

Table B.6.5-60: Incidence of malignant lymphoma at terminal sacrifice in the study by ██████████ (1997, ASB2012-11493), revised

Sex	Male				Female				
	Dose group (ppm)	0	1600	8000	40000	0	1600	8000	40000
78 Tk (N=)	(26)	(34)	(27)	(29)	(32)	(36)	(40)	(35)	
Hematopoietic & Lymphatic system:	0	0	1	5*	4	8	8	0*	
General: Malignant lymphoma	0	0	0	2	4	0*	5	3	

Tk: Terminal kill

(N=): Number of animals examined

* p<0.05 (Fisher's exact probability test)

If these figures are used, the paragraph that is written below in the original text becomes clear.

Total incidence of malignant lymphoma (including animals that were prematurely found dead or had to be killed in extremis) is given in the following Table B.6.5-61 that was introduced by the RMS.

Table B.6.5-61: Total incidence of malignant lymphoma in the study by ██████████ (1997)

Sex	Male				Female				
	Dose group (ppm)	0	1600	8000	40000	0	1600	8000	40000
No. examined	50	50	50	50	50	50	50	50	
Hematopoietic & Lymphatic system:									
General: Malignant lymphoma	2	2	0	6	6	4	8	7	

The slight increase in high dose males was not statistically significant. Unfortunately, no historical control data for malignant lymphoma from the performing laboratory was provided. On request, the GTF submitted historical control data for malignant lymphoma from the performing laboratory (Kitazawa, 2013; ASB2014-9146). A total of 9 long-term studies (no information on actual duration provided) in the same mouse strain was covered that had been performed or at least terminated (perhaps commenced before) between 1993 and 1998, i.e., exactly the time in which the study under review was conducted. In male mice, the total incidence of malignant lymphoma in control groups varied considerably, ranging from ca 4 (actually 3.58) to ca 19 % (19.23). In fact, 8 of 9 studies had a control incidence below 12 % (6 % or lower) as observed now at the top dose level but, in principle, this incidence fell into the historical control range. Thus, the conclusion is that the higher incidence at the exaggerated dose level of 40,000 ppm as compared to the control group is a chance findings and cannot be used to support the assumption of a carcinogenic effects of glyphosate in mice that is based on the results of the study by ██████████ (2001, ASB2012-11491). In female control groups, malignant lymphoma incidence was between 8 and 27 % and, thus, the actual incidences in the control and treated groups were well covered.

Furthermore, it was noted that the study director was actually Mika Kinoshita. The report writer (Kayoko Sugimoto) was as a pathologist involved in histopathological examination.

B.6.5.3 Published data on carcinogenicity (released since 2000)

Epidemiology studies

A number of epidemiology studies over the last decade have focused on pesticide exposure and associated health outcomes. Publications vary in the specificity of their conclusions regarding pesticides in general, classes of pesticides and in some cases individual insecticides, herbicides or fungicides. While some of these publications specifically mention glyphosate, few draw tenable associations with any specific cancer outcome. Publications suggesting glyphosate is associated with any cancer outcome are discussed below.

An essential consideration in both, risk assessment and interpreting the relevance of toxicology data is exposure assessment. An inherent low level of confidence exists for epidemiological studies where tenuous links to exposure exist. Suggested associations between health outcomes and any possible causative agent are merely speculation if exposures are not identifiable. Pivotal to the understanding of glyphosate exposure are data published by Acquavella et al. (2004, ASB2012-11528; 2005, ASB2012-11530), which quantified human systemic glyphosate exposure levels in farmer applicators and their families. The geometric mean systemic dose for farmers applying glyphosate, some of whom applied glyphosate to areas up to 400 acres, was 0.0001 mg/kg/day, approximately 0.03 % of the EU glyphosate acceptable operator exposure Level (AOEL) according to EU Review Report 6511/VI/99-final (21 January 2008, ASB2009-4191). The highest systemic dose, skewed well above the geometric mean, was 0.004 mg/kg/day, which is 1.95 % EU glyphosate AOEL according to EU Review Report 6511/VI/99-final (21 January 2008, ASB2009-4191) and 1.3 % of the current EU glyphosate acceptable daily intake (ADI) according to EU Review Report 6511/VI/99-final (21 January 2008, ASB2009-4191). Even lower systemic doses were determined for spouses and children, 0.00004 mg/kg and 0.0008 mg/kg, respectively. Multiple carcinogenicity studies have since been conducted by numerous glyphosate registrants demonstrating NOAELs of at least ten-fold higher than the highest dose tested in the study driving the current EU ADI calculation.

The largest epidemiological study of pesticide exposure and health outcomes in the United States is the Agricultural Health Study (AHS), which included glyphosate. Dozens of publications have resulted from data generated in this study of approximately 57,000 enrolled farmer applicators. Blair et al. (2009, ASB2012-11566) provided an overview of cancer endpoints associated with different agricultural chemicals reported in earlier AHS publications. Glyphosate was not reported to be associated with leukemia, melanoma, or cancers of the prostate, lung, breast, colon or rectum. De Roos et al. (2005, ASB2012-11605) reported AHS data evaluating glyphosate use and multiple cancer endpoints; no association was noted for glyphosate with all cancers, including cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate, melanoma, all lymphohematopoietic cancers, non-Hodgkin's lymphoma (NHL) and leukemia. In an earlier publication based on another data set, however, De Roos et al., (2003, ASB2012-11606) reported an association between NHL and glyphosate use. McDuffie et al. (2001, ASB2011-364) reported a non-significant positive association between self-reported glyphosate exposure and NHL in a Canadian study. Blair et al. (2009, ASB2012-11566) did not report an association between glyphosate use and NHL in the AHS data, but a "possible association" between glyphosate use and multiple myeloma was mentioned. The AHS publication reporting this refers to a "suggested association" between glyphosate use and multiple myeloma (De Roos et al., 2005, ASB2012-11605), yet it did not demonstrate significant increase in relative risk for multiple myeloma. Both De Roos papers will be discussed in more detail below. Interestingly, a subsequent AHS review paper for the President's Cancer Panel (Freeman, 2009, ASB2012-11623) specifically references De Roos (2005 ASB2012-11605) as providing no observed incidents of cancers of any type being associated with glyphosate.

Lee et al. (2005, ASB2012-11882) reported a glyphosate association with gliomas, with the odds ratio differing between self-respondents (OR = 0.4) and proxy respondents (OR = 3.1). The authors expressed concern that higher positive associations observed for proxy respondents with glyphosate and several other pesticides, and suggested perhaps more accurate reporting of proxies for cases, and underreporting by proxies for controls; proxy respondents were spouses in 62 % of cases versus 45 % of controls, leading to lower reported incidents in the control group.

Monge et al (2007, ASB2012-11909) investigated associations between parental pesticide exposures and childhood Leukaemia in Costa Rica. Results are not interpretable for glyphosate as exposure was estimated with “other pesticides”, including paraquat, chlorothalanyl and “others”. No association was noted for paternal exposures, but elevated leukaemias were associated with maternal exposures to “other pesticides” during pregnancy. Similarly, glyphosate is captured under “other pesticides” being associated with NHL by Fritschi et al. (2005, ASB2012-11624) and therefore should not be interpreted as an association with glyphosate.

Some further epidemiologic studies are focused on an association between pesticide exposure and Non-Hodgkin's Lymphoma (NHL). Hardell and Eriksson (1999, ASB2012-11838) investigated in a case-control study the incidence of NHL in relation to pesticide exposure in Sweden. 404 cases and 741 controls have been included. The authors discussed an increased risk for NHL especially for phenoxyacetic acids. Glyphosate was included in the uni-variate and multi-variate analyses. However, only 7 of 1145 subjects in the study gave exposure histories to this agent. The authors reported a moderately elevated odds ratio (OR) of 2.3 for Glyphosate. This OR was not statistically significant and was based on only 4 “exposed” cases and 3 “exposed” controls. The major limitations of this study were: the reliance on reported pesticide use (not documented exposure) information, the small number of subjects who reported use of specific pesticides, the possibility of recall bias, the reliance on secondary sources (next-of-kin interviews) for approximately 43 % of the pesticide use information, and the difficulty in the controlling for potential confounding factors given the small number of exposed subjects.

A further study was submitted by Hardell et al. (2002, ASB2012-11839). This study pools data from the above mentioned publication by Hardell and Eriksson (1999, ASB2012-11838) with data from a previously submitted publication from Nordström, Hardell et al. (1998, TOX1999-687).

The authors found increased risks in an uni-variate analysis for subjects exposed to herbicides, insecticides, fungicides and impregnating agents. Among herbicides, significant associations were found for glyphosate and MCPA. However, in multi-variate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above, not for glyphosate. No information is given about exposure duration, exposure concentration, as well as medical history, lifestyle factors (e.g. smoker, use of prescribed drugs etc.). In all, the above mentioned limitations of the publication from Hardell and Eriksson (1999, ASB2012-11838) are also the limitations of the publication from Hardell et al. (2002, ASB2012-11839).

Fritschi et al. (2005, ASB2012-11624) submitted a case-control study with 694 cases of NHL and 694 controls in Australia. Substantial exposure to any pesticide was associated with an increase of NHL. However, no association between NHL and glyphosate can be made on basis of this study. No information was given about exposure duration, used glyphosate products, exposure duration and application rates. Therefore, the documentation is considered to be insufficient for assessment.

Eriksson et al. (2008, ASB2012-11614) reported a case-control study which included 910 cases of NHL and 1016 controls living in Sweden. The highest risk was calculated for MCPA. Glyphosate exposure was reported by 29 cases and 18 controls, and the corresponding odds ratio (OR) was 2.02. Results and reliability of the study are discussed below.

Alavanja et al. (2013, ASB2014-9174) reviewed studies on cancer burden among pesticide applicators and others due to pesticide exposure. In this article the epidemiological, molecular biology, and toxicological evidence emerging from recent literature assessing the link between specific pesticides and several cancers including prostate cancer, non-Hodgkin lymphoma, leukemia, multiple myeloma, and breast cancer were integrated. Glyphosate was reported to be the most commonly used in conventional pesticide active ingredient worldwide. The only association between the use of glyphosate and cancer burden described in this review was the result of Eriksson et al. (2008, ASB2012-11614) which was described above.

The following epidemiology publications report a lack of association between glyphosate and specific cancer types.

- Alavanja et al. (2003, ASB2012-11535) reported on prostate cancer associations with specific pesticide exposures in the AHS; glyphosate did not demonstrate a significant exposure-response association with prostate cancer.
- Multigner et al. (2008, ASB2012-11917) also reported a lack of association between glyphosate use and prostate cancer. This data appears to have also been reported by Ndong et al. (2009, ASB2012-11922).
- The lack of association between glyphosate use and prostate cancer was also supported recently in an epidemiology study of Farmers in British Columbia, Canada by Band et al. (2011, ASB2012-11555).
- Lee et al. (2004, ASB2012-11883) reported a lack of association between glyphosate use and stomach and esophageal adenocarcinomas.
- Carreon et al. (2005, ASB2012-11585) reported epidemiological data on gliomas and farm pesticide exposure in women; glyphosate had no association with gliomas.
- Engel et al. (2005, ASB2012-11613) reported AHS data on breast cancer incidence among farmers' wives, with no association between breast cancer and glyphosate.
- Flower et al. (2004, ASB2012-11620) reported AHS data on parental use of specific pesticides and subsequent childhood cancer risk among 17,280 children, with no association between childhood cancer and glyphosate.
- Andreotti et al. (2009, ASB2012-11544) reported AHS data where glyphosate was not associated with pancreatic cancer.
- Landgren et al. (2009, ASB2012-11875) reported AHS data on monoclonal gammopathy of undetermined significance (MGUS), showing no association with glyphosate use.
- Karunanayake et al. (2011, ASB2012-11865) reported a lack of association between glyphosate and Hodgkin's lymphoma.
- Pahwa et al. (2011, ASB2012-11987) reported a lack of association between glyphosate and multiple myeloma.
- Schinasi and Leon (2014, ASB2014-4819) published the results of epidemiologic research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to pesticides. Phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and lindane were positively associated with NHL. However, no association between NHL and glyphosate was reported.

- Kachuri et al. (2013, ASB2014-8030) investigated the association between lifetime use of multiple pesticides and multiple myeloma in Canadian men. Excess risks of multiple myeloma were observed among men reported using at least one carbamate pesticide, one phenoxy herbicide and \geq organochlorines. However, no excess risk was observed for glyphosate.
- Cocco et al. (2014, ASB2014-7523) investigated the role of occupational exposure to agrochemicals in the aetiology of lymphoma overall, B cell lymphoma and its most prevalent subtypes. No increased CLL risk in relation to glyphosate was evidenced.
- Alavanja and Bonner (2012, ASB2014-9173) reviewed studies on occupational pesticide exposure and cancer risk. Twenty one pesticides identified subsequent to the last IARC review showed significant exposure-response associations in studies of specific cancers. No significant association was observed for glyphosate.
- El-Zaemy and Heyworth (2012, ASB2014-9473) reported a case control study on the association between pesticide spray drift from agricultural pesticide application areas and breast cancer in Western Australia. The findings support the hypothesis that woman who ever noticed spray drift or who first noticed spray drift at a younger age had increased risk of breast cancer. However, it was not possible to examine whether the observed associations are the result of a particular class of pesticides.
- Pahwa et al. (2011, ASB2014-9625) investigated the putative association of specific pesticides with soft-tissue sarcoma (STS). A Canadian population-based case-control study conducted in six provinces was used on this analysis. The incidence of STS was associated with insecticides aldrin and diazinon after adjustment for other independent predictors. However, no statistically significant association between STS and exposure to glyphosate or other herbicides was observed.
- Koutros et al. (2011, ASB2014-9594) studied associations between pesticide and prostate cancer. No statistically significant positive association between pesticides and prostate cancer were observed. There was suggestive evidence on an increased risk (OR>1.0) with an increasing number of days of use of petroleum oil/petroleum distillate used as herbicide, terbufos, fonofos, phorate and methyl bromide. However, no increased risk (OR>1.0) was observed for glyphosate.

In summarizing AHS publications, Weichenthal et al. (2010, ASB2012-12048) noted that increased rates in the following cancers were not associated with glyphosate use; overall cancer incidence, lung cancer, pancreatic cancer, colon or rectal cancer, lymphohematopoietic cancers, leukemia, NHL, multiple myeloma, bladder cancer, prostate cancer, melanoma, kidney cancer, childhood cancer, oral cavity cancers, stomach cancer, esophagus cancer and thyroid cancer.

Mink et al. (2012, ASB2014-9617) submitted a comprehensive review of epidemiologic studies of glyphosate and cancer. To examine potential cancer risks in humans they reviewed the epidemiologic literature to evaluate whether exposure to glyphosate is associated causally with cancer risk in humans. They also reviewed relevant methodological and biomonitoring studies of glyphosate. The review found non consistent pattern of positive associations indicating a causal relationship between total cancer (in adults or in children) or any site-specific cancer and exposure to glyphosate.

Animal studies

Just recently (*i.e.*, after submission of the GTF dossier), a two-year study in rats was published (Séralini *et al.*, 2012, ASB2012-15514). Its main objective was to show a possible impact of long-term feeding of genetically modified (and glyphosate treated) maize to rats but three of the test groups were administered a commercially available formulation (Roundup

GT Plus, apparently authorised at least in Belgium) containing 450 g glyphosate/L at different concentrations ranging from 0.1 ppb (50 ng glyphosate/L) to 0.5 % (2.25 g glyphosate/L) in drinking water. In these groups, the authors reported alterations in some clinical chemistry (blood and urine) parameters and hormone levels and histopathological lesions concerning the liver and the gastrointestinal tract but also a higher incidence of mammary tumours in females resulting in a shorter lifespan. This study was heavily discussed in the scientific community as well as in the general public where it gained remarkable attention due to massive promotion although it was clearly flawed by many serious deficiencies. A major point of concern was the small group size of only 10 males and 10 females per dose, *i.e.*, the test design was that one of a subchronic study. Such a small number of animals is not appropriate for a long-term study because age-related changes cannot be adequately taken into account. Following the receipt of contributions from many MS authorities, a comprehensive critical assessment was published by EFSA (2012, ASB2012-15513, EFSA Journal, 2012, 10 (11), 2986). The conclusion was that "the currently available evidence does not impact on the ongoing re-evaluation of glyphosate...". This opinion on the Séralini study is agreed with and supported by the RMS.

In reaction to this publication a large number of letters was sent to the editor: Barale-Thomas (2012, ASB2013-10998), Berry (2012, ASB2013-10988), Grunewald (2012, ASB2013-11001), Hammond et al. (2012, ASB2013-10995), Heinemann (2012, ASB2013-10987), Langridge (2012, ASB2013-10986), Ollivier (2012, ASB2013-11000), Panchin (2013, ASB2013-10937), Pilu (2012, ASB2013-10992), Schorsch (2013, ASB2013-10996), Tester (2012, ASB2013-10994), Tien & Huy (2012, ASB2013-10984), Trewavas (2012, ASB2013-10989), Tribe (2012, ASB2013-10997), Wager (2012, ASB2013-10993), de Souza (2012, ASB2013-10999).

Chruszielska et al. (2000, ASB2013-9829) published a combined long term toxicity and carcinogenicity study in rats. The active substance glyphosate was used in the study and the study was performed on basis of OECD guideline 453. The number of animals per dose group and sex (85 animals) was even higher than required in guideline 453. Therefore, the study is considered to be relevant. No carcinogenic effects have been registered in the study.

George *et al.*, (2010, ASB2012-11829) used a 2-stage cancer model in mice to evaluate a glyphosate formulation for tumor promotion. A known tumor promoter, 12-o-tetradecanoyl-phorbol-13-acetate (TPA) was used as a positive control and for comparison with glyphosate effects after exposure to a tumor initiator, 7, 12-dimethylbenz[a]anthracene. Proteomics were later applied to extrapolate a basis for glyphosate formulation tumor promotion. The results are considered by the authors to indicate a tumor promoting potential of glyphosate. However, the formulation Roundup was used in the study and not the active substance glyphosate. Furthermore, the up- and down-regulation of protein expression is not sufficient to prove a carcinogenic effect.

Mechanistic studies

Andreotti et al. (2012, ASB2014-9198) investigated the interaction between pesticide use and genetic variants involved in lipid metabolism on prostate cancer risk. The authors examined the interactions between 39 pesticides and 220 single nucleotide polymorphisms (SNPs) in 59 genes. They found 17 interactions that displayed a significant monotonic increase in prostate cancer risk with pesticides exposure in one genotype and no significant association in the other genotype. The most noteworthy association was for ALOXE3 rs 3027208 and terbufos. A higher risk was also reported with this method for glyphosate and other pesticides. However,

the authors emphasize that glyphosate was not associated with prostate cancer risk in the main effect studies (Agricultural Health Study AHS).

Barry et al. (2011, ASB2014-9247) evaluated interactions between 39 pesticides and 394 tag single-nucleotide polymorphisms (SNPs) for 31 BER genes among 776 prostate cancer cases and 1444 male controls in a nested case-control study of Agricultural Health Study (AHS) pesticide applicators. The authors used likelihood ratio tests from logistic regression models to determine p-values for interactions between three-level pesticide variables and SNP (assuming a dominant model) and the false discovery rate multiple comparison adjustment approach. The authors observed notable interactions between several pesticides and BER gene variants with respect to prostate cancer. However, only fonofos x NEIL3 rs 1983132 showed an interaction fitting an expected biological pattern that remained significant after adjustment for multiple comparisons. No significant association was observed for glyphosate.

The following studies are described more detailed:

Author(s)	Year	Study title
Hardell, L. Eriksson, M.	1999	A Case-Control Study of Non-Hodgkin Lymphoma and Exposure to Pesticides. Cancer, Volume: 85, Number: 6, Pages: 1353-1360 ASB2012-11838

Abstract*

Background. The incidence of non-Hodgkin lymphoma (NHL) has increased in most Western countries during the last few decades. Immunodeficient conditions are established risk factors. In 1981, the authors reported an increased risk for NHL following exposure to certain pesticides. The current study was designed to further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL.

Methods. A population-based case-control study in northern and middle Sweden encompassing 442 cases and twice as many controls was performed. Exposure data were ascertained by comprehensive questionnaires, and the questionnaires were supplemented by telephone interviews. In total, 404 cases and 741 controls answered the questionnaire. Univariate and multi-variate analyses were performed with the SAS statistical data program.

Results. Increased risk for NHL was found for subjects exposed to herbicides (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0–2.5) and fungicides (OR, 3.7; 95% CI, 1.1–13.0). Among herbicides, the phenoxyacetic acids dominated (OR, 1.5; 95% CI, 0.9–2.4); and, when subclassified, one of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL (OR, 2.7; 95% CI, 1.0–6.9). For several categories of herbicides, it was noted that only exposure during the most recent decades before diagnosis of NHL was associated with an increased risk of NHL. Exposure to impregnating agents and insecticides was, at most, only weakly related to NHL.

Conclusion. Exposure to herbicides in total, including phenoxyacetic acids, during the decades before NHL diagnosis resulted in increased risk for NHL. Thus, the risk following exposure was related to the latency period. Fungicides also increased the risk for NHL when combined, but this group consisted of several different agents, and few subjects were exposed to each type of fungicide.

* Quoted from article

Klimisch evaluation

Reliability of study: Not reliable
Comment: Study prone to selection and recall bias. No evidence of relevant glyphosate exposures. Medical history was assessed, but not reported.
Relevance of study: Not relevant (Exposure to multiple chemicals and though glyphosate exposure data were convincing (7/1145 subjects) and statistically non-significant positive associations reported.)
Klimisch code: 3

Additional comments:

Hardell and Eriksson (1999, ASB2012-11838) conducted a case control study to look for associations between reported pesticide use and non-Hodgkin’s lymphoma (NHL). The study included 404 NHL cases and 741 controls. The measure of association in this study was the odds ratio (OR), a statistic that estimates of the ratio of disease rates (in this case NHL rates) for exposed and unexposed populations.

The authors reported statistically significant associations for NHL with: reported use of any herbicide (OR = 1.6), reported use of any fungicide (OR = 3.7), and reported use of 4-chloro-2-methylphenoxyacetic acid (OR = 2.7). The major limitations of this study were: the reliance on reported pesticide use (not documented exposure) information, the small number of subjects who reported use of specific pesticides, the possibility of recall bias, the reliance on secondary sources (next-of-kin interviews) for approximately 43 % of the pesticide use information, and the difficulty in controlling for potential confounding factors, given the small number of exposed subjects.

The authors also reported a moderately elevated OR of 2.3 for glyphosate. This OR was not statistically significant and was based on only four “exposed” cases and three “exposed” controls.

This study has several important limitations: no exposure assessment, dependence on next-of-kin’s recollections of study subjects’ pesticide use for approximately 43 % of study subjects, potential recall bias, and the very small number of subjects who reported using specific herbicides. The latter leads to findings that are statistically imprecise. Due to the potential for bias and the statistical imprecision, the results of this study are not convincing.

Author(s)	Year	Study title
Hardell, L. Eriksson, M. Nordstrom, M.	2002	Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: Pooled analysis of two Swedish case-control studies. Leukemia & Lymphoma Volume: 43 Number: 5 Pages: 1043-1049 ASB2012-11839

Abstract*

Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in uni-variate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26-2.42), insecticides (OR 1.43, CI 95% 1.08-1.87), fungicides (OR 3.11, CI 95% 1.56-6.27) and impregnating agents (OR 1.48, CI 95% 1.11-1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08-8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40-4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multi-variate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above.

- Quoted from article

Klimisch evaluation

Reliability of study:

Not reliable

Comment:

This publication combines the results of two previous studies by the authors on HNL (Hardell and Eriksson, 1999, ASB2012-11838) and HCL (Nordström, et al., 1998, TOX1999-687). No information about exposure duration, exposure concentration, as well as medical history, lifestyle factors (e.g. smoker, use of prescribed drugs etc). Study documentation is insufficient for assessment.

Relevance of study:

Not relevant (Due to reliability of data set drawn from Hardell and Eriksson, 1999, ASB2012-11838)

Klimisch code:

3

Additional comments:

This study pools data from the previously reviewed publication by Hardell and Eriksson (1999, ASB2012-11838) with data from Nordström et al. (1998, TOX1999-687). Therefore the discussion of limitations of Hardell and Eriksson (1999, ASB2012-11838) also applies to Hardell et al. (2002, ASB2012-11839) (see above).

Author(s)	Year	Study title
Fritschi, L. Benke, G. Hughes, A. M. Krickler, A. Turner, J. Vajdic, C. M. Grulich, A. Milliken, S. Kaldor, J. Armstrong, B. K.	2005	Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma American Journal of Epidemiology Volume: 162, Pages: 849-857 ASB2012-11624

Abstract*

Pesticide exposure may be a risk factor for non-Hodgkin's lymphoma, but it is not certain which types of pesticides are involved. A population-based case-control study was undertaken in 2000-2001 using detailed methods of assessing occupational pesticide exposure. Cases with incident non-Hodgkin's lymphoma in two Australian states (n = 694) and controls (n = 694) were chosen from Australian electoral rolls. Logistic regression was used to estimate the risks of non-Hodgkin's lymphoma associated with exposure to subgroups of pesticides after adjustment for age, sex, ethnic origin, and residence. Approximately 10 % of cases and controls had incurred pesticide exposure. Substantial exposure to any pesticide was associated with a trebling of the risk of non-Hodgkin's lymphoma (odds ratio = 3.09, 95 % confidence interval: 1.42, 6.70). Subjects with substantial exposure to organochlorines, organophosphates, and "other pesticides" (all other pesticides excluding herbicides) and herbicides other than phenoxy herbicides had similarly increased risks, although the increase was statistically significant only for "other pesticides." None of the exposure metrics (probability, level, frequency, duration, or years of exposure) were associated with non-Hodgkin's lymphoma. Analyses of the major World Health Organization subtypes of non-Hodgkin's lymphoma suggested a stronger effect for follicular lymphoma. These increases in risk of non-Hodgkin's lymphoma with substantial occupational pesticide exposure are consistent with previous work.

Quoted from article

Klimisch evaluation

Reliability of study:

Not reliable

Comment:

No information about exposure duration, used glyphosate products, exposure duration and application rates. Documentation is insufficient for assessment.

Relevance of study:

Not relevant (Multiple pesticide exposures. No definitive association between NHL and glyphosate can be made.)

Klimisch code:

3

Additional comments:

No information about exposure duration, used glyphosate products, exposure duration and application rates. Only multiple pesticide exposures are reported. No association between NHL and glyphosate can be made on basis of this study.

Author(s)	Year	Study title
De Roos, A. J. Zahm, S. H. Cantor, K. P. Weisenburger, D. D. Holmes, F. F. Burmeister, L. F. Blair, A.	2003	Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occupational and Environmental Medicine Volume: 60, Number: 9, Pages: -E11 ASB2012-11606

Abstract*

Background: An increased rate of non-Hodgkin's lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult.

Methods: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable.

Results: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these "potentially carcinogenic" pesticides suggested a positive trend of risk with exposure to increasing numbers.

Conclusion: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.

Quoted from article

Klimisch evaluation

Reliability of study:

Not reliable

Comment:

No useful information about exposure duration, exposure concentration, as well as medical history, lifestyle factors (e.g. smoker, use of prescribed drugs etc) were reported. Specific lymphomas are not identified (NHL captures all types of lymphoma other than Hodgkin's lymphoma). Documentation is insufficient to associate exposures with specific NHL diseases.

Relevance of study:

Not relevant (No report of identifying various types of lymphoma under the NHL umbrella; no definite association between specific NHL diseases and glyphosate can be made)

Klimisch code:

3

Additional comments:

No useful information about exposure duration, exposure concentration, as well as medical history, lifestyle factors (e.g. smoker, use of prescribed drugs etc) were reported. Specific lymphomas are not identified. The reported hierarchical regression did not find a statistically significant odds ratio for ever use of glyphosate and NHL.

Author(s)	Year	Study title
De Roos, A.J. Blair, A. Rusiecki, J.A. Hoppin, J.A. Svec, M. Dosemeci, M. Sandler, D.P. Alavanja, M.C.	2005	Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study Environmental Health Perspectives Volume: 113, Number: 1, Pages: 49-54 ASB2012-11605

Abstract*

Glyphosate is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. Although there has been little consistent evidence of genotoxicity or carcinogenicity from *in vitro* and animal studies, a few epidemiologic reports have indicated potential health effects of glyphosate. We evaluated associations between glyphosate exposure and cancer incidence in the Agricultural Health Study (AHS), a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. Detailed information on pesticide use and other factors was obtained from a self-administered questionnaire completed at time of enrolment (1993–1997). Among private and commercial applicators, 75.5% reported having ever used glyphosate, of which > 97% were men. In this analysis, glyphosate exposure was defined as a) ever personally mixed or applied products containing glyphosate; b) cumulative lifetime days of use, or “cumulative exposure days” (years of use × days/year); and c) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS. Given the widespread use of glyphosate, future analyses of the AHS will allow further examination of long-term health effects, including less common cancers.

* Quoted from article

Klimisch evaluation

Reliability of study:

Reliable without restrictions

Comment:

Well documented publication. Study included glyphosate exposure, as well as demographic and lifestyle factors. However, adjusted relative risk calculations eliminated a significant proportion of the data set without justification.

Relevance of study:

Relevant (Evaluation focussed on glyphosate, although other pesticides were also considered in the data evaluation)

Klimisch code:

2

Additional comments:

Study included glyphosate exposure, as well as demographic and lifestyle factors. However, adjusted relative risk calculations eliminated a significant proportion of the data set without justification.

Response 1 – summary from Letter to the Editor by Farmer et al. (2005, ASB2012-11616)

Authors provided an incomplete genotoxicity review which was inconsistent with opinions of regulatory agencies and experts around the world, that glyphosate is not genotoxic. An extensive toxicology review of glyphosate was cited by the authors, mentioning a lack of carcinogenicity with glyphosate exposures, yet neglected to cite the extensive genotoxicity review in the same publication by Williams et al. (2000, ASB2012-12053)

Biological plausibility of a cancer effect should be considered in the light of exposure. Acquavella et al (2004, ASB2012-11528) reported the maximum systemic dose to resulting from application of glyphosate to areas as large as 400 acres was 0.004 mg/kg, and the geometric mean systemic dose was 0.0001 mg/kg in farmers. If these glyphosate applications and exposures continued daily over the course of a lifetime, the systemic dose would be at least 250,000-fold lower than the cancer no-effect level in rodents.

The authors were requested to further evaluate their models for confounding and selection bias in the multiple myeloma analysis.

Response 2 – summary from Lash (2007, ASB2012-11877)

Table 2 of De Roos et al. (2005, ASB2012-11605) noted 32 cases of multiple myeloma associated with “ever-use” of glyphosate and when compared with “never-use” (adjusted for age only) yielded a rate ratio of 1.1 (95 % CI 0.5-2.4). However, when the data set was adjusted for age, demographic and lifestyle factors and other pesticide use, the rate ratio increased to 2.6 (95 % CI 0.7-9.4).

The adjusted estimate merits careful inspection and can only be undertaken with access to the primary data, not made available by the authors.

Bias analysis was conducted, accounting for confounding and exposure misclassification.

Adjustment for confounders in De Roos et al. (2005, ASB2012-11605), which resulted in limiting the data set by 25 % because of missing data on the adjustment variables, likely introduced selection bias and produced the a rate ratio of 2.6 that was substantially biased.

Author(s)	Year	Study title
Eriksson, M. Hardell, L. Carlberg, M. Akerman, M.	2008	Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis International Journal of Cancer Volume: 123, Pages: 1657-1663 ASB2012-11614

Abstract*

We report a population based case-control study of exposure to pesticides as risk factor for non-Hodgkin lymphoma (NHL). Male and female subjects aged 18-74 years living in Sweden were included during December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total 910 (91 %) cases and 1016 (92%) controls participated. Exposure to herbicides gave odds ratio (OR) 1.72, 95% confidence interval (CI) 1.18-2.51. Regarding phenoxyacetic acids highest risk was calculated for MCPA; OR 2.81, 95% CI 1.27-6.22, all these cases had a latency period >10 years. Exposure to glyphosate gave OR 2.02, 95% CI 1.10-3.71 and with >10 years latency period OR 2.26, 95% CI 1.16-4.40. Insecticides overall gave OR 1.28, 95% CI 0.96-1.72 and impregnating agents OR 1.57, 95% CI 1.07-2.30. Results are also presented for different entities of NHL. In conclusion our study confirmed an association between

exposure to phenoxyacetic acids and NHL and the association with glyphosate was considerably strengthened.

Quoted from article

Klimisch evaluation

Reliability of study:

Not reliable

Comment:

Multiple avenues for bias were introduced in study design, execution and data processing. No information about exposure duration, used glyphosate products and application rates. Other factors (i.e. smoking habits, medication etc.) were assessed but not included in the evaluation.

Relevance of study:

Relevant with reservation

Klimisch code:

3

Additional comments:

The authors (Eriksson et al. 2008, ASB2012-11614) conducted a population-based case-control study of exposure to a variety of pesticides and non-Hodgkin lymphoma (NHL), including separate analyses of histopathological categories of NHL. Study subjects were males and females, ages 18-74, living in Sweden between December 1, 1999 and April 30, 2002. The final study group included 910 cases and 1016 controls. Exposure, ascertained via an interviewer-administered questionnaire, focused on pesticide and other chemical agents, and included a total work history (although a job-exposure matrix was not used). For pesticide exposure, information on number of years, number of days per year, and approximate length of exposure per day was also obtained. A minimum of one full day of exposure was required for categorization as “exposed.”

The authors reported a statistically significant positive association between “herbicide exposure” and NHL (OR = 1.72; 95% CI: 1.18-2.51). Glyphosate exposure was reported by 29 cases and 18 controls, and the corresponding odds ratio (OR) was 2.02 (95% CI: 1.10-3.71). The ORs for glyphosate exposure of <10 days and >10 days were 1.69 (95% CI: 0.70-4.07) and 2.36 (1.04-5.37), respectively. The ORs for glyphosate were 1.11 (95% CI: 0.24-5.08) and 2.26 (95% CI: 1.16-4.40) for “latency” periods of 1-10 years and >10 years, respectively. In analyses of glyphosate and type of NHL, statistically significant positive associations were observed for small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) (OR = 3.35; 95% CI: 1.42-7.89) and for “unspecified NHL” (OR = 5.63; 95% CI: 1.44-22.0). Odds ratios for the other types (total B-cell lymphomas, grade I-III follicular lymphoma, diffuse large B-cell lymphoma, other specified B-cell lymphoma, unspecified B-cell lymphoma, and T-cell lymphomas) were above 1.0, but were not statistically significant (i.e., the 95% confidence intervals were relatively wide and included the null value of 1.0).

The authors concluded, “Glyphosate was associated with a statistically significant increased OR for lymphoma in our study, and the result was strengthened by a tendency to dose-response effect...” (p. 1662). The authors suggested that their findings are consistent with results of a previous case-control study (Hardell and Eriksson 1999, ASB2012-11838) and pooled analysis (Hardell et al. 2002, ASB2012-11839) that they conducted. In the case-control study, an OR of 2.3 (95% CI: 0.4-13.0), based on 4 exposed cases and 3 exposed controls, was reported for glyphosate and NHL. In the pooled analysis of two case-control studies, which included data from Hardell and Eriksson (1999, ASB2012-11838), an OR of

3.04 (95% CI: 1.08- 8.52) was reported, based on 8 exposed cases and 8 exposed controls. The authors also cited three studies (De Roos et al. 2003, ASB2012-11606; McDuffie et al. 2001; ASB2011-364, De Roos et al. 2005, ASB2012-11605) by other groups as being consistent with their results in that they “also associate glyphosate with different B-cell malignancies such as lymphomas and myelomas.” It should be noted, however, that the relative risk (RR) reported by De Roos et al. (2005, ASB2012-11605) for the highest versus lowest category of cumulative exposure days of glyphosate and NHL in the prospective Agricultural Health Study was 0.9.

Interpretation Issues

Identification of Cases and Potential Referral Bias. It is noteworthy that the cases in the current analysis were identified from some of the same hospitals as the authors’ prior publication; thus, referral bias may have been an issue. In particular, the researchers approached the patients after diagnosis if the physicians deemed it appropriate. Therefore, if the physicians were concerned that their patient’s NHL was associated with agricultural exposures, they may have suggested participation in the study.

Participation Rates and Potential Selection Bias. The authors report a participation rate of 91% and 92% for cases and controls, respectively; however, these figures are based on completed questionnaires out of those who had previously said they would participate in the study. The number of eligible patients (i.e., prior to physician approval to “approach”) was not reported, so the computation of an exact participation rate is difficult. Based on information provided in the paper, participation among cases is estimated to be about 80%. Nonparticipation is a concern for several reasons. First, in a case-control study, an odds ratio will be an accurate representation of the exposure-disease association when the cases are representative of all cases and the controls are representative of the exposure experience of the population that gave rise to the cases. If the final study sample is not representative of this “target population” then measures of effect (e.g., the odds ratio) may not be valid. In addition, one must be concerned about selection bias. Selection bias occurs in a case-control study when the exposure distribution for cases and controls differ for those who participate in the study compared to those who are eligible but do not participate in the study. It is not possible to determine whether there is selection bias without information about nonparticipants.

Strengths and Limitations of Using Living Cases Only versus All Cases (Living + Dead).

The authors noted that 88 potential cases died before they could be interviewed and were therefore excluded from the study. It is also stated in the Discussion that restricting the study to living cases and controls was an “advantage” of the study, as interviewing cases and controls directly compared to interviewing next-of-kin was preferable. While it is generally true that this would be an advantage, the following statement by the authors, therefore, is not accurate, “The study covered all new cases of NHL during a specified time” (p. 1660). The study did not include all new cases; it included only those cases who survived until the time of the interview. Thus, while there may have been an advantage to restricting the study to living cases, there was a trade-off in that the study population did not represent all cases, specifically those cases with more aggressive disease. This disadvantage was not discussed by the authors, nor was the potential bias that could have resulted from excluding many eligible cases.

Exposure Measurement and Information Bias. Exposure was ascertained via a questionnaire oriented towards pesticide and other chemical agents. In addition, interviewers collected information by telephone if “important” data were lacking, incomplete, or unclear. It is

unknown what is meant by “important,” and the proportion of cases and controls who received phone calls was not reported. Thus, information bias may be a concern. Even though interviewers were blinded to case and/or control status, they may have been able to determine this information during the course of the interview. Furthermore, recall bias may be an issue because exposure information was based on participant response and cases and controls may recall and/or report past pesticide exposures differently. No exposure validation techniques were implemented, nor did an industrial hygienist (or any other type of personnel trained in assessing occupational exposures) independently validate/estimate the frequency and/or intensity of exposure. The authors assumed that “some misclassification regarding quantity of exposure has probably occurred, but such misclassification would most probably be nondependent of case/control status, and therefore only weaken any true risks” (p. 1660). They do not provide any explanation as to why they believe that exposure misclassification would be “most probably” nondifferential. If NHL cases believe that pesticides may be related to their disease, then it is certainly possible that they may recall and/or report pesticide exposure differently than NHL-free controls, which could result in odds ratios that are inflated as a result of bias.

Interpretation of “dose-response” analyses. The referent group in the statistical analyses consisted of participants who were unexposed to all pesticides. The dose-response analyses were based on a dichotomy of the median number of days exposed to a particular agent. It is difficult to analyze “dose-response” when only two exposure categories are considered. Furthermore, the dose-response analyses were based on median values of exposure but heterogeneity of cut-points is evident across agents. For example, glyphosate was analyzed as < 10 days and > 10 days, whereas, “other” herbicides were analyzed as < 32 days and > 32 days. Although analytical cut-points were data driven, interpretation across the wide variety of exposures is complicated by the variability in exposure cut-points. In addition, even though the OR for the higher category of exposure days was greater than the OR for the lower category, the two 95% confidence intervals were wide and overlapped considerably (0.70-4.07 and 1.04-5.37).

Thus, it is not clear whether the two point estimates reported (1.69 and 2.36) are significantly different from each other. Finally, this result cited in the “dose-response” analyses may have been confounded by exposure to other herbicides. In Table II (Eriksson et al. 2008, ASB2012-11614), the authors observed elevated associations for other herbicides, including MCPA, 2,4,5-T and/or 2,4-D. The correlation between exposure to glyphosate and other herbicides was not provided nor were analyses of glyphosate-exposed individuals after accounting for the collinear relation between this agent and other agents. The odds ratio for “ever” exposure to glyphosate was attenuated after additional adjustment for other pesticides (Table VII, Eriksson et al. 2008, ASB2012-11614), but multi-variate -adjusted estimates for the “dose-response” odds ratios were not reported.

Unusual Pattern of Positive Associations. The authors conducted multiple comparisons, and one would expect a certain proportion of their findings to be statistically significant (whether in the positive or inverse direction) simply as a result of chance. It is somewhat surprising, therefore, that the vast majority of the ORs presented in this manuscript are greater than 1.0, regardless of the statistical significance. The authors do note that for some of the analyses (e.g., latency), only chemicals for which ORs were greater than 1.5 and for which there were at least 10 exposed cases, or for which there was a statistically significant OR were evaluated. On the other hand, dose-response was evaluated based on the number of exposed subjects and not on the strength or significance of the findings. The authors do not address this directly, but do state in their Discussion, “...several pesticides are chemically related and may exert their effects on humans through a similar mechanism of action, which may explain the wide range

of pesticides that have been related to NHL over time in different countries and with different exposure conditions” (p. 1661). On the other hand, this pattern of positive findings could be a result of bias, including recall bias (or other information bias), selection bias, uncontrolled confounding, or a combination of these and other factors.

Interpretation of Eriksson et al. (2008, ASB2012-11614) in Context of Other Studies. Despite the statement by the authors that, “Recent findings from other groups also associate glyphosate with different B-cell malignancies such as lymphomas and myeloma” (p. 1662), most multi-variate analyses of glyphosate and NHL do not report statistically significant associations (De Roos et al. 2005, ASB2012-11605; De Roos et al. 2003; ASB2012-11606, Hardell and Eriksson 1999, ASB2012-11838; Hardell et al. 2002; ASB2012-11839, Lee et al. 2004; ASB2012-11883, McDuffie et al. 2001; ASB2011-364, Nordström et al. 1998, TOX1999-687) (Tables B.6.5-62 and B.6.5-63). It is notable that Hardell et al. (2002, ASB2012-11839) reported a significant positive association between glyphosate association and NHL, but the multi-variate -adjusted odds ratio was attenuated and not statistically significant. Similar findings were reported by Eriksson et al. (2008, ASB2012-11614). Specifically, the association reported by the authors in the abstract (OR = 2.02; 95% CI: 1.10-3.71) was adjusted for age, sex and year of diagnosis or enrollment. When other pesticides were added to that model (i.e., agents with statistically significant increased odds ratios, or with an odds ratio greater than 1.5 and with at least 10 exposed subjects), the adjusted odds ratio was 1.51 (95% CI: 0.77-2.94). Thus, the authors’ final statement, “Furthermore, our earlier indication of an association between glyphosate and NHL has been considerably strengthened” is questionable. Their previous findings showed a non-significant association after multi-variate adjustment (OR = 1.85; 95% CI: 0.55-6.20). The 2008 study similarly reported a statistically non-significant association between glyphosate and NHL after multi-variate adjustment (OR = 1.51; 95% CI: 0.77-2.94). The results reported for analyses of duration of exposure and latency of exposure did not adjust for other pesticides, and one would expect that those ORs would also be attenuated.

Summary of Findings: Cohort and Case-Control Studies of Exposure to Glyphosate and Non-Hodgkin Lymphoma

Table B.6.5-62: Cohort Studies

Author Year	Description	No. of Exposed Cases	Type of Relative Risk Estimate	Relative Risk Estimate	95% Confidence Limits	Variables Included in Statistical Model
De Roos et al. 2005 (ASB2012-11605)	57-2,678 vs. 1-20 Cumulative Exposure Days ^a	17	RR	0.9	0.5-1.6	Age at enrollment, education, pack-years of cigarette smoking, alcohol consumption in the past year, family history of cancer in first-degree relatives, and state of residence
	337.2-18,241 vs. 0.1-79.5 Intensity-Weighted Exposure Days ^b	22	RR	0.8	0.5-1.4	Also adjusted for other pesticides

^a Years of use x days per year; categorized by tertiles

^b Years of use x days/year x estimated intensity level; categorized by tertiles

Table B.6.5-63: Case Control Studies

Author Year	Exposure Evaluated	Subgroup Description	No. of Exposed Cases	No. of Exposed Controls	OR	95% CI	Variables Included in Statistical Model
De Roos et al. 2003 (ASB201 2-11606)	Ever exposure to specific pesticide; men only (all 47 pesticides were regressed simultaneously)	Glyphosate (Logistic Regression)	36	61	2.1	1.1-4.0	Age, study site and other pesticides
		Glyphosate (Hierarchical Regression)	36	61	1.6	0.9-2.8	Second-level model incorporated what was known about each true effect parameter prior to seeing the study data
Hardell and Eriksson 1999 (ASB201 2-11838)	Exposure to specific pesticides (ever/never exposed to the specific pesticide vs. no exposure to any pesticide)	Glyphosate (conditional logistic regression; uni-variate analysis)	4	3	2.3	0.4-13	Age and country (matching factors)
		Glyphosate (conditional logistic regression; multi-variate analysis)	4	3	5.8	0.6-54	Multi-variate variables not listed by authors
Hardell et al. 2002 (ASB201 2-11839)	Exposure to specific pesticides (ever/never exposed to the specific pesticide vs. no exposure to any pesticide)	Glyphosate (conditional logistic regression; uni-variate analysis)	8	8	3.04	1.08-8.52	Age and county (matching factors); study, study area (county), and vital status
		Glyphosate (conditional logistic regression; multi-variate analysis)	8	8	1.85	0.55-6.20	Multi-variate variables not listed by authors
Lee et al. 2004 (ASB201 2-11883)	Exposure to individual pesticides	Glyphosate use, Non-asthmatics	53	91	1.4	0.98-2.1	Age, state, vital status
		Glyphosate use, Asthmatics	6	12	1.2	0.4-3.3	
McDuffie et al. 2001 (ASB201 1-364)	Exposure to individual active chemicals	Glyphosate (Round-Up)	51	133	1.26	0.87-1.80	Strata for age and province of residence
		Glyphosate (Round-Up)	NR	NR	1.20	0.83-1.74	Plus statistically significant medical variables

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Author Year	Exposure Evaluated	Subgroup Description	No. of Exposed Cases	No. of Exposed Controls	OR	95% CI	Variables Included in Statistical Model
Nordström et al. 1998 (TOX199 9-687)	Exposure to specific herbicides, insecticides, and fungicides	Glyphosate	4	5	3.1	0.8-12	Age and country (matching factors)
Eriksson et al. 2008 (ASB201 2-11614)	Exposure to specific herbicides regardless if they also had been exposed to phenoxyacetic acids or not	Glyphosate	29	18	2.02	1.10-3.71	Age, sex, and year of diagnosis or enrollment
			29	18	1.51	0.77-2.94	Age, sex, and year of diagnosis or enrollment and pesticides with statistically significant increased odds ratios, or with an odds ratio greater than 1.5 and with at least 10 exposed subject
	Exposure to herbicide stratified by median number of days among exposed controls	Glyphosate ≤ 10 days	12	9	1.69	0.70-4.07	Age, sex, and year of diagnosis or enrollment
		Glyphosate >10 days	19	9	2.36	1.04-5.37	
	Exposure to specific herbicides according to different lymphoma entities	Glyphosate: B-Cell lymphomas	NR	NR	1.87	0.998-3.51	Age, sex, and year of diagnosis or enrollment
		Lymphocytic lymphoma/B-CLL	NR	NR	3.35	1.42-7.89	
		Follicular grade I-III	NR	NR	1.89	0.62-5.79	
		Diffuse large B-cell Lymphoma	NR	NR	1.22	0.44-3.35	
		Other specified B-cell lymphoma	NR	NR	1.63	0.53-4.96	
		Unspecified B-cell Lymphoma	NR	NR	1.47	0.33-6.61	
		T-cell lymphomas	NR	NR	2.29	0.51-10.4	
Unspecified NHL	NR	NR	5.63	1.44-22.0			

Author(s)	Year	Study title
George, J. Prasad, S. Mahmood, Z. Shukla, Y.	2010	Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach Journal of Proteomics Volume: 73, Pages: 951-964 ASB2012-11829

Abstract*

Glyphosate is a widely used broad spectrum herbicide, reported to induce various toxic effects in non-target species, but its carcinogenic potential is still unknown. Here we showed the carcinogenic effects of glyphosate using 2-stage mouse skin carcinogenesis model and proteomic analysis. Carcinogenicity study revealed that glyphosate has tumor promoting activity. Proteomic analysis using 2-dimensional gel electrophoresis and mass spectrometry showed that 22 spots were differentially expressed (>2 fold) on glyphosate, 7, 12-dimethylbenz[a]anthracene (DMBA) and 12-O-tetradecanoyl-phorbol-13-acetate (TPA) application over untreated control. Among them, 9 proteins (translation elongation factor eEF-1 alpha chain, carbonic anhydrase III, annexin II, calcyclin, fab fragment anti-VEGF antibody, peroxiredoxin-2, superoxide dismutase [Cu-Zn], stefin A3, and calgranulin-B) were common and showed similar expression pattern in glyphosate and TPA-treated mouse skin. These proteins are known to be involved in several key processes like apoptosis and growth-inhibition, anti-oxidant responses, etc. The up-regulation of calcyclin, calgranulin-B and down-regulation of superoxide dismutase [Cu-Zn] was further confirmed by immunoblotting, indicating that these proteins can be good candidate biomarkers for skin carcinogenesis induced by glyphosate. Altogether, these results suggested that glyphosate has tumor promoting potential in skin carcinogenesis and its mechanism seems to be similar to TPA.

* Quoted from article

Klimisch evaluation

Reliability of study:	Reliable with restrictions
Comment:	Non-guideline mechanistic study. Scientifically acceptable study with deficiencies (controls with glyphosate alone, and co-formulants were not included)
Relevance of study:	Relevant with restrictions (Glyphosate formulation not glyphosate alone was tested.)
Klimisch code:	2

Additional comments:

The authors use glyphosate as a synonym for what is really a glyphosate based formulated product. Doses in this study are not representative of human exposures to glyphosate or glyphosate based formulations. Mice in the tumor promoting group VIII received topical applications of concentrated glyphosate formulated product three times per week for over thirty weeks without washing after an initial treatment with the potent tumor initiator DMBA. Glyphosate had been shown to have very low dermal absorption, even in formulated products, and since is non-volatile, would likely accumulate on mouse skin. Surfactants are typically irritating and non-volatile. Given the irritation potential of the unwashed exposed mouse skin over the course of thirty or more weeks, tumor promotion may be a physical response to substantial localized dermal irritation. Epidemiological studies reported above note no association with glyphosate and either skin or lip cancers.

Label directions outline appropriate personal protective equipment such as gloves and long sleeves. Furthermore, any dermal exposure of concentrated product to human skin would prove irritating and prompt handlers to wash off soon after dermal exposure.

Human *in vitro* dermal absorption studies reported for a range of glyphosate based formulations containing different surfactant systems all demonstrate extremely low dermal absorption of glyphosate active ingredient for concentrated products, of less than 0.2 %. Test material recovery in each of the four reported dermal absorption studies was very good, close to 100 %. Most of the glyphosate was removed during skin surface washing at either eight or twenty four hours of *in vitro* human skin exposure. This also suggests significant potential for accumulation of glyphosate on the surface of the mice skin in George et al. (2010, ASB2012-11829).

The up-regulation / down-regulation of protein expression reported after a single dermal dose of a glyphosate formulated product (proteomics experiment, group II), while interesting, does not demonstrate any toxicological endpoint. Rather, perturbations may well represent normal homeostatic fluctuations and be a natural response to insult.

Author(s)	Year	Study title
Seralini, G.-E. Clair, E. Mesnage, R. Gress, S. Defarge, N. Malatesta, M. Hennequin, D. Spiroux de Vendomois, J.	2012	Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food and Chemical Toxicology 50, 4221-4231 ASB2012-15514

Abstract*

The health effects of a Roundup-tolerant genetically modified maize (from 11% in the diet), cultivated with or without Roundup, and Roundup alone (from 0.1 ppb in water), were studied 2 years in rats. In females, all treated groups died 2–3 times more than controls, and more rapidly. This difference was visible in 3 male groups fed GMOs. All results were hormone and sex dependent, and the pathological profiles were comparable. Females developed large mammary tumors almost always more often than and before controls, the pituitary was the second most disabled organ; the sex hormonal balance was modified by GMO and Roundup treatments. In treated males, liver congestions and necrosis were 2.5–5.5 times higher. This pathology was confirmed by optic and transmission electron microscopy. Marked and severe kidney nephropathies were also generally 1.3–2.3 greater. Males presented 4 times more large palpable tumors than controls which occurred up to 600 days earlier. Biochemistry data confirmed very significant kidney chronic deficiencies; for all treatments and both sexes, 76% of the altered parameters were kidney related. These results can be explained by the non linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GMO and its metabolic consequences.

* Quoted from article

Klimisch evaluation

Reliability of study:	Not reliable
Comment:	The study was performed to investigate the long term toxicity and carcinogenicity. However the study design does not agree with the OECD guidelines on long term toxicity and carcinogenicity.
Relevance of study:	Relevant with restrictions (Glyphosate formulation not glyphosate alone was tested.)
Klimisch code:	3

Comments:

Seralini et al. (2012, ASB2012-15514) submitted a report of long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. The health effects have been studied 2 years in rats. Six groups of rats were fed with 11, 22 and 22 % of genetically modified NK603 maize either treated or not with Roundup. Three further groups of rats were fed with control diet and had access to water supplemented with 50 ng/L, 400 mg/L and 2.25 g/L of the commercial product Roundup (GT Plus, 450 g/L of glyphosate). The pure active substance glyphosate was not tested in this study.

The study is not considered reliable because of several important limitations. According to the authors the studies have been performed to investigate the long term toxicity and carcinogenicity. However, the number of animals per dose and sex was only 10 and also the further study design does not agree with the OECD guidelines on long term toxicity and carcinogenicity. The spontaneous incidence of mammary tumors in the used Sprague Dawley rats is much higher than in most other rat strains. Therefore, a higher number of animals would be necessary for the differentiation between treatment related carcinogenicity and accidental aberrations. Also for the assessment of mortality and further described toxic effects a higher number of animals would be needed.

The presented results in the publication are incomplete and therefore, an evaluation of the presented results was complicated.

The study was extensively discussed and criticized in the public. In an additional paper Seralini et al. (2013, ASB2013-10985) gave some answers to the critics. The authors admit that the study “should not be considered as a final point in knowing the toxicological effects of NK603 and R (oundup)” and that the study has limits.

Jany (2012, ASB2014-9580) submitted a critical review of the study by Seralini et al. (2012). The authors conclude that the scientific value of this publication would be limited and non conclusions are possible concerning maize NK603 with and without Roundup treatment.

Ollivier (2012, ASB2013-11000) proposes to use the Chi-square test to compare mortality rates in the study of Seralini et al. (2012). In result of this test there would be no statistical significance.

In a further paper Seralini et al. (2014, ASB2014-9632) discuss criticisms which have been published in reaction on the study by Seralini et al. (2012, ASB2012-15514).

John (2014, ASB2014-9584) reacts in a letter on the decision of the publisher to retract the article of Seralini et al. (2012). John concludes that there would be no grounds for retraction.

Wallace-Hayes (2014, ASB2014-9559), the editor-in-chief of Food and Chemical Toxicology, gives answers on questions on the retraction of the paper of Seralini et al. (2012). He concludes once more that “a careful and time-consuming analysis found that the data were inconclusive, and therefore the conclusion described in the article were unreliable. Accordingly, the article was retracted.”

Folta (2014, ASB2014-9478) writes in a letter to the editor that he would see this work of Seralini (2012) as a manipulation of the scientific process to achieve activist gains. He stands behind the journal's decision to retract the work.

Rosanoff (2014, ASB2014-9397) proposes in a letter concerning the Seralini (2012) study that the raw data should be published.

Roberfroid (2014, ASB2014-9393) writes in a letter concerning the Seralini (2012) study that he is ashamed about the decision to retract this paper.

In a further letter Roberfroid (2014, ASB2014-9392) writes that in his understanding the study of Seralini (2012) remains an important scientific (not a regularory) observation that can not be ignored.

Pilu (2012, ASB2014-9387) writes in a letter to the editor on the Seralini (2012) study that mycotoxins in maize could have influenced the results of the study. Therefore, he asks for further information on the mycotoxin content in the maize used in the Seralini study.

Author(s)	Year	Study title
Chruscielska, K. Brzezinski, J. Kita, K. Kalhorn, D. Kita, I. Graffstein, B. Korzeniowski, P.	2000	Glyphosate Evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity Pestycydy 2000, (3-4), 11-20 ASB2013-9829

Abstract*:

The combined test of chronic toxicity and carcinogenicity of glyphosate was performed on Wistar-RIZ rats. The herbicide was administered in water at concentrations: 0, 300, 900, 2700 m/L. The examination of the peripheral blood parameters and the smears of bone marrow did not reveal harmful effect of the herbicide on haematopoietic system of rats. The biochemical parameters determined on blood and urine only in some cases showed significant deviations in comparison with the control group, but in any examined indices dose-effect-time occurred what could manifest the toxic influence of glyphosate. In pathomorphological studies on the organs no correlation was stated between the number of observed tumours and the concentrations of the herbicide. It indicates lack of pathogenic influence of glyphosate on neoplastic pathogenesis.

* Quoted from article

Klimisch evaluation

Reliability of study: Reliable with restrictions
 Comment: The published details of the study are limited. However, according to the authors the study was performed on basis of OECD guideline No. 453
 Relevance of study: Relevant
 Klimisch code: 2

Comments:

The active substance glyphosate was used in the study and the study was performed on basis of OECD guideline 453. The number of animals per dose group and sex (85 animals) was

