios for SLL mostly strengthened with the exclusion of proxy respondents in models both unadjusted for 2,4-D, dicamba, and malathion and models adjusted for these chemicals. For instance, among subjects who ever used glyphosate the risk of SLL excluding data from proxy respondents was 1.89 (OR[a], 95% CI: 1.03, 3.49) which was slightly greater than the risk of SLL based on data provided by self- and proxy respondents (OR[a]=1.77, 95% CI: 0.98, 3.22). Trends of increasing risk of SLL in association with longer duration, greater frequency and lifetime days of glyphosate use were also marginally stronger when data from proxy respondents were excluded.

Effect of PPE

Potential effect modification by PPE usage was evaluated based on data pooled from Canadian and Nebraskan participants. The association between ever glyphosate use and NHL risk overall was generally higher among subjects who reportedly used any type of PPE in their lifetime (OR=0.83, 95% CI: 0.40, 1.73) compared to subjects who never used any type of PPE (OR=0.65, 95% CI: 0.31, 1.35) (Table 4). This pattern of elevated NHL risks in subjects who ever used PPE compared to subjects who never used PPE persisted when glyphosate use was also evaluated by duration, frequency, and lifetime days. Similar to the results in Tables 2 and 3, there were inverse associations between the duration of glyphosate use and NHL risk and positive (increasing) associations between frequency and lifetime days of glyphosate use and NHL risk, regardless of PPE use status. There were many subjects with unknown or missing PPE use information and they were separately modeled in order to reduce the possibility of analyzing

misclassified PPE use data. Risks were high and unstable in this latter group due to the small number of subjects in each glyphosate usage category.

DISCUSSION

The objective of this study was to evaluate potential associations between glyphosate use and NHL risk in the NAPP, a large pooled dataset with detailed information about glyphosate use reported by 1690 NHL cases and 5131 controls. Glyphosate use was associated with elevated NHL risk, a finding that was consistent with previous analyses. Odds somewhat differed by histological sub-type, although there wasn't a consistent pattern across glyphosate use metrics. The novelty of this analysis and increased precision of risk estimates compared to smaller individual studies were major strengths. Yet, the limitations of this study illustrate the need for more research that can better characterize the relationship between glyphosate exposure and the development of NHL.

This report confirms previous analyses indicating increased risks of NHL in association with glyphosate exposure. The odds of NHL for glyphosate use was 1.43 (OR[a], 95% CI: 1.11, 1.83), a value that was situated approximately in between the risks observed in earlier analyses of the Canadian study (OR=1.26, 95% CI: 0.87, 1.80, adjusted for age and province, N=51 exposed cases) (5) and the three pooled U.S. studies (logistic regression OR=2.1, 95% CI: 1.1, 4.0, adjusted for age, study site, and other pesticides, N=36 exposed cases) (7). Further adjusting OR[a] for the pesticides 2,4-D, dicamba, and malathion resulted in an attenuated risk of NHL overall in the NAPP (OR[b]=1.13, 95% CI: 0.84, 1.51). De Roos et al. (2003) (7) used a more conservative approach, a hierarchical regression model, for assessing NHL risk in the three U.S. pooled case-control studies and found that this reduced the odds of NHL overall (OR=1.6, 95% CI: 0.9, 2.8, adjusted for age, study site, and other pesticides). A statistically significant excess of NHL was found in association with more than 2 days per year of use (OR=2.12, 95% CI: 1.20, 3.73) (5) in the Canadian study, a finding that was in agreement with our analogous pooled risk estimate for NHL (OR[a]=2.42, 95% CI: 1.48, 3.96).

Our results are also aligned with findings from epidemiological studies of other populations that found an elevated risk of NHL for glyphosate exposure and with a greater number of days/year of glyphosate use (9), as well as a meta-analysis of glyphosate use and NHL risk (8). From an epidemiological perspective, our results were supportive of the IARC evaluation of glyphosate as a probable (group 2A) carcinogen for NHL (11).

The large sample size of the NAPP was conducive to analyzing NHL risks with different metrics of glyphosate use. Evaluations of dichotomous glyphosate use showed nearly universal increases in risks of NHL overall and by sub-type, but results were more varied upon further examination by duration, frequency, and lifetime days. The odds of NHL, overall and by sub-type, were higher among subjects who reportedly used glyphosate more often in a year or who had greater cumulative use in their lifetime compared to unexposed subjects. Subjects who used glyphosate reported mostly initiating its use in the year 1980. Glyphosate was used by cases and controls for an average of 5 years and handled for an average of 5 days/year. The short duration of use made it challenging to calculate risks associated with longer-term usage, although the mean frequency of handling was typical of how often farmers

reportedly apply glyphosate to agricultural crops (27). For the days/year and lifetime days analyses some trends and risks were statistically significant while others were not, likely due to the lack of sufficient numbers of exposed cases for some sub-types.

There were some differences in risks by sub-type but these were not consistent between the different glyphosate use metrics and were unlikely to be statistically significant. For example, the significant trends observed for lifetime days of glyphosate use and the risks of NHL overall, FL, and SLL were not present for the frequency analysis, where significant trends were only found for NHL overall and DLBCL. In the duration analysis an upward trend was observed for SLL but not for any of the other sub-types or for NHL overall. Despite these uneven results the risks of FL were consistently lower than other sub-types in association with any of the glyphosate use metrics. There was a relatively large number of FL cases in this analysis compared to the numbers available for other sub-types, lessening the likelihood that findings for FL were primarily due to chance. FL is a type of B-cell lymphoma that is the second most common type of NHL, accounting for 22% of all NHLs (28). The observation of lowered FL risks for glyphosate use in this study was a lead for further evaluation. Additionally, the classification of NHL has changed since the case-control studies in the NAPP were conducted. Multiple myeloma is now considered a sub-type of NHL but was not evaluated in this analysis.

A fairly consistent decrease in NHL risk was found when ORs were further adjusted for the pesticides 2,4-D, dicamba, and malathion. This observation suggested that elevated risks of NHL may be attributed, in part, to pesticides other than glyphosate. Formulations of glyphosate reported by NAPP subjects may have contained other active ingredients. In addition or alternatively, glyphosate may have been used in combination with other pesticide active ingredients at the time of application or in the same growing season or year. It is relatively unknown how combinations of pesticides might interact, and we were not able to evaluate this in our analysis. There is a need to further investigate other individual compounds with respect to NHL risk, such as the herbicide 2,4-D, which IARC recently assessed as possibly carcinogenic to humans based on inadequate evidence in humans and limited evidence in animals for NHL (29).

Glyphosate and covariate data provided by self-respondents generally resulted in attenuated risks compared to odds derived from information provided by both self- and proxy respondents. The proportion of proxy respondents used for cases and controls was similar (about one third). Excluding proxies appreciably reduced the numbers of subjects in the sensitivity analysis which might have partly explained differences in risks. There was also the possibility of exposure misclassification by proxy respondents due to inaccurate recall of glyphosate use, which was likely non-differential (27, 30). Non-differential pesticide exposure misclassification was also an issue amongst self-respondents (31). There was less agreement between self-respondents and surrogates for detailed glyphosate use metrics (years and days/year) compared to the dichotomous variable (32). Nevertheless, significant trends of increasing risks in association with greater lifetime days of glyphosate use persisted for NHL overall, FL, and SLL, even when the analysis was limited to self-respondents.

The evaluation of PPE as an effect modifier of the relationship between glyphosate use and overall NHL risk raised some interesting observations. We expected that the use of any PPE such as masks, gloves,

clothing and/or other equipment may confer a protective effect on the development of NHL from glyphosate use by reducing the probability and degree of dermal, respiratory, and oral contact with glyphosate. However, in this study PPE was found to have no effect on the association between glyphosate use and NHL risk overall. This analysis was limited because PPE usage was not specific to glyphosate use or the type or timing of PPE worn. It was also based on pooled data from Canada and Nebraska only and there was a large proportion of missing data. This hypothesis warrants further investigation in larger studies with more information about PPE used with glyphosate in particular.

The exact causes of lymphatic and hematopoietic cancers are not yet known. A suppressed immune system is the most well established risk factor for NHL. It has been hypothesized that pesticides may play a role in modifying immune function (24-26), but there is little evidence to support this hypothesis for glyphosate specifically (11, 25). An alternative or additional explanation is that pesticides may influence the risk of lymphatic and hematopoietic cancers through pathways involving oxidative stress and receptor-mediated mechanisms. The pathway that glyphosate affects in plants is not present in mammals, but there is strong evidence from mechanistic studies that glyphosate causes genotoxicity and the production of reactive oxygen species (11).

The limitations of this study were primarily related to statistical power for some analyses and the possibility of biases and unmeasured confounding. We endeavoured to use data from all subjects for this analysis as reflected by the inclusion of both men and women and alive and deceased subjects. In Canada alone, 50 NHL cases and 133 controls reported ever using glyphosate; pooling resulted in an additional 63 NHL cases and 111 controls who ever used glyphosate in Iowa, Minnesota, Kansas, and Nebraska. Nevertheless, there were small numbers for some categories of duration, frequency, and lifetime days by NHL sub-type due to the absence of duration data collected in Kansas and frequency and lifetime days information from Iowa, Minnesota, and Kansas. Risk estimates based on small numbers may be unstable and could represent chance findings.

To evaluate possible recall bias of self-reported pesticide use, in the study in Kansas, pesticide suppliers were asked to provide information on crops and pesticide purchases for a sample of 130 subjects with farming experience (13, 27). In the Iowa and Nebraska studies, case recall bias was assessed by comparing information on pesticides used that was volunteered versus information that required probing by the interviewer (14, 27, 33). In the Iowa and Minnesota study, interviews were conducted with both farmers and their wives for a sample of subjects (32). There was a moderate level of correspondence between pesticide use information reported by farmers and their pesticide suppliers in Kansas (13, 27). In Iowa and Nebraska, the number of insecticides and herbicides voluntarily identified was similar and suggested the absence of case-response bias, but probing increased the number of positive responses for individual agents (14, 27, 33). In Iowa and Minnesota, surrogate responders were generally a poorer source of information compared to farmers as they had reported a smaller number of pesticides ever used and a greater proportion of "I don't know" answers (32). No similar analysis of recall bias has been conducted in the Canadian case-control study, but the similarity of study designs between the U.S. and Canada make it likely that recall bias is not a major concern in the Canadian study and NAPP as a whole.

Adjusting for several pesticides (2,4-D, dicamba, and malathion) was a useful way to attempt to disentangle the effect of glyphosate from other pesticides on NHL risk. These agents have been shown to be independently associated with NHL in individual case-control studies (5-7). However, they are somewhat correlated with glyphosate exposure in the NAPP and thus their inclusion as confounders may have introduced some degree of collinearity. Unmeasured confounding by other pesticides, agricultural exposures, or unknown factors cannot be ruled out.

While these results are not independent from previous studies, the evaluations by histological sub-type and for detailed glyphosate use metrics are a new and important contribution to the epidemiological literature. NHL is a constellation of heterogeneous cancers that each has its own causes, risk factors, and etiologies. Pesticides, including individual agents such as glyphosate, may exert different effects on these sub-types, and the large size of the NAPP made it possible to parse this out.

The large sample size also resulted in more precise results than possible in previous smaller studies that only had sufficient power to assess risks for dichotomous glyphosate exposure. We were able to model different glyphosate use categories and identify potential trends in NHL risk by sub-type with increasing duration, frequency, and lifetime days of glyphosate use. This made it possible to characterize possible dose-response relationships between glyphosate exposure and lymphoma risk. The effect modification analysis by PPE further allowed an examination of factors that might modify glyphosate exposure (and risk). Both agricultural and non-agricultural uses of glyphosate were reported by cases and controls in this population-based, pooled case-control study, making this evaluation externally valid.

The results of this analysis may be considered in future scientific and regulatory reviews of glyphosate in North America and globally. Stakeholders may also use these results as part of future approaches that communicate the health risks of pesticides using information directly ascertained from the North American population. This will help to inform efforts aimed at mitigating occupational and environmental exposure to pesticides. It will also provide high-quality risk estimates that can be used in future estimations of the burden of cancer from pesticide exposure.

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COMPETING INTERESTS

The authors declare no competing interests.

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AUTHORS' CONTRIBUTION

MP designed and conducted this analysis and wrote this manuscript. SAH, JJS, and LBF collectively form the NAPP Executive Committee and approved the proposal for this analysis and provided scientific input during the analytic and manuscript preparation phases. AB, SHZ, DDW, and KPC led the original case-control studies in the U.S. JJS, JAM, and JAD were among the principal investigators of the CCSPH in Canada. All co-authors reviewed and approved this manuscript for submission.

DATA SHARING

Unpublished NAPP data is available upon formal request to the NAPP Executive Committee (SAH, JJS, LBF).

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May 24, 2017

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

[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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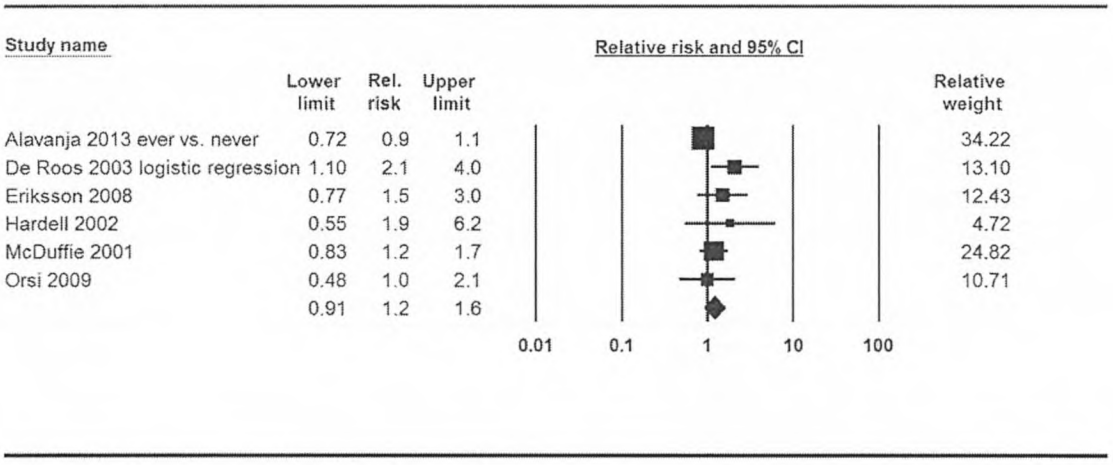
Exponent, Inc.

Center for Health Sciences

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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May 24, 2017

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

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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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January 28, 2016

PRIVILEGED AND CONFIDENTIAL

VIA ELECTRONIC MAIL

Dr. Jennifer Rider
[redacted]

Re: Monsanto Roundup® Litigation

Dear Dr. Rider:

This letter confirms that Hollingsworth LLP ("HLLP"), on behalf of Monsanto Company ("Monsanto"), has retained you to provide expert consulting services to HLLP, for the purpose of assisting HLLP in representing Monsanto in connection with potential and/or actual litigation against Monsanto involving injuries allegedly caused by Roundup® and/or glyphosate ("the Litigation"). You acknowledge that you have received, and/or likely will receive, confidential information from HLLP and that you likely will generate work product (orally and/or in writing) to assist us in representing Monsanto in the Litigation. You agree that you will maintain all information exchanged between HLLP and you (whether orally or in writing) as strictly confidential and privileged, unless we inform you, at some time in the future, that certain information needs to be disclosed in the Litigation. You also agree to maintain the fact that you have been retained by HLLP as strictly confidential and privileged, unless we inform you, at some time in the future, that your identity as HLLP's expert has been disclosed in the Litigation. Furthermore, you agree to not do any consulting or other work for any other corporation, law firm, or person with respect to any actual or potential legal claims involving Roundup® and/or glyphosate. You will be compensated at your standard hourly rate for time spent working with HLLP on the Litigation, namely $400.00 per hour for general review of material and $550.00 per hour for deposition and trial testimony.

Hollingsworth LLP

If you agree to these terms, please sign the letter below and send it back to me. We look forward to working with you.

Sincerely,

Heather A. Pigman

SEEN AND AGREED:

Dr. Jennifer Rider

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 105: DIESEL AND GASOLINE ENGINE EXHAUSTS AND SOME NITROARENES
Lyon, France: 5-12 June 2012

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Martie van Tongeren, Institute of Occupational Medicine, United Kingdom[4] (on-line attendance only)

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[1] Because of a 2001 U.S. District Court ruling involving the NCI/NIOSH Diesel Study, involved scientists are barred from publicly releasing data underlying the articles from the diesel study. Roel Vermeulen will participate in the meeting respecting this position.
[2] Aaron Cohen is the principal scientist of the Health Effects Institute (HEI) which conducts research worldwide on the health effects of air pollution. The Institute's core funding comes in equal part from the U.S. Environmental Protection Agency and the makers of motor vehicles for sale in the United States.
[3] David B. Kittelson has received significant research funding from Caterpillar on the influence of biofuels on particulate emissions (ended in 2009); and from BP for methods of measuring ash in engine exhausts (current).
[4] Martie van Tongeren has received significant research funding from Statoil, CONCAWE and CEFIC.

Representatives of national and international health agencies

Matthias Möhner, Federal Institute for Occupational Safety and Health, Germany
Matteo Redaelli, French Agency for Food, Environment and Occupational Health Safety (ANSES), France
Cheryl Siegel Scott, U.S. Environmental Protection Agency, USA

Observers

Nicole Falette, for the Léon Bérard Centre, France
John F. Gamble, for the IARC Review Stakeholder Group[5], USA[6]
Daniel S. Greenbaum, for the Health Effects Institute, USA[7]
Thomas W. Hesterberg, for the IARC Review Stakeholder Group[5], USA[8]
Timothy L. Lash, for the Association of American Railroads (AAR), USA[9]
Markus Mattenklott, German Social Accident Insurance (DGUV), Germany (8-12 June)
Roger O. McClellan, for the IARC Review Stakeholder Group[5], USA[10]
Peter Morfeld, for the European Research Group on Environment and Health in the Transport Sector (EUGT e.V), Germany[11]
Dirk Pallapies, German Social Accident Insurance (DGUV), Germany[12] (5-7 June)
John Carson Wall, for the IARC Review Stakeholder Group[5], USA[13]

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[5] The IARC Review Stakeholder Group represents the AAM (Alliance of Automobile Manufacturers), ACEA (European Automobile Manufacturers Association), AECC (Association for Emissions Control by Catalyst), API (American Petroleum Institute), CONCAWE (Conservation of Clean Air Water and Environment, the oil companies European association for environment, health, and safety in refining and distribution), EMA (Truck and Engine Manufacturers of America), IPIECA (International Petroleum Industry Environmental Conservation Association), MECA (Manufacturers of Emission Controls Association), and OICA (International Organization of Motor Vehicle Manufacturers).

[6] John Gamble has received significant research funding from CONCAWE.

[7] Dan Greenbaum is the President of the Health Effects Institute (HEI) which conducts research worldwide on the health effects of air pollution. The Institute's core funding comes in equal part from the U.S. Environmental Protection Agency and the makers of motor vehicles for sale in the United States.

[8] Thomas Hesterberg is a full-time employee of Navistar, Inc., a manufacturer of diesel trucks and engines. He provided expert opinion to California Air Resources Board in 2010 regarding emissions from diesel engines.

[9] Timothy L. Lash served as a consultant to the diesel industry through Cambridge Environmental Inc.

[10] Roger McClellan serves as a consultant for the Engine Manufacturers Association, Navistar International, Cummins Engine Co., Shell Exploration and Production Co., Union Pacific, and the American Petroleum Institute.

[11] Peter Morfeld is a member of the Scientific Advisory Group of European Research Group on Environment and Health in the Transport Sector (EUGT); in addition, he has received significant research funding from EUGT.

[12] Dirk Pallapies holds small amounts of stock of Daimler-Benz AG and was employed until 2008 by BASF, a chemical company with business in trap technology, catalysts and additives for diesel and gasoline engines.

[13] John C. Wall is Vice President – Chief Technical Officer of Cummins Inc., a manufacturer of diesel engines. He also holds stock and patents of Cummins Inc.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 116: COFFEE, MATE AND VERY HOT BEVERAGES
Lyon, France: 24-31 May 2016

Working Group Members and Invited Specialists serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

LIST OF PARTICIPANTS

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Manami Inoue, University of Tokyo, Japan
Farhad Islami, American Cancer Society, Inc., USA (unable to attend)
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Farin Kamangar, Morgan State University, USA
Siegfried Knasmüller, Medical University of Vienna, Austria
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David L. McCormick, IIT Research Institute, USA (Subgroup Chair, Cancer in Experimental Animals)
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Luis Felipe Ribeiro Pinto, Brazilian National Cancer Institute, Brazil
Ivan I. Rusyn, Texas A&M University, USA (Subgroup Chair, Mechanisms)
Rashmi Sinha, National Cancer Institute, USA (Subgroup Chair, Cancer in Humans)
Leslie T. Stayner, University of Illinois at Chicago, USA (Overall Chair)
Mariana C. Stern, University of Southern California, USA
Alessandra Tavani, Mario Negri Institute of Pharmacological Research, Italy
Piet van den Brandt, Maastricht University, The Netherlands
Kathryn M. Wilson, Harvard T.H. Chan School of Public Health, USA

Invited Specialists

None

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 105: DIESEL AND GASOLINE ENGINE EXHAUSTS AND SOME NITROARENES
Lyon, France: 5-12 June 2012

IARC secretariat

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Dana Loomis, Section of *IARC Monographs*[14]
Suzanne Moore, Section of Cancer Information[15]
Karen Müller, Communications Group *(editor)*
Ann Olsson, Section of Environment and Radiation
Kurt Straif, Section of *IARC Monographs (Section Head)*
Jelle Vlaanderen, Section of Environment and Radiation

NOTE REGARDING CONFLICTS OF INTERESTS: Each participant submitted WHO's Declaration of Interests, which covers employment and consulting activities, individual and institutional research support, and other financial interests. Participants identified as Invited Specialists did not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. The Declarations were updated and reviewed again at the opening of the meeting.

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Posted on 12 April 2012, updated on 6 June

[14] Dana Loomis consulted in a lawsuit involving exposure to diesel exhaust (ceased in 2011).
[15] Suzanne Moore holds significant stock of BHP Billiton Limited, a global natural resources company with business in oil and gas exploration, production, development and marketing.

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

EXHIBIT 23 - 15
WIT: Ryder
DATE: 9/21/17
Maureen Pollard, RMR

The Nutrition Source

Research Roundup

Noteworthy nutrition studies highlighted by members of The Chan School's Department of Nutrition

Glyphosate, the primary active ingredient in the herbicide "Roundup," is a broad-spectrum, non-selective, systemic herbicide, which effectively kills all plant types. Glyphosate-based herbicide was introduced to the US in 1974 and now has become the world's most common herbicide.

1) Guyton KZ, Loomis D, Grosse Y, et al. (2015) Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. *The Lancet Oncology* 16(5): 490-1.

In March, 2015, 17 experts from 11 countries assessed the carcinogenicity of five pesticides including glyphosate at the International Agency for Research on Cancer. A summary of the final evaluations was published in *The Lancet Oncology*.

- In this report, glyphosate was classified as "probably carcinogenic to humans" (Group 2A) for non-Hodgkin lymphoma, indicating there was limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in animals. Specifically, increased risk of non-Hodgkin lymphoma was consistent across case-control studies of occupational exposure in the USA, Canada, and Sweden. However, no evidence of increased risk of non-Hodgkin lymphoma was observed in the large Agricultural Health Study cohort (AHS).
- The evidence of other cancer sites (skin tumors, renal tubule carcinoma, haemangiosarcoma, and pancreatic islet-cell adenoma) was limited to animal studies.
- Evidence suggested the potential mechanisms for cancer were primarily through two pathways: First, the chemicals damaged DNA, which caused mutations or alterations in their gene codes. Second, glyphosate could induce oxidative stress. Oxidative stress

happens when highly reactive chemicals overwhelm the capacity of cells to deactivate them. Often, free radicals will be produced during this process, and they can interact with molecules in the body and damage various cell components. If the cells cannot effectively counteract this production, cells can become necrotic and die.

2) Mesnage R, Arno M, Costanzo M, et al. (2015) Transcriptome profile analysis reflects rat liver and kidney damage following chronic ultra-low dose Roundup exposure. *Environmental Health* 14(1): 70.

An experimental study published in *Environmental Health* showed that chronic exposure to an ultra-low dose of glyphosate resulted in liver and kidney damage in rats.

- In this study, researchers administered 2-year minute doses (0.1ppb) of Roundup via drinking water, which was representative of what could be found in contaminated tap water.
- First, the authors observed the signs of pathological and biochemical changes in the liver and kidneys of the exposed rats.
- Then, they analyzed the changes in gene expression of these organs. Compared to the control group, more than 4000 gene transcript clusters in the liver and kidneys showed alterations in the exposed rats.
- The findings demonstrated that chronic exposure to glyphosate at an environmental level resulted in liver and kidney damage in an animal toxicity model, which may potentially have health implications for both animal and human populations.

3) Balbuena MS, Tison L, Hahn ML, et al. (2015) Effects of sublethal doses of glyphosate on honeybee navigation. *The Journal of Experimental Biology* 218(Pt 17): 2799-805.

An experimental study published in *The Journal of Experimental Biology* showed that exposure to sublethal doses of glyphosate affect the homeward flight path of honeybees in an open field.

- The authors performed an experiment in which forager honeybees were fed with a sugar solution containing traces of glyphosate in three sublethal concentrations (2.5, 5, and 10 mg/l) and released from a new site.

- The honeybees treated with a higher glyphosate concentration (10mg/l) spent more time performing homeward flights than control bees or bees treated with lower concentrations.
- The results suggest that exposure to glyphosate in a level commonly found in agricultural settings impaired the honeybees' navigation, with potential long-term negative consequences for the foraging success of honeybees.

Due to widespread use of glyphosate, the residues are found in American's urine, breast milk, and drinking water. The IARC has concluded that glyphosate is probably carcinogenic for non-Hodgkin lymphoma, and the risk of other cancer sites is inconclusive. In addition to health concerns, weed resistance to glyphosate has been increasing, which will adversely affect farm production. Due to the developing weed resistance, the Environmental Protection Agency is planning to place new restrictions on glyphosate. However, the details of the regulations have not yet been released at this time.

This month's Research Roundup was compiled by Yu-Han Chiu, a third year doctoral student who has been researching dietary factors in relation to semen quality and other reproductive outcomes. Dr. Chiu has been working with her advisor Dr. Jorge Chavarro and her colleagues on developing a dietary pesticide burden score to estimate an individual's pesticide exposure from food intake. Using this method, they recently presented important new data on pesticide exposure via fruit and vegetable intake in relation to semen quality in the journal Human Reproduction.

Emily H Phares October 16, 2015 Research Roundup

PREVIOUS

Coffee Talk: How It Stacks Up Against Water

NEXT

How risky is it to eat red meat?

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

Faculty and Researcher Directory

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Research

Philippe Grandjean was born in Denmark in 1950. He graduated with his MD from the University of Copenhagen at age 23, and six years later he defended his doctoral thesis on the 'Widening perspectives of lead toxicity'. He became Professor of Environmental Medicine at the University of Southern Denmark in 1982. A Fulbright Senior Scholarship award brought him to Mt.Sinai Hospital in New York, and he later served as Adjunct Professor of Neurology and Environmental Health at Boston University. In 2003, he became Adjunct Professor of Environmental Health at Harvard University. In 2004, he received an unusual recognition – the Mercury Madness Award for excellence in science in the public interest, from eight US environmental organizations. He has also received the Science Communication Award from the University of Southern Denmark, and in 2015, he received the Bernardino Ramazzini Award for "his long career conducting and promoting environmental health research, especially his groundbreaking work on the effects of methylmercury and other environmental toxins affecting children and for his tireless advocacy of the need to protect future generations from the devastating effects of neuro- and developmental toxins." In 2016, Grandjean received the John F. Goldsmith Award from the International Society for Environmental Epidemiology for his sustained and outstanding contributions to the knowledge and practice of environmental epidemiology.

He lives in Copenhagen, Denmark and in Cambridge, MA, and travels widely to study environmental problems and to examine children whose lives have been affected by pollution, more specifically, the delayed effects of developmental exposure to environmental chemicals.

His most recent projects examine brain development and immune functions in regard to exposures to environmental pollutants, such as perfluorinated compounds and mercury. The results have inspired downward revisions of methylmercury exposure limits internationally and, most recent, the UN's Minamata Convention. Other recent studies have targeted age-related functional deficits and degenerative diseases, such as Parkinson's disease, cardiovascular disease, and type 2 diabetes in regard to life-time exposure to methylmercury, arsenic, persistent lipophilic contaminants, and perfluorinated compounds. Other efforts relate to biomarker development and validation, endocrine disruption caused by organochlorine substances. adverse effects of fluoride exposure, and the neurotoxicity of lead. Dr. Grandjean has also published on research ethics, genetic susceptibility, the setting of exposure limits, and the impact of the precautionary principle on prevention and research.

Recent News

Consensus document: Consensus on early origins (2015)

Web Site: Chemical Brain Drain

Video: Chemical Brain Drain

Open Access publishing: Champion

New Book: Only One Chance

Publications

(Selected articles from 2012-2016)

Grandjean P. Paracelsus Revisited: The dose concept in a complex world. Basic Clin Pharmacol Toxicol 2016; 119: 126-32.

Grandjean P. Learning from Bernardino Ramazzini, a tribute to the Magister from Carpi and to the Fellows of the Collegium Ramazzini. Eur J Oncol 2016: 21: 51-60.

Yorifuji T, Kato T, Ohta H, Bellinger DC, Matsuoka K, Grandjean P. Neurological and neuropsychological functions in adults with a history of developmental arsenic poisoning from contaminated milk powder. Neurotoxicol Teratol 2016; 53: 75-80.

Debes F, Weihe P, Grandjean P. Cognitive deficits at age 22 years associated with prenatal exposure to methylmercury. Cortex 2016; 74: 358-69.

Grandjean P, Clapp R. Perfluorinated alkyl substances: emergence of insights into health risks. New Solutions 2015; 25: 147-63.

Jensen TK, Andersen LB, Kyhl HB, Nielsen F, Christensen HT, Grandjean P. Association between perfluorinated compounds and miscarriage in a case-control study of Danish pregnant women. PLoS One 2015; 10: e0123496.

Mogensen UB, Grandjean P, Nielsen F, Weihe P, Budtz-Jørgensen E. Breastfeeding as an exposure pathway for perfluorinated alkylates. Environ Sci Technol 2015; 49: 10466-73.

Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. Neurobehavioral deficits, diseases and associated costs of exposure to endocrine disrupting chemicals in the European Union. J Clin Endocrinol Metab 2015; 100: 1256-66.

Grandjean P, Landrigan PJ. Neurobehavioural effects of developmental toxicity. Lancet Neurol 2014; 13: 330-8.

Audouze K, Brunak S, Grandjean P. Computational approach to chemical etiologies of diabetes. Sci Comm 2013; 3: 2712.

Julvez J, Davey-Smith G, Golding J, Ring S, St. Pourcain B, Gonzalez JR, Grandjean P. Prenatal methylmercury exposure and genetic predisposition to cognitive deficit at age 8 years. Epidemiology 2013; 24: 643-50.

Grandjean P, Ozonoff D. Transparency and translation of science in a modern world. Environ Health 2013; 12: 70.

Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Grandjean P, Hancock C, Hanson MA, Heindel JJ, Hoffman K, Jensen GK, Keeling A, Neira M, Rabadán-Diehl C, Ralston J, Tang KC. Early-life prevention of non-communicable diseases (Comment). Lancet 2013; 381: 3-4.

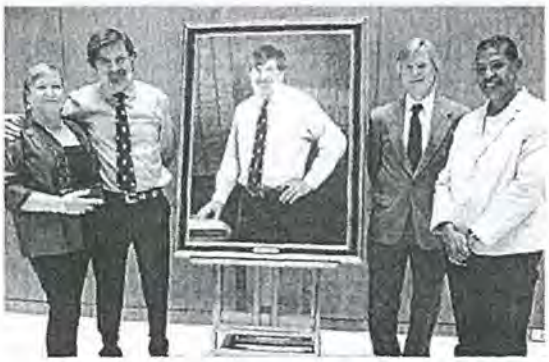
Budtz-Jørgensen E, Bellinger D, Lanphear B, Grandjean P, International Pooled Lead Study Investigators. An international pooled analysis for obtaining a Benchmark dose for environmental lead exposure in children. Risk Anal 2013; 33: 450-61.

Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Decreased serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA 2012; 307: 391-7.

Choi AL, Sun G, Zhang Y, Grandjean P. Developmental fluoride neurotoxicity: A systematic review and meta-analysis. Environ Health Perspect 2012; 120: 1362-8.

News from the School

Helping Harvey survivors



David Hunter honored

Social responsibility

Brand marketing gone bad

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 112: SOME ORGANOPHOSPHATE INSECTICIDES AND HERBICIDES:
DIAZINON, GLYPHOSATE, MALATHION, PARATHION, AND TETRACHLORVINPHOS
Lyon, France: 3-10 March 2015

LIST OF PARTICIPANTS

Working Group Members and Invited Specialists served in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

Members

Isabelle Baldi, University of Bordeaux, France
Aaron Blair, National Cancer Institute, USA [retired] (Overall Chair)
Gloria M. Calaf, Tarapaca University, Chile
Peter P. Egeghy, U.S. Environmental Protection Agency, USA[1] (Unable to attend)
Francesco Forastiere, Regional Health Service of the Lazio Region, Italy (Subgroup Chair, Cancer in Humans)
Lin Fritschi, Curtin University, Australia (Subgroup Chair, Exposure)
Gloria D. Jahnke, National Institute of the Environmental Health Sciences, USA
Charles W. Jameson, CWJ Consulting, LLC, USA (Subgroup Chair, Cancer in Experimental Animals)
Hans Kromhout, Utrecht University, The Netherlands
Frank Le Curieux, European Chemicals Agency, Finland
Matthew T. Martin, U.S. Environmental Protection Agency, USA
John McLaughlin, University of Toronto, Canada
Teresa Rodriguez, National Autonomous University of Nicaragua, Nicaragua (Unable to attend)
Matthew K. Ross, Mississippi State University, USA
Ivan I. Rusyn, Texas A&M University, USA (Subgroup Chair, Mechanisms)
Consolato Maria Sergi, University of Alberta, Canada
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Lauren Zeise, California Environmental Protection Agency, USA

Invited Specialists

Christopher J. Portier, Agency for Toxic Substances and Disease Registry, USA [retired][2]

---

[1] Peter P Egeghy received "in kind" support and reimbursement of travel expenses of on average less than US $2.000 per year during the last 4 years from participation in meetings sponsored by the American Chemistry Council, an industry trade association for American chemical companies, and the Health and Environmental Sciences Institute (HESI), a nonprofit scientific research organization based in Washington and funded by corporate sponsors.

[2] Christopher J Portier receives a part-time salary from the Environmental Defense Fund, a United States–based nonprofit environmental advocacy group.

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Representatives of national and international health agencies

Amira Ben Amara, National Agency for Sanitary and Environmental Product Control, Tunisia (Unable to attend)
Catherine Eiden, U.S. Environmental Protection Agency, USA (Unable to attend)
Marie-Estelle Gouze, for the French Agency for Food, Environment and Occupational Health and Safety, France
Jesudosh Rowland, U.S. Environmental Protection Agency, USA

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Béatrice Fervers, for the Léon Bérard Centre, France
Elodie Giroux, University Jean-Moulin Lyon 3, France
Thomas Sorahan, for Monsanto Company, USA[4]
Christian Strupp, for the European Crop Protection Association, Belgium[5]
Patrice Sutton, for the University of California, San Francisco, Program on Reproductive Health and the Environment, USA[6]

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Kathryn Guyton, Section of *IARC Monographs (Responsible Officer)*
Charlotte Le Cornet, Section of the Environment and Radiation
Maria Leon Roux, Section of the Environment and Radiation

---

[3] Mette Kristine Boye Kristensen is employed by Cheminova A/S, Denmark, a global company developing, producing and marketing crop protection products.

[4] Tom Sorahan is a member of the European Glyphosphate Toxicology Advisory Panel, and received reimbursement of travel cost from Monsanto to attend EuroTox 2012.

[5] Christian Strupp is employed by ADAMA Agricultural Solutions Ltd, Israel, a producer of Diazinone and Glyphosphate.

[6] Patrice Sutton's attendance of this Monographs meeting is supported by the Clarence E. Heller Charitable Foundation, a philanthropic charity with a mission to protect and improve the quality of life through support of programs in the environment, human health, education and the arts.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
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Heidi Mattock, Section of *IARC Monographs (Editor)*
Chiara Scoccianti, Section of *IARC Monographs*
Andy Shapiro, Visiting Scientist, Section of *IARC Monographs*
Kurt Straif, Section of *IARC Monographs (Section Head)*
Jiri Zavadil, Section of Mechanisms of Carcinogenesis

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Posted on 26 January 2015, updated 19 October 2016

Lung Cancer

Molecular Pathology of Cancer Boot Camp
January 4, 2012
Jennifer Rider, ScD

Learning objectives

- Basic descriptive epidemiology
- Major risk factors
- Historical perspective on establishing smoking as a causal agent
- Key differences in disease among smokers and non-smokers

Leading Sites of New Cancer Cases and Deaths – 2011 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 240,890 (29%)	Breast 230,480 (30%)	Lung & bronchus 85,600 (28%)	Lung & bronchus 71,340 (26%)
Lung & bronchus 115,060 (14%)	Lung & bronchus 106,070 (14%)	Prostate 33,720 (11%)	Breast 39,520 (15%)
Colon & rectum 71,850 (9%)	Colon & rectum 69,360 (9%)	Colon & rectum 25,250 (8%)	Colon & rectum 24,130 (9%)
Urinary bladder 52,020 (6%)	Uterine corpus 46,470 (6%)	Pancreas 19,360 (6%)	Pancreas 18,300 (7%)
Melanoma of the skin 40,010 (5%)	Thyroid 36,550 (5%)	Liver & intrahepatic bile duct 13,260 (4%)	Ovary 15,460 (6%)
Kidney & renal pelvis 37,120 (5%)	Non-Hodgkin lymphoma 30,300 (4%)	Leukemia 12,740 (4%)	Non-Hodgkin lymphoma 9,570 (4%)
Non-Hodgkin lymphoma 36,060 (4%)	Melanoma of the skin 30,220 (4%)	Esophagus 11,910 (4%)	Leukemia 9,040 (3%)
Oral cavity & pharynx 27,710 (3%)	Kidney & renal pelvis 23,800 (3%)	Urinary bladder 10,670 (4%)	Uterine corpus 8,120 (3%)
Leukemia 25,320 (3%)	Ovary 21,990 (3%)	Non-Hodgkin lymphoma 9,750 (3%)	Liver & intrahepatic bile duct 6,330 (2%)
Pancreas 22,050 (3%)	Pancreas 21,980 (3%)	Kidney & renal pelvis 8,270 (3%)	Brain & other nervous system 5,670 (2%)
All sites 822,300 (100%)	All sites 774,370 (100%)	All sites 300,430 (100%)	All sites 271,520 (100%)

*Excludes basal and squamous cell skin cancers and in situ carcinoma except urinary bladder.

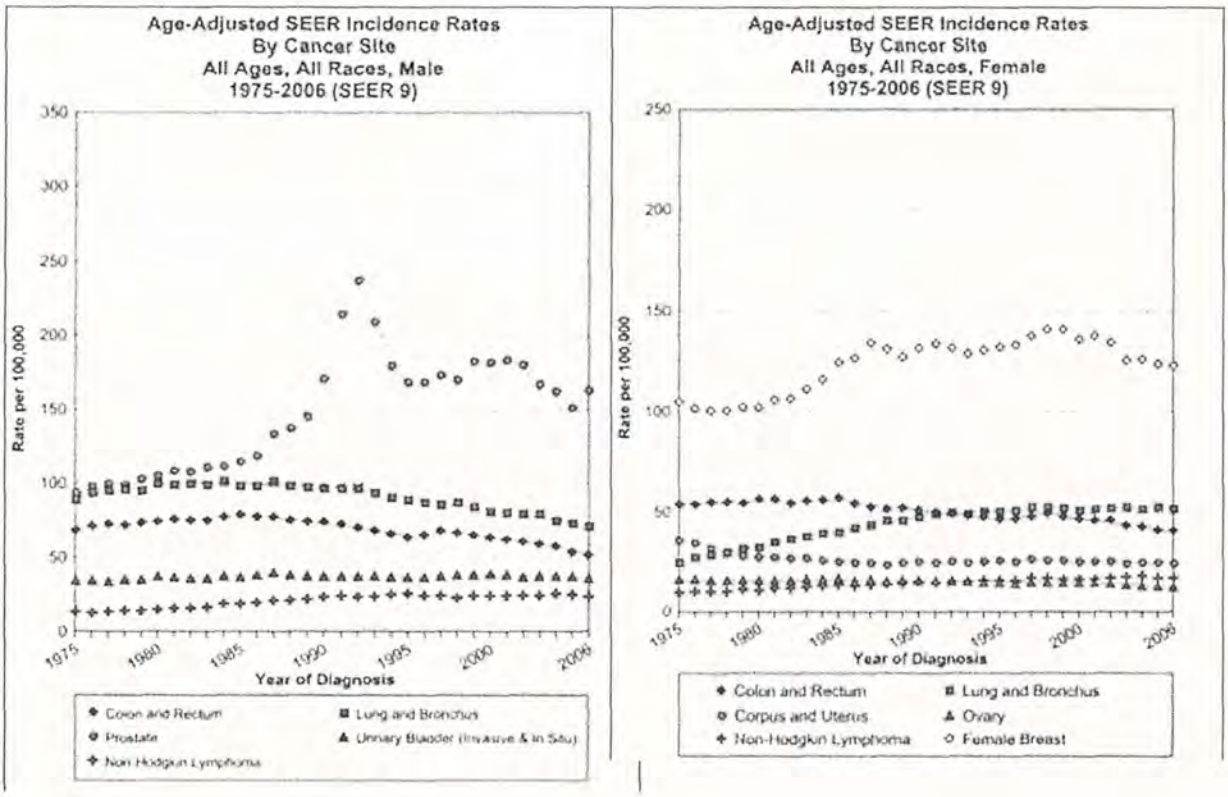
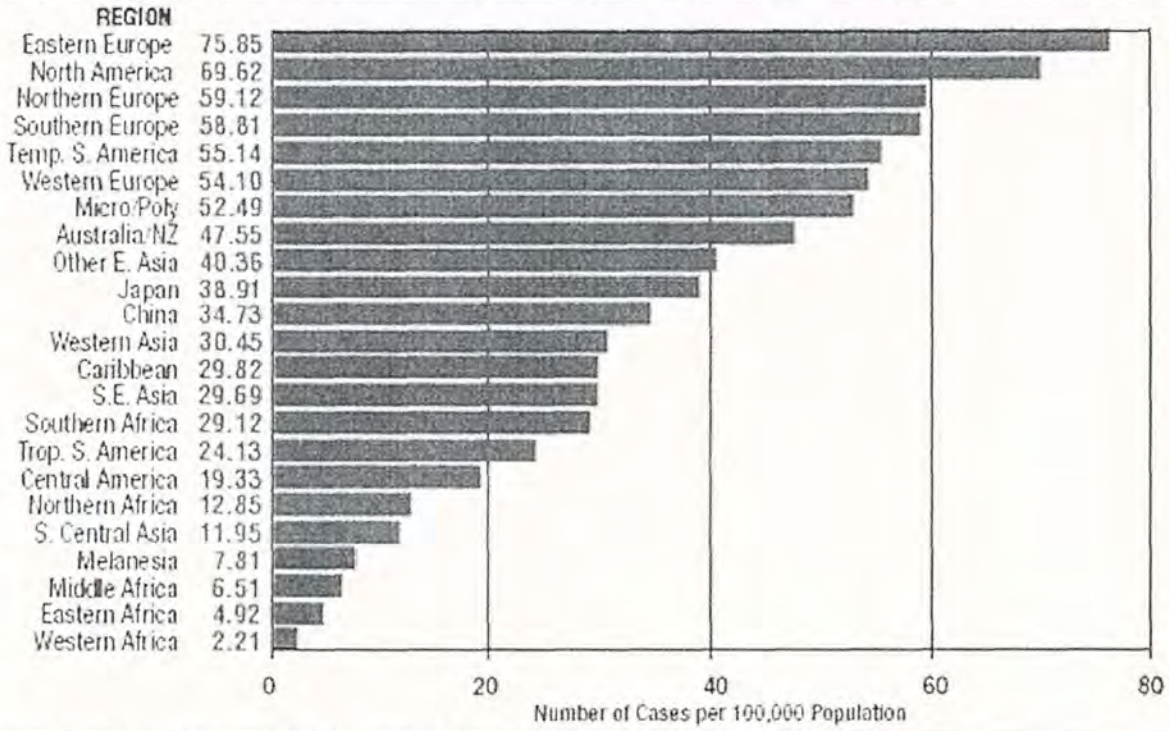
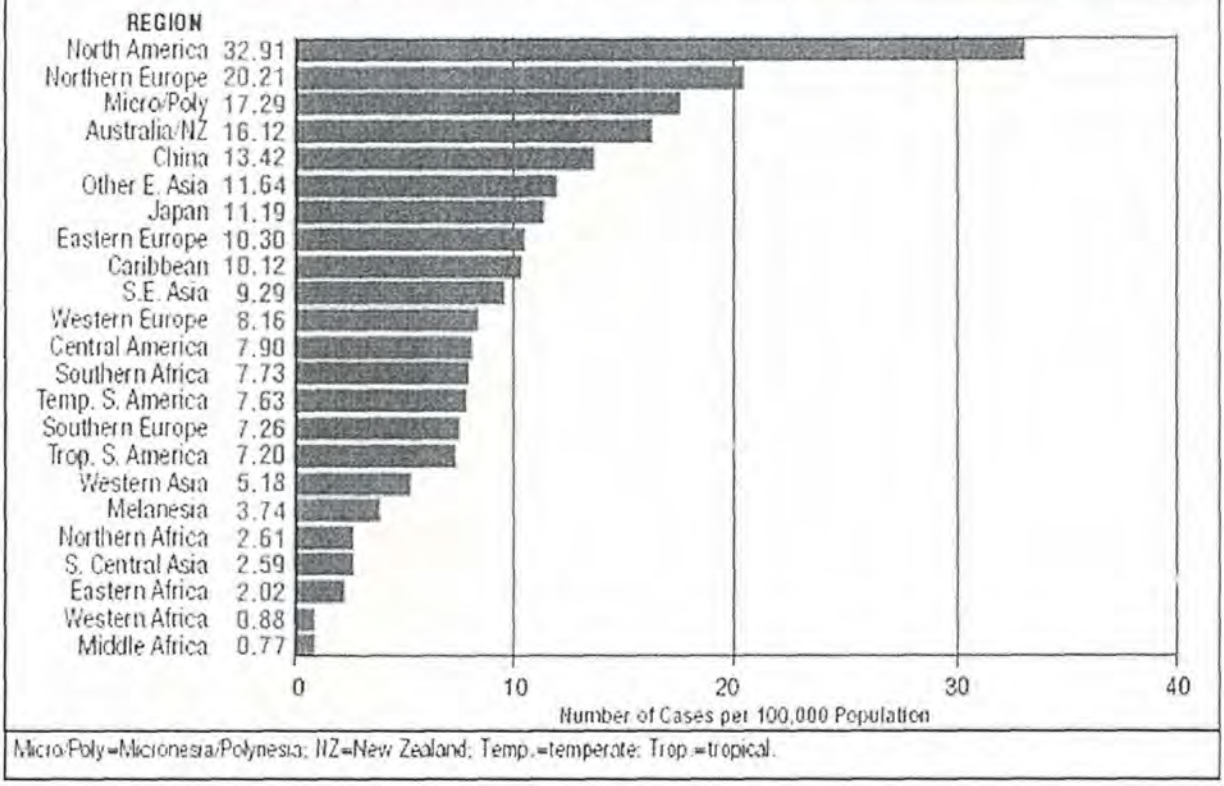

Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Male
1975-2006 (SEER 9)
Rate per 100,000
Year of Diagnosis
Colon and Rectum
Lung and Bronchus
Prostate
Urinary Bladder (Invasive & In Situ)
Non-Hodgkin Lymphoma
Age-Adjusted SEER Incidence Rates
By Cancer Site
All Ages, All Races, Female
1975-2006 (SEER 9)
Rate per 100,000
Year of Diagnosis
Colon and Rectum
Lung and Bronchus
Corpus and Uterus
Ovary
Non-Hodgkin Lymphoma
Female Breast

Figure 3A
Incidence of Lung Cancer in Males by World Region



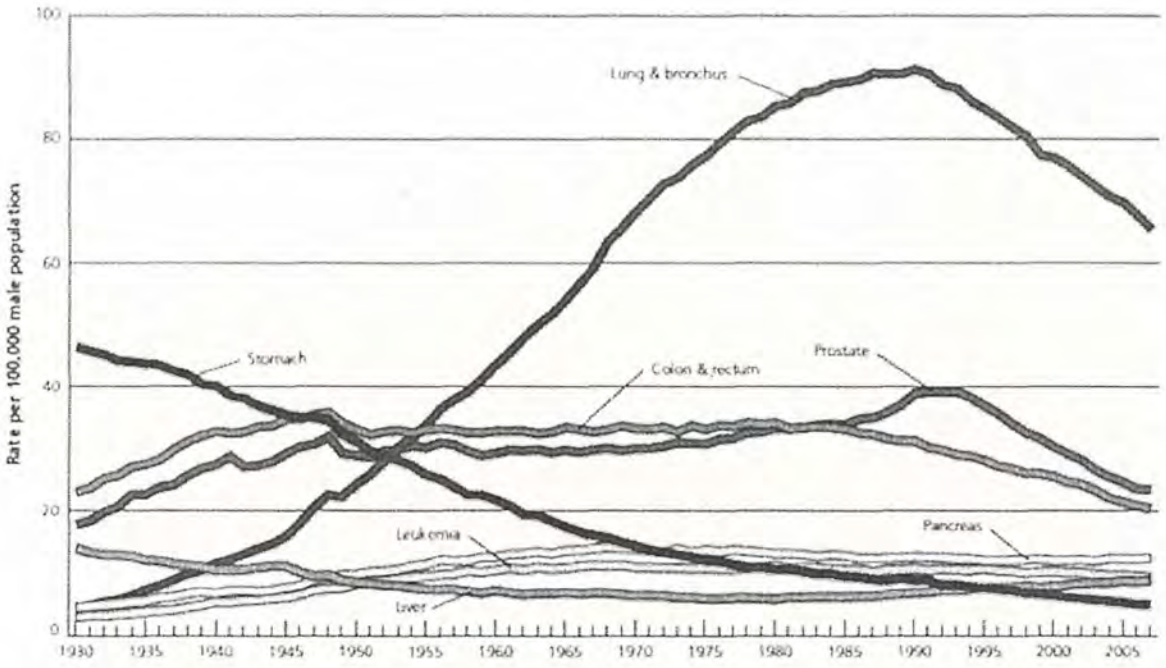
Micro/Poly=Micronesia/Polynesia; NZ=New Zealand; Temp.=temperate; Trop.=tropical.

Figure 3B
Incidence of Lung Cancer in Females by World Region



Micro/Poly=Micronesia/Polynesia; NZ=New Zealand; Temp.=temperate; Trop.=tropical.

Age-adjusted Cancer Death Rates,* Males by Site, US, 1930-2007

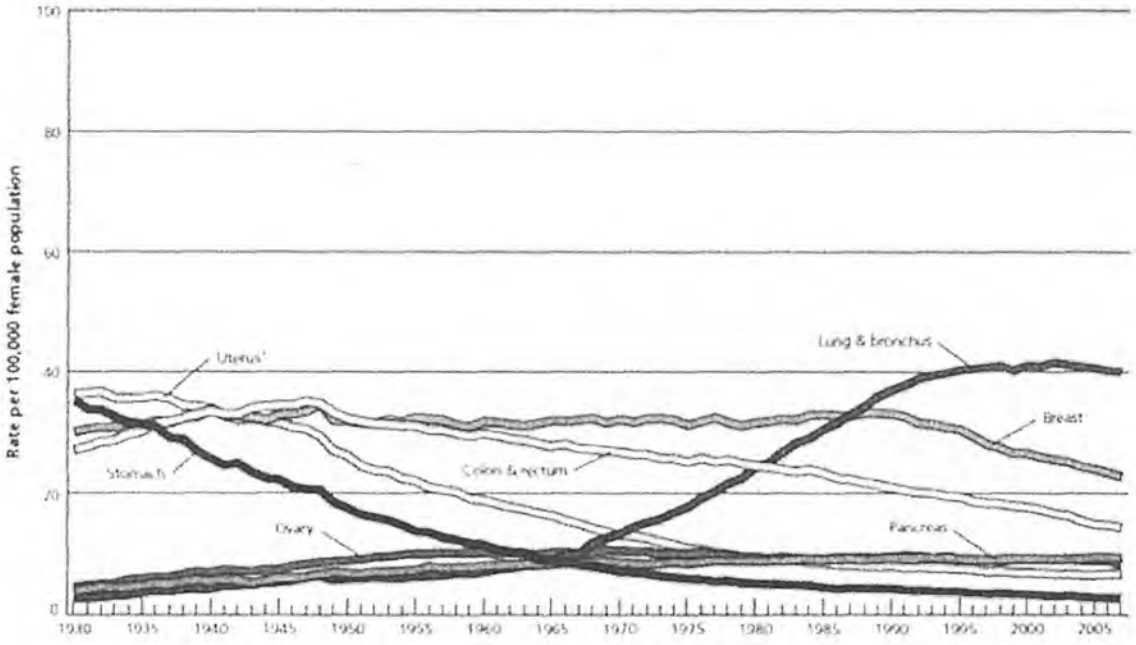


*Per 100,000, age adjusted to the 2000 US standard population

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these changes.

Source: US Mortality Data, 1960 to 2007, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

Age-adjusted Cancer Death Rates,* Females by Site, US, 1930-2007

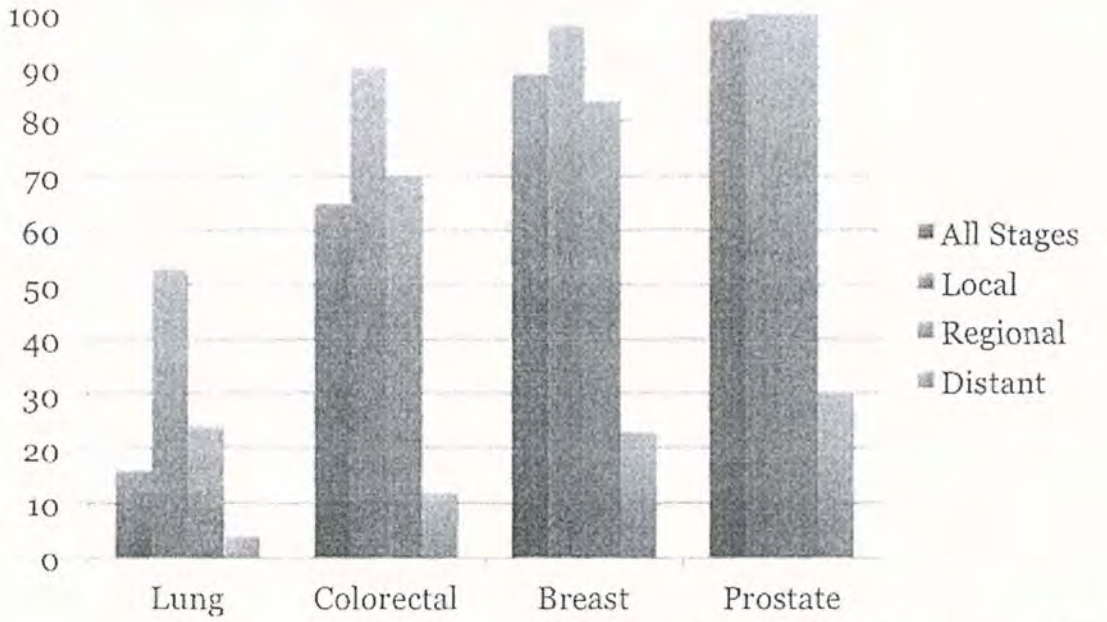


*Per 100,000, age adjusted to the 2000 US standard population.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancer of the liver, lung and bronchus, and colon and rectum are affected by these changes.

Source: US Mortality Data, 1960 to 2007, US Mortality Volumes, 1930 to 1959, National Center for Health Statistics, Centers for Disease Control and Prevention.

Five-year survival rates



ACS Cancer Facts & Figures 2011

Lung Cancer Epidemiology: Risk factors

1. Cigarette smoking
2. Environmental tobacco smoke
3. Radon
4. Occupational exposures
    a. Asbestos
    b. Asbestos x smoking interaction
    c. Cooking oil vapors and indoor coal burning
5. Ambient air pollution
6. Genetic factors

Smoking

- Lung cancer risk depends on:
  - Years smoked
  - Age smoking initiated
  - Number of cigarettes smoked per day
  - Tar/Nicotine
    - Risk roughly proportional to yield (down to one-half risk)
    - BUT negated by compensation in numbers smoked
- Risk elevated in cigar/pipe smokers
  - Amount smoked and inhaling contribute

Constituents of the cigarette

- 7000 chemicals
  - Carbon monoxide/vapor phase components
  - Nicotine
  - "Tar" = particulate – (nicotine + water)
  - 60 carcinogens
  - Additives

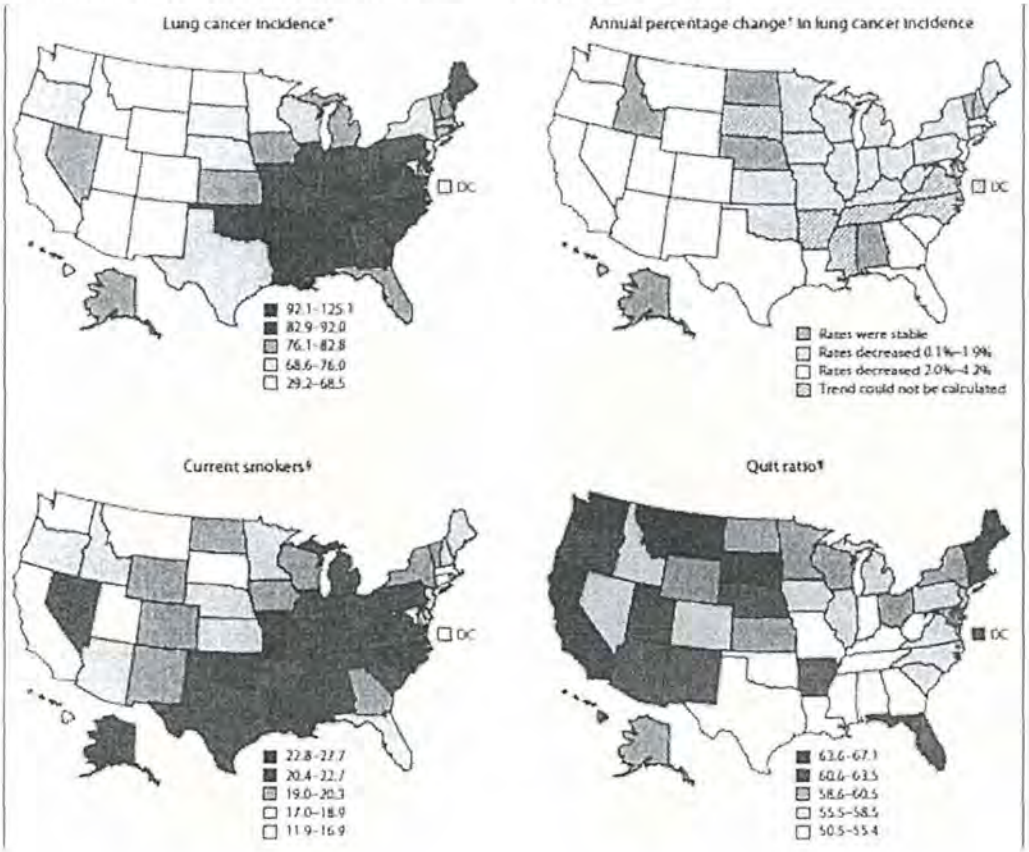
Selected carcinogens in cigarette smoke

- Policyclic aromatic hydrocarbons (PAH): benzo[a]pyrene
- Tobacco-specific nitrosamines (TSNA)
- Aromatic amines: 4-aminobiphenyl
- Benzene
- Arsenic, Nickel, Chromium
- Polonium-210

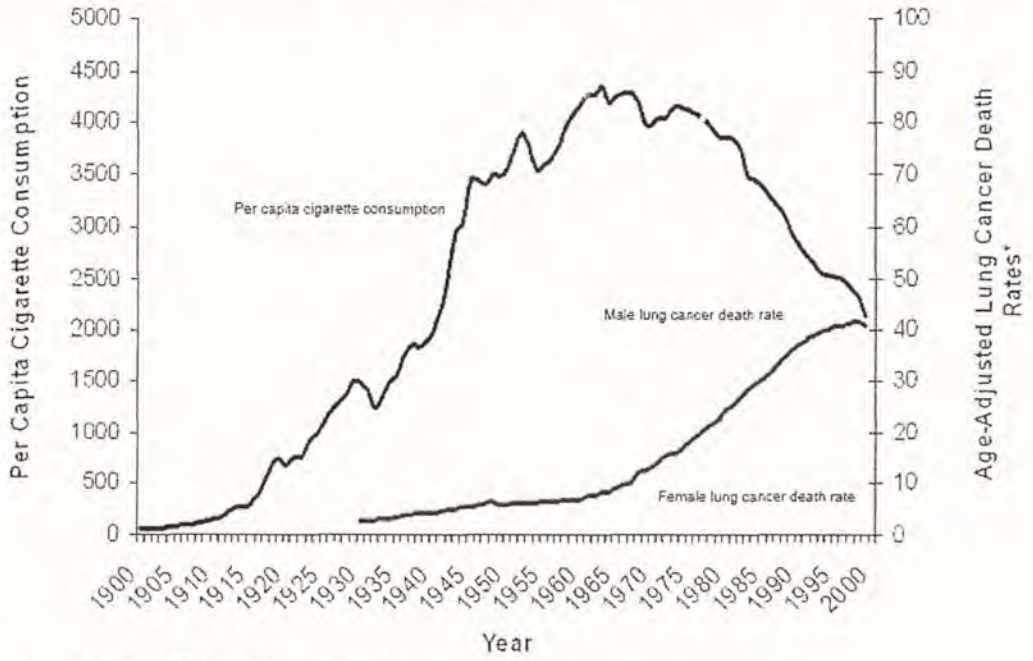
Smoking Cessation

- Among individuals who have smoked less than 20 years
  - Lung cancer risk reverts to non-smoker level after about 15 years of cessation.
- Among individuals who have already developed lung cancer
  - Quitting reduces risks of developing a second cancer

Lung cancer incidence and trends, and smoking behavior among men – United States

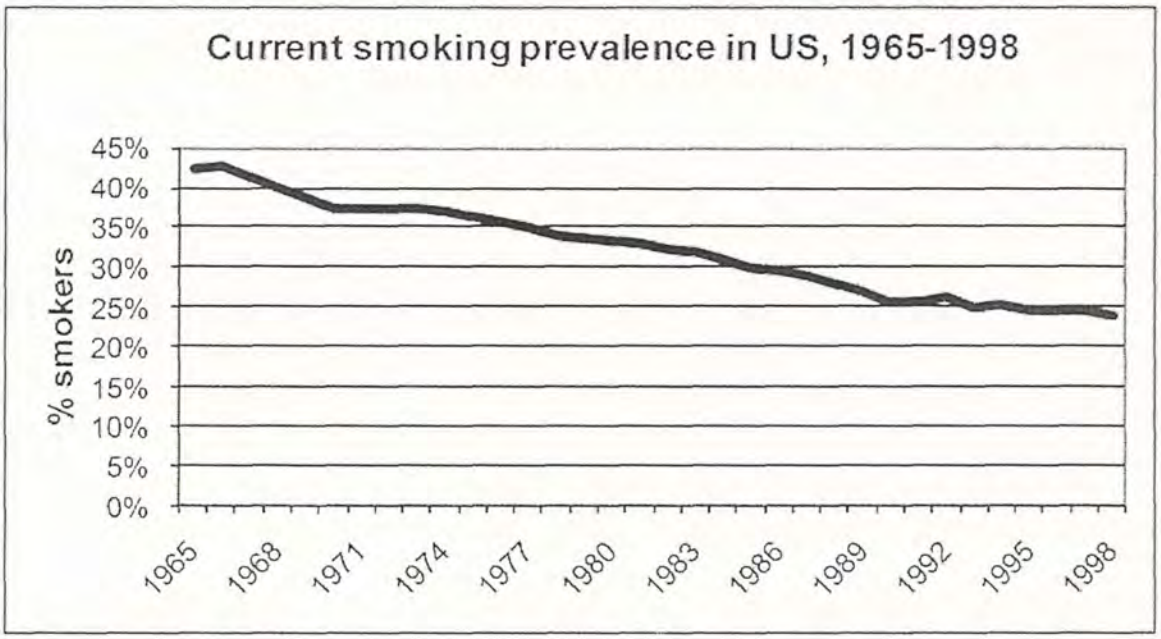


Tobacco Use in the US, 1900-1999

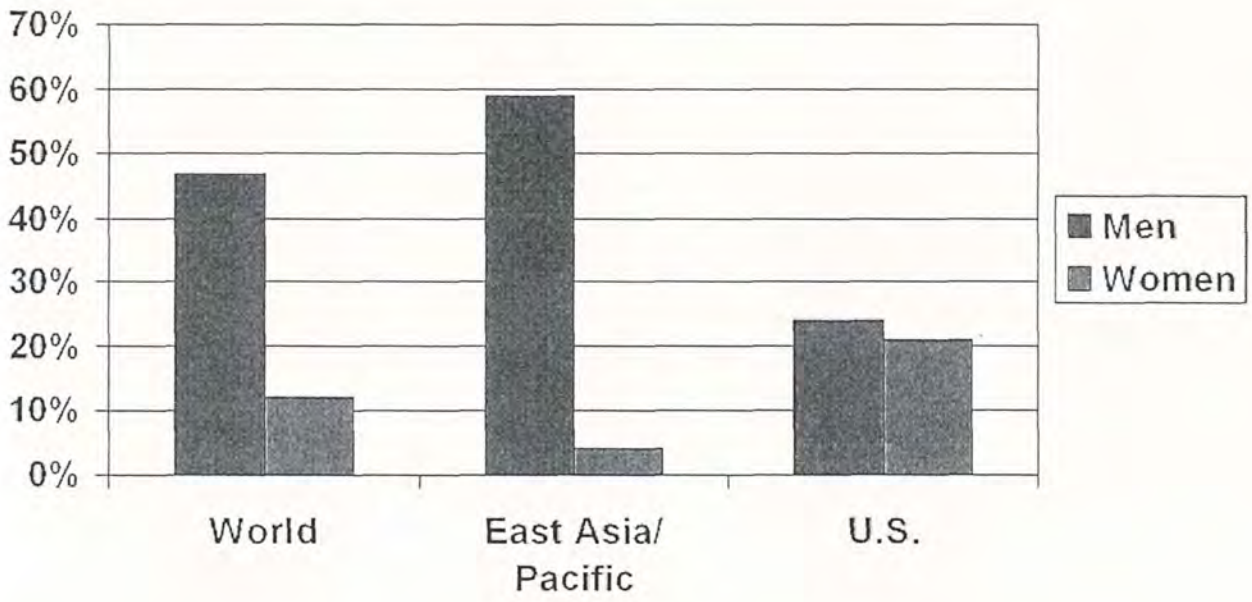


*Age-adjusted to 2000 US standard population.

Source: Death rates: US Mortality Public Use Tapes, 1960-1999, US Mortality Volumes, 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2001. Cigarette consumption: Us Department of Agriculture, 1900-1999.


Current smoking prevalence in US, 1965-1998
% smokers
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
1965
1968
1971
1974
1977
1980
1983
1986
1989
1992
1995
1998

Smoking prevalence by sex



1933: JAMA begins to accept advertising for cigarettes

"Just as pure as the water you drink...and practically untouched by human hands."

--Chesterfield advertisement, NY State Journal of Medicine, 1933

"The following hints may prove helpful. In combination they are nearly perfect and 99 44/100% of the nicotine will go into the filter or your friends' faces." Consumer Reports, 1938

HOW TO AVOID NICOTINE AND FOOL PEOPLE

BRITISH MEDICAL JOURNAL

LONDON SATURDAY SEPTEMBER 30 1950

SMOKING AND CARCINOMA OF THE LUNG

PRELIMINARY REPORT

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, Ph.D., D.Sc.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

In England and Wales the phenomenal increase in the number of deaths attributed to cancer of the lung provides one of the most striking changes in the pattern of mortality recorded by the Registrar-General. For example, in the quarter of a century between 1922 and 1947 the annual number of deaths recorded increased from 612 to 9,287, or roughly fifteenfold. This remarkable increase is, of course, out of all proportion to the increase of popula-

whole explanation, although no one would deny that it may well have been contributory. As a corollary, it is right and proper to seek for other causes.

Possible Causes of the Increase

Two main causes have from time to time been put forward: (1) a general atmospheric pollution from the exhaust fumes of cars from the surface

BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 10 1956

LUNG CANCER AND OTHER CAUSES OF DEATH IN RELATION TO SMOKING

A SECOND REPORT ON THE MORTALITY OF BRITISH DOCTORS

BY

RICHARD DOLL, M.D., M.R.C.P.

Member of the Statistical Research Unit of the Medical Research Council

AND

A. BRADFORD HILL, C.B.E., F.R.S.

Professor of Medical Statistics, London School of Hygiene and Tropical Medicine; Honorary Director of the Statistical Research Unit of the Medical Research Council

On October 31, 1951, we sent a simple questionary to all members of the medical profession in the United Kingdom. In addition to giving their name, address, and age, they were asked to classify themselves into one of three groups, namely, (a) whether they were at that time

previously have been a light smoker or may since then have given up smoking altogether; we shall have continued to count him, or her, as a heavy smoker. If there is a differential death rate with smoking, we must by such errors tend to inflate the mortality among the light

Barriers to acceptance of smoking-lung cancer relationship

- Ecologic data - other plausible alternatives
- Smoking common in scientific community
- Influence of tobacco companies
- Novelty of epidemiological techniques
- Strength of infectious disease model
  - Necessary and sufficient causes
  - Isolate and identify agent
  - Laboratory/animal evidence key
  - Smoking associated with multiple diseases

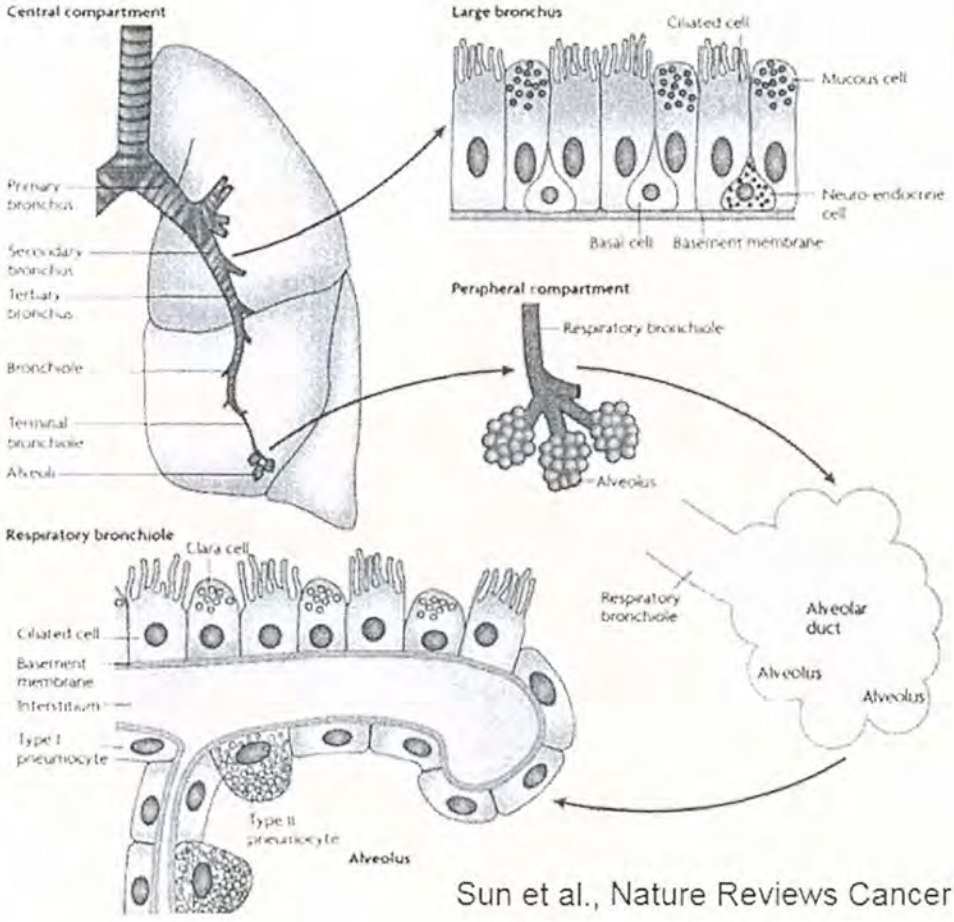
A new model of causality

- Bradford Hill's guidelines
  - Strength of association
  - Consistency
  - Specificity
  - Temporal sequence
  - Dose-response/biologic gradient
  - Biological plausibility
  - Coherence
  - Experimental evidence
  - Analogy

- Active smoking accounts for 90% of lung cancer deaths, but only 10% smokers develop lung cancer

Lung Cancer Subtypes

- Squamous cell carcinoma
- Adenocarcinoma
- Large-cell carcinoma
- Small-cell undifferentiated carcinoma

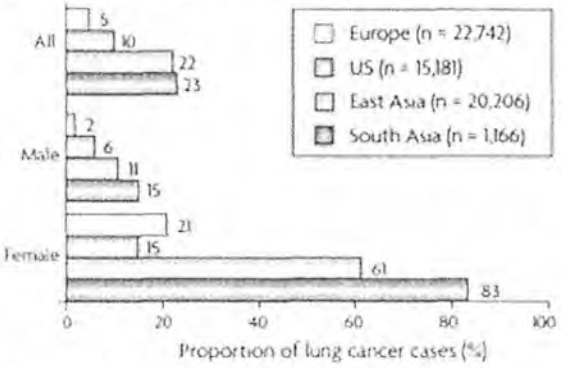


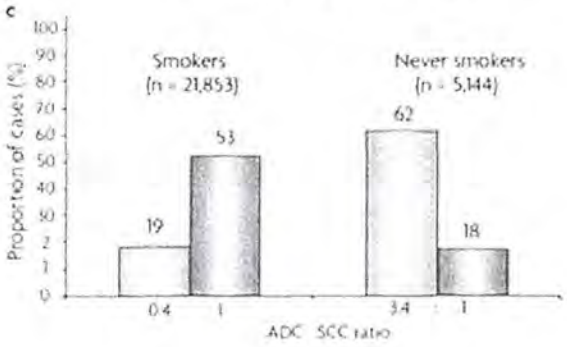
Sun et al., Nature Reviews Cancer 2007

Lung Cancer in Never Smokers

- Estimated 25% of lung cancers *not* attributable to smoking
  - 15% among men
  - 53% among women
- 7th leading cause of cancer death worldwide
- Only relatively weak risk factors identified
- Distinct histological, geographical and gender distribution

Proportion of Lung Cancer in Never Smokers

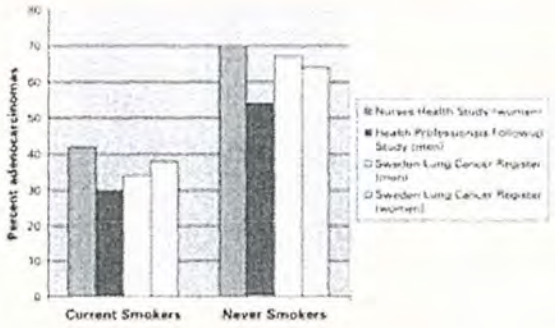




Sun et al., Nature Reviews Cancer 2007

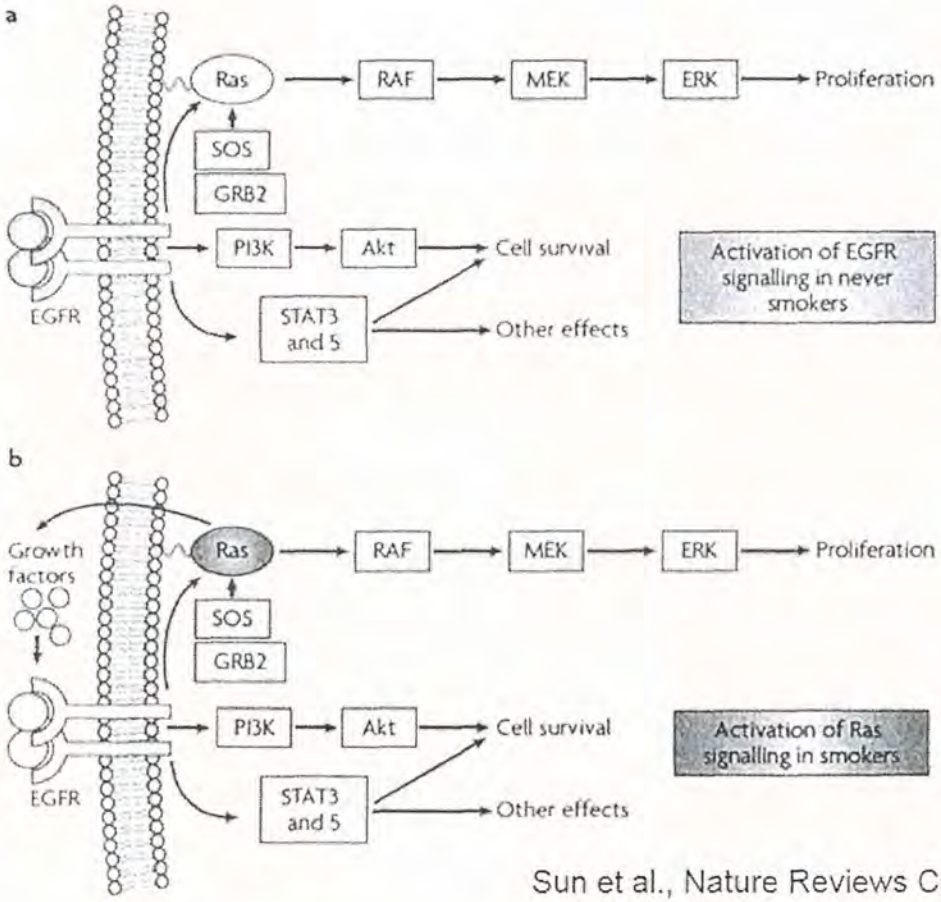
STATBITE

Lung Adenocarcinoma in Smokers vs. Never Smokers



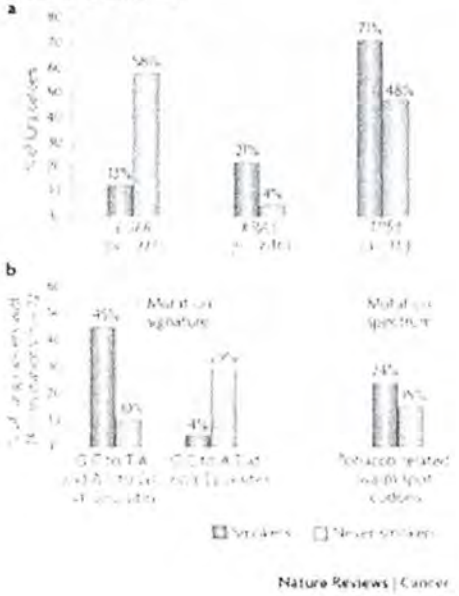
Lung cancer patients who never smoked are more likely to have adenocarcinomas than those who smoke. In the large population-based cohorts shown above, the percentage of adenocarcinomas ranged from 30% to 42% in current smokers compared to 64% to 70% in never smokers. As a group, never smoker lung cancer patients have other distinct biological characteristics, including a higher proportion of ALK fusion genes (see accompanying news story, p. 672).

Source: Wakelee HA, et al. Lung Cancer Incidence in Never Smokers. J Clin Oncol. 2007; 25(5):472-478.



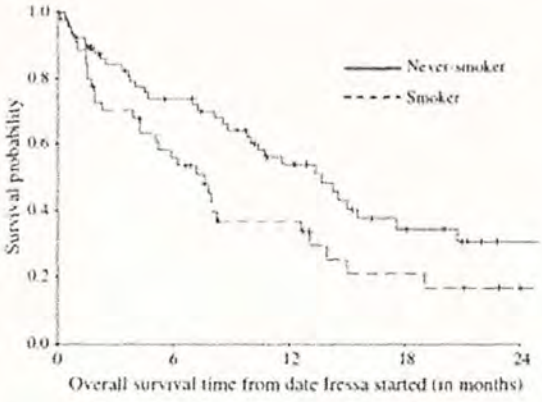
Sun et al., Nature Reviews Cancer 2007

Mutation profile among smokers vs. nonsmokers



Sun et al., Nature Reviews Cancer 2007

Gefitinib (Iressa) effectiveness among Asian patients with NSCLC



No. at risk					
Never-smoker	66	41	24	11	4
Smoker	44	23	12	5	1

Lim et al., Br J Cancer 2005

Thank you!

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

EXHIBIT 23-18
WIT: Rider
DATE: 9/21/17
Maureen Pollard, RMR

News

Report links welding fumes with risk of cancer

More priority needs to be given to protecting the world's estimated 111 million welders and other workers from exposure to potentially toxic welding fumes, according to David Christiani, Elkan Blout Professor of Environmental Genetics at Harvard T.H. Chan School of Public Health. He was among 17 scientists from 10 countries who met in March 2017 at the International Agency for Research on Cancer (IARC) in Lyon, France, to review scientific literature and evaluate the carcinogenicity of several welding chemicals to humans.

An executive summary of the monograph, entitled *IARC Monograph on the Evaluation of Carcinogenic Risks to Humans*, was published online April 10, 2017 in *The Lancet Oncology*. The entire volume (#118) will be available online via http://monographs.iarc.fr/.

"The Working Group found new evidence to support the conclusion that welding fumes are a likely cause of lung cancer in humans, possible cause of kidney cancer, and definite cause of melanoma of the eye," Christiani said. In addition to fumes, welding can expose workers to radiation and asbestos, which are known to cause cancer.

Two other chemicals evaluated — molybdenum trioxide (sometimes used in welding) and indium tin oxide (used to make computer screens) — were determined to be possibly cancer-causing in humans.

The IARC is a World Health Organization body that has among its activities to produce independent scientific consensus reports on the causes of cancer. These monographs, 118 to date, have been used by governments for protective regulations for years and have included reports on air pollution, diesel exhaust, smoking, sedentary behavior, diet, asbestos, and radiation.

Learn more

Keeping workers safe from health hazards on the job (Harvard Chan School news)

Global Cervical Cancer: HPV Vaccination and Diagnostics

Investigators:

Sue J. Goldie
Jane Kim
Sun-Young Kim
Stephen Resch
Stephen Sy

The risk of dying from cervical cancer is unequally borne by women in developing countries

In response to new etiologic evidence, improved technology, and promising HPV vaccine efforts, cervical cancer epidemiologic and preventive efforts are being reshaped throughout the world. The Harvard School of Public Health (Center for Health Decision Science), the International Agency for Research on Cancer (IARC), PATH, and the World Health Organization (WHO) are pursuing a coordinated strategy to make new diagnostics and HPV vaccines accessible, affordable, and sustainable in developing countries. The objective of this project is to promote evidence-based decision making in a global effort to prevent deaths from cervical cancer, and to catalyze global cancer prevention efforts by synthesizing the best available data and identifying effective, cost-effective, and affordable strategies to prevent cancer-causing HPV infection using new vaccines, and to detect infection at a treatable stage using new diagnostics. Specific goals include:

(1) To develop regional and country-specific models representing different epidemiologic settings using empiric data from multiple study sites on cancer incidence, type-specific HPV prevalence and distribution across the disease spectrum, and key cofactors.

(2) To conduct comprehensive policy analyses to estimate the avertable burden of disease and cost-effectiveness of various HPV vaccination strategies, and identify potential synergies between vaccination and screening, and the most influential factors on the sustainability and affordability of different policy alternatives.

(3) To develop a Core Modeling Center that will analytically support partner activities (e.g., PATH operational research in four countries), assist with or conduct cost-effectiveness analyses for different stakeholders in the HPV vaccine initiative (e.g., analyses to support GAVI investment case), and inform country decision making with analyses that reflect local costs and regional priorities.

Our partners include:

(1) The International Agency for Research on Cancer (IARC), which coordinates and conducts epidemiological and laboratory research on the causes of cancer. In this partnership, IARC collates published data on HPV type distribution in cervical cancer around the globe and co-ordinates new studies in regions where such data are missing, with special reference to populations where HIV is common. IARC also conducts surveys to determine the age-specific and genotype-specific prevalence of HPV in populations where very little or no knowledge is available.

(2) PATH, an international nonprofit organization that improves the health of people around the world through sustainable and culturally-relevant health related solutions. PATH is organizing HPV vaccination operational research projects in four countries (India, Peru, Uganda, and Vietnam) to generate experience addressing the sociocultural, logistic, policy, and clinical needs related to HPV vaccine introduction. In addition, PATH is negotiating partnerships with HPV vaccine manufacturers to accelerate access to HPV vaccine in developing countries. PATH is working with the partners to develop an investment case for public-sector HPV vaccine financing by potential funders (the GAVI Alliance, bilateral donors, and countries), and will disseminate research

project results and other educational and advocacy messages to global, regional, and national audiences.

(3) The World Health Organization's Initiative for Vaccine Research (WHO-IVR), charged with reinforcing linkages between vaccine research and development and immunization. WHO-IVR focuses on harmonizing and standardizing laboratory procedures and creating a global HPV Laboratory Network to facilitate vaccine licensure and monitoring in developing countries. Additionally, WHO-IVR generates an enabling environment for HPV vaccine introduction by creating an international multidisciplinary policy platform and setting a global agenda for future HPV vaccine introduction in consultation with regions and countries.

(4) Catalan Institute of Oncology (ICO)'s Epidemiology and Cancer Registration Unit, in Barcelona, Spain, which has been involved in the design and development of research initiatives around the world related to the causes and prevention of cancer. ICO analyzes data to assess the prevalence and natural history of HPV infections, the etiology of cervical cancer, and the attributable risk due to cofactors. In partnership with WHO, ICO has created an Information Centre on HPV and Cervical Cancer to facilitate global, regional, and country-specific decisions on current and novel options for cervical cancer prevention.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 114: RED MEAT AND PROCESSED MEAT
Lyon, France: 6-13 October 2015

LIST OF PARTICIPANTS

Members

Frederick A. Beland, National Center for Toxicological Research, USA (Subgroup Chair, Cancer in Experimental Animals)
Giovanna Caderni, University of Florence, Italy
Marie Cantwell, Queens' University Belfast, United Kingdom
Eunyoung Cho, Brown University, USA
Denis Corpet, University of Toulouse, France [retired] (Subgroup Chair, Mechanisms)
Stefaan De Smet, Ghent University, Belgium
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Sabine Rohrmann, University of Zürich, Switzerland
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Kana Wu, Harvard School of Public Health, USA

Invited Specialists

None

Representatives of national and international health agencies

Anna Christodoulidou, for the European Food Safety Authority (EFSA), Italy
Irini Margaritis, for the French Agency for Food, Environment and Occupational Health and Safety (ANSES), France
Harold Seifried, for the National Cancer Institute, USA [unable to attend]
Yukari Totsuka, for the National Cancer Center Research Institute, Japan

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 114: RED MEAT AND PROCESSED MEAT
Lyon, France: 6-13 October 2015

Observers

Dominik D. Alexander, Observer for the EpidStat Institute, USA[1]
Betsy L. Booren, Observer for the North American Meat Institute, USA[2]
Julien Carretier, Observer for the Léon Bérard Centre, France
Jason J. Hlywka, Observer for the Kraft Heinz Company, USA[3]
Daniel A. Kovich, Observer for the National Pork Producers Council, USA[4]
Hector J. Lazaneo, Observer for the National Meat Institute (INAC), Uruguay[5]
Marjorie McCullough, Observer for the American Cancer Society, USA
Shalene McNeill, Observer for Beef Checkoff, USA[6]

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Kurt Straif, Section of IARC Monographs (Section Head)

---

[1] Dominik D. Alexander is the Principal Epidemiologist of the EpidStat Institute, USA; he receives significant financial support from Beef Checkoff for research, consulting, travel and speaking engagements.
[2] Betsy L. Booren is employed as Vice President of Scientific Affairs by the North American Meat Institute, and as President by the North American Meat Institute Foundation.
[3] Jason J. Hlywka is currently employed by the Kraft Heinz Company. He holds significant retirement investments from the Kraft Heinz Company and Cargill Inc.
[4] Daniel A. Kovich is Assistant Director of Science and Technology of the National Pork Producers Council.
[5] Hector J. Lazaneo attends as an Observer for the National Meat Institute (INAC) which has the purpose of promoting, ruling, coordinating and monitoring activities concerning production, transformation, trade, storing and transport of meats.
[6] Shalene McNeill is employed by the National Cattlemen's Beef Association, and Beef Checkoff will be funding her travel.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans
VOLUME 114: RED MEAT AND PROCESSED MEAT
Lyon, France: 6-13 October 2015

NOTE REGARDING CONFLICTS OF INTERESTS: Each participant first received a preliminary invitation with the request to complete and sign the IARC/WHO Declaration of Interests, which covers employment and consulting activities, individual and institutional research support, and other financial interests.

Official invitations were extended after careful assessment of any declared interests that might constitute a real or perceived conflict of interest. Pertinent and significant conflicts are disclosed here. Information about other potential conflicts that are not disclosed may be sent to the Head of the Monographs Programme at imo@iarc.fr.

Participants identified as Invited Specialists did not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations. The Declarations were updated and reviewed again at the opening of the meeting.

Posted on 31 August 2015, updated 15 October 2015

HARVARD T.H. CHAN | SCHOOL OF PUBLIC HEALTH
Center for Health and the Global Environment

EXHIBIT 23-21
WIT: Rider
DATE: 9/21/17
Maureen Pollard, RMR

About Us: Scientific Advisor

Richard Clapp D.Sc, MPH
Professor Emeritus of Environmental Health, Boston University School of Public Health
Adjunct Professor, University of Massachusetts Lowell

Person Type:
Scientific Advisor

What does working with the Center mean to you?

My interest in the Center began when it was co-founded by my dear friend, the late Dr. Paul Epstein, and throughout its twenty-year history. I look forward to providing advice and assistance in its next phase of work, including the health impacts of poor indoor air quality.

Biography

An epidemiologist with more than forty years experience in public health practice, teaching, and consulting, Richard (Dick) Clapp is a both an Emeritus Professor of Environmental Health at Boston University School of Public Health and an Adjunct Professor at the University of Massachusetts Lowell. His research interests have focused on analyzing data related to environmental and occupational causes

of cancer and other diseases. He served as Director of the Massachusetts Cancer Registry from 1980-1989 and is a former Co-Chair of Greater Boston Physicians for Social Responsibility.

Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

Christopher J Portier,[1] Bruce K Armstrong,[2] Bruce C Baguley,[3] Xaver Baur,[4] Igor Belyaev,[5] Robert Bellé,[6] Fiorella Belpoggi,[7] Annibale Biggeri,[8] Maarten C Bosland,[9] Paolo Bruzzi,[10] Lygia Therese Budnik,[11] Merete D Bugge,[12] Kathleen Burns,[13] Gloria M Calaf,[14] David O Carpenter,[15] Hillary M Carpenter,[16] Lizbeth López-Carrillo,[17] Richard Clapp,[18] Pierluigi Cocco,[19] Dario Consonni,[20] Pietro Comba,[21] Elena Craft,[22] Mohamed Aqiel Dalvie,[23] Devra Davis,[24] Paul A Demers,[25] Anneclaire J De Roos,[26] Jamie DeWitt,[27] Francesco Forastiere,[28] Jonathan H Freedman,[29] Lin Fritschi,[30] Caroline Gaus,[31] Julia M Gohlke,[32] Marcel Goldberg,[33] Eberhard Greiser,[34] Johnni Hansen,[35] Lennart Hardell,[36] Michael Hauptmann,[37] Wei Huang,[38] James Huff,[39] Margaret O James,[40] C W Jameson,[41] Andreas Kortenkamp,[42] Annette Kopp-Schneider,[43] Hans Kromhout,[44] Marcelo L Larramendy,[45] Philip J Landrigan,[46] Lawrence H Lash,[47] Dariusz Leszczynski,[48] Charles F Lynch,[49] Corrado Magnani,[50] Daniele Mandrioli,[51] Francis L Martin,[52] Enzo Merler,[53] Paola Michelozzi,[54] Lucia Miligi,[55] Anthony B Miller,[56] Dario Mirabelli,[57] Franklin E Mirer,[58] Saloshni Naidoo,[59] Melissa J Perry,[60] Maria Grazia Petronio,[61] Roberta Pirastu,[62] Ralph J Portier,[63] Kenneth S Ramos,[64] Larry W Robertson,[65] Theresa Rodriguez,[66] Martin Röösli,[67] Matt K Ross,[68] Deodutta Roy,[69] Ivan Rusyn,[70] Paulo Saldiva,[71] Jennifer Sass,[72] Kai Savolainen,[73] Paul T J Scheepers,[74] Consolato Sergi,[75] Ellen K Silbergeld,[76] Martyn T Smith,[77] Bernard W Stewart,[78] Patrice Sutton,[79] Fabio Tateo,[80] Benedetto Terracini,[81] Heinz W Thielmann,[82] David B Thomas,[83] Harri Vainio,[84] John E Vena,[85] Paolo Vineis,[86] Elisabete Weiderpass,[87] Dennis D Weisenburger,[88] Tracey J Woodruff,[89] Takashi Yorifuji,[90] Il Je Yu,[91] Paola Zambon,[92] Hajo Zeeb,[93] Shu-Feng Zhou[94]

The International Agency for Research on Cancer (IARC) Monographs Programme identifies chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, and physical and biological agents that cause cancer in humans and has evaluated about 1000 agents since 1971. Monographs are written by ad hoc Working Groups (WGs) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publicly available scientific information on each substance and, through a transparent and rigorous process,[1] decides on the extent to which the scientific evidence supports that substance's potential to cause or not cause cancer in humans.

For Monograph 112,[2] 17 expert scientists evaluated the carcinogenic hazard for four insecticides and the herbicide glyphosate.[3] The WG concluded that the data for glyphosate meet the criteria for classification as a *probable human carcinogen*.

The European Food Safety Authority (EFSA) is the primary agency of the European Union for risk assessments regarding food safety. In October 2015, EFSA reported[4] on their evaluation of the Renewal Assessment Report[5] (RAR) for glyphosate that was prepared by the Rapporteur Member State, the German Federal Institute for Risk Assessment (BfR). EFSA concluded that 'glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential'. Addendum 1 (the BfR Addendum) of the RAR[5] discusses the scientific rationale for differing from the IARC WG conclusion.

Serious flaws in the scientific evaluation in the RAR incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate. Since the RAR is the basis for the European Food Safety Agency (EFSA) conclusion,[4] it is critical that these shortcomings are corrected.

THE HUMAN EVIDENCE

EFSA concluded 'that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma (NHL), overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies'. The BfR Addendum (p. ii) to the EFSA report explains that 'no consistent positive association was observed' and 'the most powerful study showed no effect'. The IARC WG concluded there is *limited evidence of carcinogenicity in humans* which means "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[1]

The finding of *limited evidence* by the IARC WG was for NHL, based on high-quality case–control studies, which are particularly valuable for determining the carcinogenicity of an agent because their design facilitates exposure assessment and reduces the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity

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of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7–1.9) with no apparent exposure–response relationship in the results. Despite potential advantages of cohort versus case–control studies, the AHS had only 92 NHL cases in the unadjusted analysis as compared to 650 cases in a pooled case–control analysis from the USA.[7] In addition, the median follow-up time in the AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency.[8]

The RAR classified all of the case–control studies as 'not reliable,' because, for example, information on glyphosate exposure, smoking status and/or previous diseases had not been assessed. In most cases, this is contrary to what is actually described in the publications. Well-designed case–control studies are recognised as strong evidence and routinely relied on for hazard evaluations.[9 10] The IARC WG carefully and thoroughly evaluated all available epidemiology data, considering the strengths and weaknesses of each study. This is key to determining that the positive associations seen in the case–control studies are a reliable indication of an association and not simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to quality rather than simply count the number of positives and negatives. The two meta-analyses cited in the IARC Monograph[11] are excellent examples of objective evaluations and show a consistent positive association between glyphosate and NHL.

The final conclusion[5] (Addendum 1, p.21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human cancer data.[1] *Sufficient evidence* means 'that a causal relationship has been established' between glyphosate and NHL. BfR's conclusion is equivalent to deciding that there is not *sufficient evidence*. Legitimate public health concerns arise when 'causality is credible', that is, when there is *limited evidence of carcinogenicity*.

EVIDENCE FROM ANIMAL CARCINOGENICITY STUDIES

EFSA concluded "No evidence of carcinogenicity was confirmed by the majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pairwise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/maximum tolerated dose (MTD), lack of preneoplastic lesions and/or being within historical control range". The IARC WG review found a significant positive trend for renal tumours in male CD-1 mice,[12] a rare tumour, although no comparisons of any individual exposure group to the control group were statistically significant. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice,[13] again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in male Sprague-Dawley rats.[14–16] In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. By the IARC review criteria,[1] this constitutes *sufficient evidence* in animals.

The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[1]). On the basis of the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished and available to EFSA. Two of the additional studies were reported to have a significant trend for renal tumours, one in CD-1 mice (Sugimoto. *18-Month Oral Oncogenicity Study in Mice*. Unpublished, designated ASB2012–11493 in RAR. 1997), and one in Swiss-Webster mice (Unknown. *A chronic feeding study of glyphosate (roundup technical) in mice*. Unpublished, designated ABS2012–11491 in RAR. 2001). One of these studies (Sugimoto. Unpublished, 1997) also reported a significant trend for hemangiosarcoma. The RAR also reported two studies in CD-1 mice showing significant trends for malignant lymphoma (Sugimoto. Unpublished, 1997; Unknown. *Glyphosate Technical: Dietary Carcinogencity Study in the Mouse*. Unpublished, designated ABS2012–11492 in RAR. 2009).

The RAR dismissed the observed trends in tumour incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3–1, p.90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines,[1 17 18] scientific reports[19] and publications[20–23] on this issue, the recommended first choice is the use of concurrent controls and trend tests, even in the EC regulations cited in the RAR[18] (see p.375). Trend tests are more powerful than pairwise comparisons, particularly for rare tumours where data are sparse. Historical control data should be from studies in the same time frame, for the same animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist.[17 18] While the EFSA final peer review[4] mentions the use of historical control data from the original laboratory, no specifics are provided and the only referenced historical control data[24] are in the BfR addendum.[5] One of the mouse studies[12] was clearly done before this historical control database was developed, one study (Sugimoto. Unpublished, 1997) used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[13] did not specify the substrain and was reported in 1993 (probably started prior to 1988). Hence, only a single study (Unknown. Unpublished, 2009) used the same mouse strain as the cited historical controls, but was reported more than 10 years after the historical control data set was developed.

The RAR dismissed the slightly increased tumour incidences in the studies considered because they occurred "only at dose levels at or above the limit dose/maximum tolerated dose (MTD)", and because there was a lack of preneoplastic lesions. Exceeding the MTD is demonstrated by an increase in mortality or other serious toxicological findings at the highest dose, not by a slight reduction in body weight. No serious toxicological findings were reported at the highest doses for the mouse studies in the RAR. While some would argue that these high doses could cause cellular disruption (eg, regenerative hyperplasia) leading to cancer, no evidence of this was reported in any study. Finally, a lack of preneoplastic lesions for a significant neoplastic finding is insufficient reason to discard the finding.

MECHANISTIC INFORMATION

The BfR Addendum dismisses the IARC WG finding that 'there is strong evidence that glyphosate causes genotoxicity' by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the reviewed studies were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. The use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion. Further weakening their interpretation,

the BfR did not include evidence of chromosomal damage from exposed humans or human cells that were highlighted in Tables 4.1 and 4.2 of the IARC Monograph.[3]

The BfR confirms (p.79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimise the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. In contrast, the WG concluded that (p.77) 'Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress'. From a scientific perspective, these types of mechanistic studies play a key role in distinguishing between the effects of mixtures, pure substances and metabolites.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Compliance with guidelines and Good Laboratory Practice does not guarantee validity and relevance of the study design, statistical rigour and attention to sources of bias.[25 26] The majority of research after the initial marketing approval, including epidemiology studies, will be conducted in research laboratories using various models to address specific issues related to toxicity, often with no testing guidelines available. Peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality, not just on compliance with guideline rules.

GENERAL COMMENTS

Science moves forward on careful evaluations of data and a rigorous review of findings, interpretations and conclusions. An important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the elements of transparency do not exist for the RAR.[5] For example, citations for almost all references, even those from the open scientific literature, have been redacted. The ability to objectively evaluate the findings of a scientific report requires a complete list of cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals where financial support, conflicts of interest and affiliations of authors are fully disclosed. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting.[27]

Several guidelines have been devised for conducting careful evaluation and analysis of carcinogenicity data, most after consultation with scientists from around the world. Two of the most widely used guidelines in Europe are the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[17] and the European Chemicals Agency Guidance on Commission Regulation (EU) No 286/2011;[18] both are cited in the RAR. The methods used for historical controls and trend analysis are inconsistent with these guidelines.

Owing to the potential public health impact of glyphosate, which is an extensively used pesticide, it is essential that all scientific evidence relating to its possible carcinogenicity is publicly accessible and reviewed transparently in accordance with established scientific criteria.

SUMMARY

The IARC WG concluded that glyphosate is a 'probable human carcinogen', putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* evidence for two carcinogenic mechanisms.

- The IARC WG found an association between NHL and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for rare kidney tumours and hemangiosarcoma in two mouse studies and benign tumours in two rat studies.
- The IARC WG concluded that there was strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

The RAR concluded[5] (Vol. 1, p.160) that 'classification and labelling for carcinogenesis is not warranted' and 'glyphosate is devoid of genotoxic potential'.

- EFSA[4] classified the human evidence as 'very limited' and then dismissed any association of glyphosate with cancer without clear explanation or justification.
- Ignoring established guidelines cited in their report, EFSA dismissed evidence of renal tumours in three mouse studies, hemangiosarcoma in two mouse studies and malignant lymphoma in two mouse studies. Thus, EFSA incorrectly discarded all findings of glyphosate-induced cancer in animals as chance occurrences.
- EFSA ignored important laboratory and human mechanistic evidence of genotoxicity.
- EFSA confirmed that glyphosate induces oxidative stress but then, having dismissed all other findings of possible carcinogenicity, dismissed this finding on the grounds that oxidative stress alone is not sufficient for carcinogen labelling.

The most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a *probable human carcinogen*. On the basis of this conclusion and in the absence of evidence to the contrary, it is reasonable to conclude that glyphosate formulations should also be considered likely human carcinogens. The CLP Criteria[18] (Table 3.6.1, p.371) allow for a similar classification of Category 1B when there are 'studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals'.

In the RAR, almost no weight is given to studies from the published literature and there is an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide. The IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of published scientific literature on glyphosate and, on the face of it, unpublished studies to which EFSA refers.

Most of the authors of this commentary previously expressed their concerns to EFSA and others regarding their review of glyphosate[28] to which EFSA has published a reply.[29] This commentary responds to the EFSA reply.

The views expressed in this editorial are the opinion of the authors and do not imply an endorsement or support for these opinions by any organisations to which they are affiliated.

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Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

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Commentary

IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans

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Background: Recently, the International Agency for Research on Cancer (IARC) Programme for the Evaluation of Carcinogenic Risks to Humans has been criticized for several of its evaluations, and also for the approach used to perform these evaluations. Some critics have claimed that failures of IARC Working Groups to recognize study weaknesses and biases of Working Group members have led to inappropriate classification of a number of agents as carcinogenic to humans.

Objectives: The authors of this Commentary are scientists from various disciplines relevant to the identification and hazard evaluation of human carcinogens. We examined criticisms of the IARC classification process to determine the validity of these concerns. Here, we present the results of that examination, review the history of IARC evaluations, and describe how the IARC evaluations are performed.

Discussion: We concluded that these recent criticisms are unconvincing. The procedures employed by IARC to assemble Working Groups of scientists from the various disciplines and the techniques followed to review the literature and perform hazard assessment of various agents provide a balanced evaluation and an appropriate indication of the weight of the evidence. Some disagreement by individual scientists to some evaluations is not evidence of process failure. The review process has been modified over time and will undoubtedly be altered in the future to improve the process. Any process can in theory be improved, and we would support continued review and improvement of the IARC processes. This does not mean, however, that the current procedures are flawed.

Conclusions: The IARC Monographs have made, and continue to make, major contributions to the scientific underpinning for societal actions to improve the public's health.

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Introduction

Important advances in human health have come from the recognition of health hazards and the development of policy actions to address them (Brownson et al. 2009; Espina et al. 2013; Samet 2000). Government and nongovernmental organizations use expert panels to review the scientific literature and to assess its relevance to public health policies. Scientific experts are charged with reviewing the quality and quantity of the scientific evidence and providing scientific interpretations of the evidence that underpin a range of health policy decisions.

The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* of the International Agency for Research on Cancer (IARC) are a prominent example of such an expert review process. The goal of the Monograph Programme is to assess carcinogenic hazards from occupational, environmental, and lifestyle exposures and agents, thus providing an essential step in the societal decision-making process to identify and then control carcinogenic hazards. For these evaluations, IARC assembles groups of scientists with a range of relevant scientific expertise (called "Working Groups") to review and assess the quality and strength of evidence from informative publications and perform a hazard evaluation to assess the likelihood that the agents of concern pose a cancer hazard to humans (Tomatis 1976). IARC has used this approach for four decades, since the first Monograph in 1972 (IARC 1972). Although widely accepted internationally, there have been criticisms of the classification of particular agents in the past, and more recent criticisms have been directed at the general approach adopted by IARC for such evaluations (Boffetta et al. 2009; Epidemiology Monitor 2012; Ioannidis 2005; Kabat 2012; McLaughlin et al. 2010, 2011).

The Monographs are widely used and referenced by governments, organizations, and the public around the world; therefore, it is critical that Working Group conclusions be clear and transparent. In addition to the actual evaluation, a major contribution of the Monographs is the assembly of relevant literature and its dissemination to the public. We recognize that no system of evaluation is perfect. It is important to foster continuing improvement of the methods used by IARC and other bodies that review scientific evidence. The IARC process itself has been modified from time to time (e.g., addition of specific evaluation of mechanistic data and greater use of formal meta-analyses and data-pooling approaches). Indeed, as recently as April 2014, the IARC Monographs program has been a subject of a review by the Advisory Group to recommend priorities for IARC Monographs during 2015–2019 (Straif et al. 2014). The Advisory Group has made a number of recommendations on further improvements in the Monographs process specifically related to conflict of interest, transparency, and the use of the systematic review procedures in data gathering and evaluation. Thus, possible changes to the process are periodically considered by IARC

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governing groups (Scientific Council and Governing Council) and Advisory Groups.

Here, we focus on current IARC processes and practices because these have been the focus of recent criticisms. The authors of this Commentary are scientists from a wide range of disciplines who are involved in designing and conducting studies that provide data used in hazard evaluations, such as those performed by IARC. Many (but not all) of us have served on IARC Monograph Working Groups, but none are current IARC staff. We first discuss the history of IARC, and describe how the IARC evaluations are performed in order to foster evidence-based policy. We then describe why unbiased evaluations, based on the evidence and free of conflicts of interest, are necessary for public health decision making. Finally, we discuss the recent criticisms of the IARC approach.

The IARC Monographs

History of the IARC Monographs. Shortly after IARC's establishment, its parent entity, the World Health Organization (WHO), asked IARC to prepare a list of agents known to cause cancer in humans. IARC recognized the need for a systematic process to determine which agents should be listed. Such a process was launched in 1972 by Lorenzo Tomatis, then Chief of the Division of Carcinogenicity of IARC (Tomatis 1976). IARC is funded by the governments of 24 countries that have decided to become members, in addition to competitive grants from funding agencies. The IARC Monograph Programme is mainly funded by the U.S. National Cancer Institute through a renewable grant subject to peer review of the program. Other sources of external funding have included the European Commission Directorate-General of Employment, Social Affairs and Equal Opportunities; the U.S. National Institute of Environmental Health Sciences; and the U.S. Environmental Protection Agency.

The IARC process antedates current systematic review methods, but anticipated some of them, for example, with regard to transparent literature identification. In the IARC process, agents are assessed for carcinogenic hazard and assigned to one of five categories, ranging from carcinogenic to humans to probably not carcinogenic to humans (Appendix 1). The classification categories are described in the preamble to the Monographs (IARC 2006). Carcinogenic hazard identification refers to an assessment of whether an agent causes cancer. Hazard identification does not predict the magnitude of cancer risks under specific conditions; this can be determined only with appropriate exposure–response information (National Research Council 2009).

The IARC Monograph process. The process for the preparation of an IARC Monograph is clearly described in the Preamble, which is published as part of each Monograph (e.g., IARC 2014a). It starts with the nomination of candidate agents. Nominations come from national regulatory agencies, scientists, and stakeholders, including public health professionals, experts in environmental or occupational hygiene, industry representatives, and private citizens. It is important to note that anyone (including private citizens) can participate in the nomination process. The Monograph Programme convenes meetings of special Advisory Groups (composed of external scientists that possess a broad range of relevant professional skills) to review agents nominated for evaluation and to suggest IARC priorities for such reviews (Ward et al. 2010). Announcements of a review are made on the IARC website (http://monographs.iarc.fr/ENG/Meetings/). For example, in 2013 IARC sought nominations for agents to be evaluated in 2015–2019 (IARC 2014b). An Advisory Group reviewed the nominated agents and exposures, added several new ones, and discussed the priorities for each.

The IARC staff makes the final selection of agents for review by taking into account the prevalence and intensity of exposure (of both occupational groups and the general population) and availability of sufficient literature for an evaluation of carcinogenicity, as well as advice from the Advisory Groups. The large majority of evaluations concern specific compounds, but there are also monographs on various occupations or industries, for example, aluminum production, insecticide applicators, firefighters, manufacture of leather goods, leather tanning and processing, welding, painters, petroleum refining, and pulp and paper manufacturing. Some individual exposures that occur in these settings have also been evaluated.

The next step is the selection of members of the Working Group (WG). IARC staff review the literature to identify Working Group candidates and specialists in relevant areas of expertise; they also seek names of possible candidates from the scientific community and advisory groups. The list of potential members, including disclosure of relevant conflicts of interest, is posted on the IARC website (http://monographs.iarc.fr/ENG/Meetings/) before the WG is convened, and anyone can send comments. Members are typically scientists who have conducted research relevant to the agent under review, but not necessarily on the specific agent. Selection procedures are evaluated yearly by the Scientific and the Governing Councils. The IARC Section of Monographs also has an external Advisory Board, made up of independent scientists, that periodically peer reviews its activities. In addition to Working Group members, invited specialists, representatives of health agencies, stakeholder observers, and the IARC Secretariat also attend meetings.

The responsibility of the Working Group is to review the literature before the Monograph meeting, discuss the literature at the meeting, and then classify whether an agent is carcinogenic, probably carcinogenic, possibly carcinogenic, not classifiable, or probably not carcinogenic to humans (see Appendix 1). Working Group members are also responsible for writing the IARC Monograph, which must both review the literature and explain why the Working Group came to their specific conclusions.

The procedures used to evaluate the scientific evidence are described in the Preamble to the Monographs (IARC 2006). It is important to stress that only Working Group members conduct the actual evaluation (Wild and Cogliano 2011; Wild and Straif 2011). IARC staff facilitate the evaluation process and ensure that the procedures described in the Preamble are followed; however, they do not determine the outcomes.

IARC assessments of carcinogenicity are based on, and necessarily limited to, scientific evidence available at the time of the review. The evidence comes from epidemiologic studies, animal bioassays, pharmacokinetic/mechanistic experiments, and surveys of human exposure. The aim is to include all relevant papers on cancer in humans and experimental animals that have been published, or accepted for publication, in peer-reviewed scientific journals and also any publicly available government or agency documents that provide data on the circumstances and extent of human exposure. To that end, the search of the literature takes a comprehensive approach. Papers that are found not to provide useful evidence can be excluded later in the process. IARC staff first use previous IARC Monographs (if available), database searches using relevant text strings, and contact with investigators in the field to identify potentially relevant material. Thus, the initial assembly of the literature is performed by individuals who are not engaged in the actual evaluation. Working Group members are then assigned various writing tasks and are instructed to perform their own literature searches to identify any further papers that might have been missed. In addition, all of the papers assembled by IARC are made available to the full Working Group before they meet, and any member can recommend other papers not previously identified that they think should be considered. Finally, papers can be recommended by stakeholder representatives before or during the Working Group meeting.

At the meeting of the Working Group, the assembled documents are reviewed and summarized by discipline-related subgroups.

However, any member of the Working Group has access to all of the assembled literature. The summaries are distributed to all subgroups, and information from all disciplines is discussed in plenary sessions prior to assigning the agents to a specific carcinogenicity category.

Because new findings continually emerge in the literature, agents are reconsidered when IARC and IARC Advisory Groups judge that there is sufficient additional information that might alter a previous evaluation. Thus, conclusions regarding human carcinogenicity of particular substances may change as new evidence becomes available. For some agents, this reevaluation has resulted in progression toward greater certainty regarding their human carcinogenicity, whereas for others the progress has been moved toward less certainty. Such movements are expected in an open, transparent, and evidence-based process. A comprehensive update of all Group 1 carcinogens was recently accomplished in Volume 100 A through F (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php).

Usually, several agents are evaluated in a single meeting lasting more than 1 week. After discussing the evidence fully, the Working Group members follow the published IARC procedures for combining information from epidemiologic studies and bioassays to arrive at a preliminary classification (IARC 2014a). Mechanistic data are then considered in order to determine whether they warrant a change from the preliminary classification. The Working Group then votes on the final determination. Many votes are unanimous, but on occasion some reviewers may favor a higher or lower ranking than the majority. When there is dissent, alternative interpretations and their underlying reasoning are sometimes reported in the rationale for the evaluation if the dissenters feel their point of view is not sufficiently addressed in the monograph.

Consideration of the totality of the evidence. IARC Working Groups make every effort to provide full and transparent documentation of what evidence was assembled, how it was evaluated, and which papers were most important for the hazard evaluation. Consequently, the monographs are often quite lengthy, containing many evidence tables [see, for example, the recent monograph on trichloroethylene (IARC 2014c)]. Evaluations involve consideration of all of the known relevant evidence from epidemiologic, animal, pharmacokinetic/mechanistic, and exposure studies to assess cancer hazard in humans. Information on human exposure is not formally graded as part of the overall assessment of carcinogenic hazard; however, these data make a critical contribution to the process by characterizing the timing, duration, and levels of exposure in the population, and in evaluating the quality of the exposure assessment in epidemiologic studies.

Doubts and criticisms have sometimes been expressed about the relative weights attributed to evidence from individual disciplines to the assessment of cancer hazards to humans; however, each discipline provides important evidence toward the overall evaluation of causality according to the Bradford Hill considerations (Hill 1965). Because the totality of the evidence is considered, deficiencies in one discipline are often offset by strengths in another. For example, epidemiologic studies may focus on population-relevant exposures, whereas findings from animal experiments usually involve higher exposures but are less susceptible to confounding.

Long-term animal bioassays and mechanistic studies provide critical information on the capacity of an agent to produce cancer in mammalian systems, including humans, and to contribute to decisions that would lead to better protection of human health. Bioassays are the backbone of regulatory science because they provide the opportunity to rigorously evaluate potential hazards before there is widespread human exposure. Bioassays and mechanistic studies are sometimes criticized for employing exposure routes and doses that in most instances humans would not experience, although experimental dose categories sometimes approach exposure levels found in occupational situations. There is evidence that carcinogenicity in human and animal studies is often concordant, although data may differ as to the affected cancer site (Haseman 2000; Maronpot et al. 2004; Tomatis 2002). A major effort to evaluate the concordance between animal and human results is currently under way; two Working Groups were convened at IARC in 2012, and a systematic evaluation of the correspondence between human and animal data was undertaken (a report is not yet publicly available).

Criticisms of the IARC Process

IARC Monographs are widely used to identify potential carcinogenic hazards to humans and serve as reference documents summarizing the literature on many different agents. In recent years, however, individuals have criticized both the classification of individual agents as well as the general evaluative approach (Boffetta et al. 2009; Epidemiology Monitor 2012; Kabat 2012; McLaughlin et al. 2010, 2011). We discuss four of these criticisms below.

Criticisms of epidemiology. Some of the criticisms of the IARC process have occurred in the context of more general criticisms of epidemiology as a science (Kabat 2008); these were discussed in detail by Blair et al. (2009). Potential methodological weaknesses for observational epidemiologic studies are well recognized and can be found in any epidemiologic textbook (Checkoway et al. 2004; Rothman et al. 2008). Most studies are subject to one or more methodological limitations, but this does not necessarily invalidate their findings (Blair et al. 2009). In fact, the value of epidemiologic studies has been shown by the identification of a number of well-established human carcinogens, including tobacco, asbestos, benzene, hexavalent chromium, and some viruses, in multiple studies. Some critics also argue that small or nonexistent health risks are unjustifiably highlighted and hyped by researchers who have a vested interest in continued research funding and the need to publish to benefit their careers (Boffetta et al. 2008; Kabat 2008; McLaughlin et al. 2010, 2011; Taubes 1995). However, such overstated results are unlikely to exert much of an influence in a Monograph because IARC evaluations are based on the totality of the evidence. The problem would have to occur in multiple studies, and the Working Group would have to be unable to identify it or be unwilling to weigh such studies appropriately. Incorrect positive conclusions regarding carcinogenicity may also occur in reviews of multiple studies because of publication bias, which may selectively populate the literature only with "positive" findings. However, once a topic is recognized as scientifically important, reports on relevant studies will be published regardless of the findings, so publication bias is mainly a concern for newly arising issues. To evaluate the potential for publication bias, Working Groups consider whether stronger negative studies (both in terms of design and sample size) have emerged after publication of an initial cluster of smaller and/or weaker positive studies. Funnel plots help in the assessment of bias relating to sample size and publication bias (Borenstein et al. 2009). In contrast, there are no established statistical techniques to clearly characterize strength of design.

One of the distinctive features of epidemiology is that criticism and self-criticism are firmly embedded in the discipline. A great deal of work has been done on developing methods for critical appraisal (Elwood 2007) and for assessing the likely strength and direction of possible biases (Rothman et al. 2008). Epidemiologists and other members on Working Groups routinely use various approaches to assess possible bias in study design and analysis when weighing the strengths of different studies.

The issue of false positives. Epidemiology specifically has been criticized for a tendency to produce false-positive results (i.e., individual study associations not borne out by the weight of the evidence) or to preferentially report positive findings over negative

or inconclusive findings (i.e., publication bias) (Bofferta et al. 2008, 2009; Ioannidis 2005; Kabat 2012; McLaughlin and Tarone 2013). This criticism has been most often applied to potential false positives from individual studies, but it has been inferred that this problem may also apply to overall hazard evaluations, which use findings from multiple studies. We will consider each of these issues in turn.

False-positive findings may occur by chance, particularly when many combinations of exposures and health outcomes have been examined in a single study without strong prior expectations of association; this happens often, for example, in genome-wide association studies where thousands of gene–disease associations are evaluated. Chance, of course, operates in all disciplines and in both observational and experimental studies. However, there are well-known statistical techniques to reduce the probability of declaring chance findings as "positive" (Rothman et al. 2008). Independent replication, however, is the most convincing way of checking for "chance" findings; hazard evaluations, such as those conducted by IARC Working Groups, rely heavily on reproducibility in independent studies and also interpret data following Bradford Hill principles (Hill 1965).

False negatives are more difficult to address, and perhaps they occur more frequently than false positives because of low statistical power, nondifferential misclassification of exposure and/or outcome, and incomplete follow-up, which tends to reduce the observed difference in risk between the exposed and nonexposed populations (Ahlbom et al. 1990; Blair et al. 2009; Grandjean 2005; Rothman et al. 2008). A new positive association stimulates research, whereas studies finding no associations tend to stifle further work.

There are difficulties in conducting epidemiologic studies of agents that are relatively "weak" carcinogens, or for stronger carcinogens where exposure is very low because bias and confounding can obscure weak positive associations (MacMahon et al. 1981). In general, weak carcinogens and low levels of exposure result in a smaller "signal-to-noise" ratio making the real signal more difficult to detect. Although the identification of small relative risks to humans poses special challenges to scientific research, the refinement of study designs, improvements in methods of exposure assessment, and the use of biomarkers have helped to address the problems (e.g., newer studies on the effects of air pollution, the growth in opportunities to examine gene–environment interactions) (Gallo et al. 2011). In some situations, there is less of a problem. For example, in occupational studies, exposures and relative risks may be higher while differences in lifestyle factors between different groups of workers are smaller (Checkoway et al. 2004); thus, any confounding by nonoccupational factors is likely to be weak, even from potent causes of cancer such as cigarette smoking (Siemiatycki et al. 1988). Of course, the interpretation of such studies is enhanced when there is supporting evidence from bioassays and/or mechanistic studies.

False-positive and false-negative findings in individual studies may arise by chance or bias, including bias due to confounding (Rothman et al. 2008). However, the evaluation of multiple independent epidemiologic studies from various geographic locations, involving a variety of study designs, as well as evidence from experimental studies, reduces the possibility that false-positive findings from any individual study influences the overall evaluation process. Some studies may have greater influence than others because of methodological strengths and/or large sample size. The use of information from a variety of study designs reduces the likelihood of false-positive evaluations because it is unlikely that the same biases will occur in multiple studies based on different populations under different study designs. Moreover, apparently conflicting results from epidemiologic studies do not necessarily indicate that some are false positive or false negative. This might, for example, reflect differences in levels of exposure or susceptibility to the effects of exposure (effect modification). Finally, judgment by the Working Group is not based exclusively on epidemiologic studies but usually also on results from laboratory and mechanistic studies that provide further evidence and biological coherence. For the Monographs that evaluate carcinogenic hazards associated with specific occupations or industries, the exposures of interest usually involve a complex mixture of chemicals. For these evaluations, most information comes from epidemiologic studies, although exposures to individual agents occurring at these workplaces may have been evaluated in experimental studies.

Discontent with IARC Monograph processes. The IARC Monograph evaluation process has been criticized and it has been alleged that "a number of scientists with direct experience of IARC have felt compelled to dissociate themselves from the agency's approach to evaluating carcinogenic hazards" (Kabat 2012). This is a serious charge. However, the author of this claim provided no evidence to support the charge that a "number of scientists" have dissociated themselves from the process, nor has there been any indication of how many scientists have taken this step, or for what reason. In science, we expect sweeping statements such as this to be appropriately documented. We have not been able to identify any credible support for this contention.

There is an IARC Governing Council and a Scientific Council to provide oversight and guidance to the agency. The Governing Council represents the participating states and sets general IARC policy. It appoints the IARC Director and members of the Scientific Council. The latter are independent scientists who are selected to provide scientific expertise and not as representatives of the member states. They serve for 4 years and serve without pay. The voting members of Monograph Working Groups are not employed by IARC, and they perform this task without financial compensation. There have been 111 volumes, including six separate documents under Volume 100, and three Supplements. Over the years, as the number of publications for each agent to be evaluated increased, the size of Working Groups has increased. Early in the process they were sometimes as small as 10, but now they sometimes include as many as 30 scientists. We estimate that over the entire Monograph series, approximately 1,500 scientists have served as Working Group members, and of course many scientists have also served on the Advisory Groups, Scientific Council, and Governing Council. Thus, if even a small percentage of these scientists were disenchanted with the IARC process, it would result in a considerable number of such individuals and should be easy to document. To be taken seriously, the "dissociation" criticism needs to be supported by documented information describing the number of scientists who have taken this action.

Criticisms of specific evaluations. Some criticisms of the IARC process relate to specific agents, where it is asserted that the hazard evaluations of category 2B, 2A, or 1 are not supported by the scientific literature. In the 111 volumes of the Monographs produced over the four decades since 1971, 970 agents have been considered, 114 (12%) have been classified as carcinogenic to humans (Group 1), 69 (7%) as probably carcinogenic (Group 2A), 283 (29%) as possibly carcinogenic (Group 2B), 504 (52%) as not classifiable regarding their carcinogenicity (Group 3), and 1 (< 1%) as probably not carcinogenic to humans (Group 4). Thus, even for this highly select group of agents (i.e., those selected for evaluation because there was some concern that they might be carcinogenic), more than one-half were "not classifiable" or "probably not carcinogenic," and a further 29% were placed into the category of possibly carcinogenic to humans. This distribution, based on nearly 1,000 evaluations in which fewer than one in five agents were classified as carcinogenic or probably carcinogenic to humans, does not support a conclusion that the process is heavily biased

toward classifying agents as carcinogenic (Boffetta et al. 2009; Kabat 2012).

The monographs for formaldehyde, coffee, DDT, and radiofrequency electromagnetic radiation have been cited as examples of problematic evaluations by some (Kabat 2012) [among these, only formaldehyde was classified as known to be carcinogenic to humans (Group 1) by an IARC Working Group]. These are important agents. However, to accept the charge that IARC evaluations are fundamentally biased, one has to assume that the scientists who were members of the Working Groups were incapable of appropriately evaluating weaknesses in the data, or that they distorted the evaluative process because of personal biases. In our experience, neither of these assertions is correct. Dissent among scientists is not unusual in any area of science. It is a strength of the scientific process. The IARC process capitalizes on this by bringing scientists from different disciplines together in one room to evaluate the literature and to reach a reasoned conclusion. Differences of opinion occur among Working Group members. These differences, however, typically involve disputes related to assignment to adjacent classification categories. It is instructive that there are no instances in which a carcinogen classified at the Group 1 level by one Working Group has been reversed by another. The recent review of all Group 1 agents for Volume 100 provided ample opportunity to reverse such previous classifications, but none occurred. Every scientist could probably name a substance that has been reviewed by IARC that they might personally place in a different category from that assigned by the Working Group, but this is one opinion against the collective wisdom and process of the Working Group.

Criticisms of the composition of the working groups. The composition of the Working Groups has also been criticized (Erren 2011; McLaughlin et al. 2010, 2011); it has been argued that members of the Working Groups who have conducted research on the agents under evaluation have a vested interest in advancing their own research results in the deliberations. This criticism has been addressed directly by Wild and colleagues (Wild and Cogliano 2011; Wild and Straif 2011) from IARC, and we know of no evidence to support this contention. Even if some scientists on the Working Group have performed research on some of the agents being considered, they make up a minority of the Working Group because several agents are usually evaluated in a single meeting, so the number of Working Group members who have conducted research on any one agent is typically small. Our experience has been that having some scientists who are knowledgeable about the studies of the agent under evaluation (and can therefore answer technical queries) and others from different, but related, fields provides a knowledgeable and balanced mix of scientific backgrounds for a thoughtful evaluation of the literature.

Working Group members do not receive any fee for their work, but they are paid travel expenses, and there is some prestige associated with service on an IARC Monograph. However, most scientists asked to serve on IARC Working Groups have already achieved some measure of scientific stature, and there is no reason why this should bias their evaluation in one direction or the other. In addition,

Appendix 1: Classification Categories for the Overall Evaluation for the IARC Monographs (IARC 2006)

Group 1: The agent is *carcinogenic to humans.*
This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic.*

Group 2A: The agent is *probably carcinogenic to humans.*
This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*
This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*
This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of noncarcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

IARC strictly requires that any conflict of interests be divulged, and does not allow those with conflicts of interest to serve on Working Groups, although nonvoting observers who may have conflicts of interest are able to attend the Working Group meetings.

Conclusions

For more than four decades the IARC Monograph Programme has provided evaluations of cancer hazards to humans from many different exposures and agents. These are often the first evaluations of new and emerging threats to public health and, consequently, are subject to intense scrutiny. Although these evaluations are widely respected and used by many organizations, institutions, companies, and government agencies to improve the public's health, IARC has recently been subject to criticism over conclusions on specific agents, the process that leads to such conclusions, and membership of the Working Groups. Debate and criticism facilitate self-correction and a check on the validity in science. We are concerned, however, that the criticisms expressed by a vocal minority regarding the evaluations of a few agents may promote the denigration of a process that has served the public and public health well for many decades for reasons that are not supported by data.

There has been very broad involvement of the scientific community in the IARC Monograph Programme through participation in the Working Groups and service on the IARC Governing and Scientific Councils and ad hoc Advisory Board for the Monograph Programme. The long list of scientists who are coauthors of this paper attests to the strong support that IARC has in the scientific community. Many exposures that IARC has evaluated have also been independently evaluated by other institutions, such as the U.S. National Toxicology Program (https://ntp.niehs.nih.gov/); U.S. Environmental Protection Agency (http://www.epa.gov/); National Academy of Sciences (http://www.nasonline.org/); the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (http://www.acgih.org/); the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (http://www.av.se/arkiv/neg/); Institute of Occupational Medicine (http://www.iom-world.org/); World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) Expert Reports; European Chemicals Agency (https://echa.europa.eu); Swedish Criteria Group for Occupational Standards (2013); California Office of Environmental Hazard Assessment (Proposition 65; http://oehha.ca.gov/prop65/background/p65plain.html), Health Canada's Bureau of Chemical Safety (http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/fd-da/bcs-bsc/index-eng.php); Scientific Committee on Occupational Exposure Limits (SCOEL), European Commission, Employment, Social Affairs and Inclusion (http://ec.europa.eu/social/main.jsp?catId=148&langId=en&intPageId=684); European Food Safety Authority (EFSA 2013); and European Chemicals Agency (ECHA; http://echa.europa.eu/). Assessments from these groups typically come to conclusions similar to those from IARC. This further indicates broad agreement within the scientific community regarding evidence on carcinogenicity in the scientific literature and expands the number of scientists who do not have a "vested interest" but who have generally agreed with those conclusions.

Disagreement with the conclusions in an IARC Monograph for an individual agent is not evidence for a failed or biased approach. Some disagreement about the carcinogenic hazard of important agents seems inherent to the scientific enterprise and is unavoidable at early stages of the hazard evaluation, where IARC usually operates. Because the evaluations are not—and should not be—static, it is difficult to see how such assessments could be addressed any differently. Substances now universally recognized as human carcinogens (e.g., tobacco, asbestos) at one time went through a quite lengthy period of contentious debate (Michaels 2006, 2008). Any process can in theory be improved with fair and constructive criticism; appropriate reviews may take place from time to time, and we would support continued review and improvement of the IARC processes. However, as a group of international scientists, we have looked carefully at the recent charges of flaws and bias in the hazard evaluations by IARC Working Groups, and we have concluded that the recent criticisms are unfair and unconstructive.

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