Glyphosate and Non-Hodgkin lymphoma: No causal relationship

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Abstract

Objective: Herbicides are used worldwide by both residential and agricultural users. Due to the statistical analysis of some epidemiologic studies the International Agency for Research on Cancer classified the broad-spectrum herbicide glyphosate (GS) in 2015, as potentially carcinogenic to humans especially with respect to non-Hodgkin lymphoma (NHL). In this systematic review and re-analysis, the relationship between glyphosate and NHL was re-investigated.

Methods: A systematic review and re-analysis of studies which investigated the relationship between GS and NHL was conducted. The method of the conditio sine qua non relationship, the method of the conditio per quam relationship, the method of the exclusion relationship and the mathematical formula of the causal relationship k were used to proof the hypothesis. Significance was indicated by a p-value of less than 0.05.

Results: The studies analyzed do not provide any direct and indirect evidence that NHL is caused GS.

Conclusion: In this re-analysis, no causal relationship was apparent between glyphosate and NHL and its subtypes.

Keywords: Glyphosate, Non-Hodgkin lymphoma, no causal relationship

1. Introduction

Historically, Marcell Malpighi (1628-1694) described in 1666 as one of the first authors Hodgkin lymphoma (HL) in his publication: *De viscerum structura exercitatio anatomica* (Malpighi, 1666). Centuries later, the English physician Thomas Hodgkin (1798–1866) of Guy’s Hospital, London, published 1832 a remarkable paper entitled as “On some morbid cases of the absorbent glands and spleen” (Hodgkin, 1832) and described a new disease, in medical literature known through the use of the term ‘Hodgkin’s disease’ (Wilks, 1865). Lymphomas are traditionally divided into non-Hodgkin lymphoma and Hodgkin's lymphoma, which are responsible for about 10% of all lymphomas (Armitage, Gascoyne, Lunning, & Cavalli, 2017) and known since centuries too. Independently of Hodgkin, the non-Hodgkin lymphoma i. e. leukaemia were described by Virchow (Virchow, 1845), Bennett (Bennett, 1845) and by Cohnheim (Cohnheim, 1865) under the descriptive term `pseudoleukaemia. Non-Hodgkin lymphoma (NHL) is a group of blood cancers with a wide range of histological appearances and clinical features at presentation which includes all different types of lymphoma but Hodgkin's lymphomas. The first systematic and widely accepted classification of lymphomas other than Hodgkin was proposed by Henry Rappaport in 1956 (Rappaport, 1966). Meanwhile, NHL is the leading hematological malignancy worldwide. Non-Hodgkin lymphoma (also known as non-Hodgkin’s lymphoma, NHL, or sometimes just lymphoma) starts when white blood cells called (B- or T-) lymphocytes begin to grow out of control. NHL can start anywhere in the body but is usually found in lymph nodes or other lymph tissues (spleen, bone marrow, thymus, adenoids and tonsils, digestive tract). Several NHL risk factors like age, gender, family history, weakened immune system, radiation exposure, exposure to certain chemicals and drugs and glyphosate too have been discussed in literature, but the cause or a cause of NHL has not been identified. Finally, in 2015, the International Agency for Research on Cancer (IARC, 2017) Working Group published limited evidence of increased risk of non-Hodgkin lymphoma (NHL) in some epidemiologic studies. Glyphosate [N-(phosphonomethyl)glycine], sold in the commercial as Roundup (R) (Monsanto Company, St. Louis, MO), was registered in the U.S. in 1974 and re-registrated 1993 by the US Environmental Protection Agency (EPA, 1993). Since its introduction in the 1970s Glyphosate has been frequently (Williams, Kroes, & Munro,

2000) used in forestry, in cropland and noncropland areas like gardens and lawns et cetera to control vegetation. Especially after genetically engineered glyphosate-tolerant crops were introduced, the use of glyphosate increased dramatically in the late-1990s and 2000s. Glyphosate inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (Steinrücken & Amrhein, 1980), which is responsible via a mechanism specific to plants for the biosynthesis of aromatic amino acids like phenylalanine, tyrosine, and tryptophan. Questions regarding the safety of glyphosate, its major breakdown product aminomethylphosphonic acid (AMPA) and the predominant surfactant polyethoxylated tallow amine (POEA) have been periodically raised (Olorunsogo, Bababunmi, & Bassir, 1979) (Hietanen, Linnainmaa, & Vainio, 1983) (Yousef et al., 1995) (Bolognesi et al., 1997) (Lioi, Scarfi, et al., 1998) (Lioi, Scarfi, et al., 1998) (Peluso, Munnia, Bolognesi, & Parodi, 1998) (Walsh, McCormick, Martin, & Stocco, 2000) (Daruich, Zirulnik, & Gimenez, 2001) (El-Demerdash, Yousef, & Elagamy, 2001) raised. In the following, different studies have been conducted by several regulatory agencies and scientific institutions worldwide to re-evaluate the relationship between glyphosate and some parameters. Glyphosate had no effects on fertility or reproductive parameters, there was no convincing evidence for direct DNA damage in vitro or in vivo, and neither AMPA nor glyphosate bioaccumulates in any animal tissue (Williams et al., 2000). Nevertheless, the question whether Glyphosate does pose a health risk to humans has not been finally answered. Thus far, considering use of glyphosate in both the United States and the rest of the world, an ongoing risk assessment is necessary. Here we have re-investigated the relationship between GS and NHL by some new statistical methods.

2. Material and Methods

In one way or another, testing hypotheses and theories about the natural world is not completely free of errors. Still, when all goes well, systematic observation and experimentation should assure that different scientists at different times and places are able to generate the same scientific knowledge.

2.1 Definitions

Definition 2.1.1. (The 2x2 Table)

A two by two table (also called a contingency table, a notion first used by Karl Pearson(K. Pearson, 1904) in 1904) is a useful tool for examining relationships between Bernoulli (i. e. Binomial) distributed random variables. Consider the case of a Bernoulli distributed random variable A_t occurring/existing et cetera with the probability $p(A_t)$ at the Bernoulli trial (period of time) t. Furthermore, consider the case of another Bernoulli distributed random variable B_t occurring/existing et cetera with the probability $p(B_t)$ at the same Bernoulli trial (period of time) t. Furthermore, let $p(a_t)= p(A_t \cap B_t)$ denote the joint probability distribution of A_t and B_t at the same Bernoulli trial (period of time) t. The following table (**Table 1**) may show the relationships in more details.

Table 1. The probabitlities of a contingency table

		Conditioned B („Curvature")		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	$p(a_t)$	$p(b_t)$	$p(A_t)$
(“Momentum”)	No = +0	$p(c_t)$	$p(d_t)$	$p(\underline{A}_t)$
	Total	$p(B_t)$	$p(\underline{B}_t)$	**1**

In this context, it is per definitionem

$$
\begin{array}{ccccc}
p(A_t) & \equiv & p(a_t)+p(b_t) & = & 1-p(\underline{A}_t) \\
p(B_t) & \equiv & p(a_t)+p(c_t) & = & 1-p(\underline{B}_t) \\
p(a_t) & \equiv & p(A_t \cap B_t) & = & 1-p(b_t)-p(c_t)-p(d_t) \\
+1 & \equiv & p(a_t)+p(b_t) & + & p(c_t)+p(d_t) \\
+1 & \equiv & p(A_t)+p(\underline{A}_t) & = & p(B_t)+p(\underline{B}_t) \\
p(B_t)+p(\Lambda_t) & \equiv & p(A_t) & = & 1-p(\underline{B}_t)+p(\Lambda_t) \\
p(\underline{A}_t) & = & 1-\left(1-p(\underline{B}_t)+p(\Lambda_t)\right) & = & p(\underline{B}_t)-p(\Lambda_t) \\
p(\Lambda_t) & = & p(A_t)-p(B_t) & = & p(b_t)-p(c_t) \\
p(b_t)+p(c_t) & = & \left(2\times p(c_t)\right)+p(\Lambda_t) & = & 1-p(a_t)-p(d_t)
\end{array}
\qquad (1)
$$

while +1 denotes the normalized sample space of A_t and B_t. We obtain some of the relationships *per definitionem*

$$
\begin{array}{lcccc}
A & \equiv & n \times p(a_t) + n \times p(b_t) & = & n \times p(A_t) \\
B & \equiv & n \times p(a_t) + n \times p(c_t) & = & n \times p(B_t) \\
a & \equiv & n \times p(a_t) & = & n \times p(A_t \cap B_t) \\
b & & n \times p(b_t) & & \\
c & & n \times p(c_t) & & \\
d & & n \times p(d_t) & & \\
n & \equiv & n \times p(a_t) + n \times p(b_t) & + & n \times p(c_t) + n \times p(d_t) \\
n & \equiv & n \times p(A_t) + n \times p(\underline{A}_t) & = & n \times p(B_t) + n \times p(\underline{B}_t)
\end{array} \tag{2}
$$

The meaning of the abbreviations a, b, c, d, n et cetera are explained by following 2 by 2-table (**Table 2**).

Table 2. The sample space of a contingency table

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	b	A
(risk factor)	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

Definition 2.1.2. (Fisher's exact test)

Many times, the sampling distribution of a test statistic which is calculated is only approximately equal to the theoretical chi-squared distribution. Under these circumstances, a chi-squared test provides only approximative significance values. The approximation by a chi-squared distribution is inadequate when the data are very unequally distributed or sample sizes are small. Fisher (Fisher, 1922) developed an exact statistical significance test for the analysis of contingency tables valid for all sample sizes and demonstrated that the probability was given by the hypergeometric distribution as

$$
p_{Fisher}(a) = \left(\binom{A}{a} \times \binom{\underline{A}}{c}\right) / \binom{n}{B} = \left(\binom{A}{b} \times \binom{\underline{A}}{d}\right) / \binom{n}{\underline{B}} = \frac{(A!) \times (\underline{A}!) \times (B!) \times (\underline{B}!)}{(a!) \times (b!) \times (d!) \times (d!) \times (n!)} \tag{3}
$$

Definition 2.1.3. (Fisher's exact test for the sufficient condition)

Under conditions of a conditio per quam relationship, we expect that b = 0 as illustrated by the following table (**Table** 3).

Table 3. Fisher's exact test and conditio per quam

		Conditioned B (Outcome)		
		No = +0	**Yes = +1**	**Total**
Condition A	Yes =+1	**b**	a	A
(risk factor)	No = +0	d	c	$\underline{A}$
	Total	$\underline{B}$	B	*n*

The Fisher exact test statistic for the conditio per quam relationship is calculated as

$$p_{Fisher}(b) = \left(\binom{A}{b} \times \binom{\underline{A}}{d}\right) / \binom{n}{\underline{B}} = \frac{(A!) \times (\underline{A}!) \times (B!) \times (\underline{B}!)}{(a!) \times (b!) \times (d!) \times (d!) \times (n!)} \qquad (4)$$

Definition 2.1.4. (Fisher's exact test for the necessary condition)

Under conditions of a conditio sine qua non relationship, we expect that c = 0 as illustrated by the following table (**Table** 4).

Table 4. Fisher's exact test and conditio sine qua non

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	No = +0	**c**	d	$\underline{A}$
(risk factor)	Yes =+1	a	b	A
	Total	B	$\underline{B}$	*n*

The Fisher exact test statistic for the conditio sine qua non relationship is calculated as

$$p_{Fisher}(c) = \left(\binom{\underline{A}}{c} \times \binom{A}{a}\right) / \binom{n}{B} = \frac{(A!) \times (\underline{A}!) \times (B!) \times (\underline{B}!)}{(a!) \times (b!) \times (d!) \times (d!) \times (n!)} \qquad (5)$$

Definition 2.1.5. (Fisher's exact test for the exclusion relationship)

Under conditions of a exclusion relationship, we expect that a = 0 as illustrated by the following table (**Table 5**).

Table 5. Fisher's exact test and exclusion relationship

		Conditioned B (Outcome)		
		Yes = +1	**No = +0**	**Total**
Condition A	Yes =+1	a	b	A
(risk factor)	No = +0	c	d	$\underline{A}$
	Total	B	$\underline{B}$	*n*

The Fisher exact test statistic for the exclusion relationship is calculated as

$$p_{Fisher}(a) \quad = \quad \left(\binom{A}{a} \times \binom{\underline{A}}{c}\right) / \binom{n}{B} \quad = \frac{(A!) \times (\underline{A}!) \times (B!) \times (\underline{B}!)}{(a!) \times (b!) \times (d!) \times (d!) \times (n!)} \tag{6}$$

2.2 Material

2.2.1 Search Strategy

To answer the questions addressed in this paper, the electronic database PubMed was searched for appropriate studies conducted in any country which investigated the relationship between glyphosate and NHL. The search in PubMed was performed while using some medical key words. Those articles were considered for a re-view which provided access to data without any data access barrier. Additionally, the reference list of identified articles was used as a potential source of articles appropriate for this study. Preferred Reporting Items for Systematic Reviews and Meta - analysis (PRISMA) (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). The screening process and results are shown in **Table 6**.

Table 6.

1. Identification of records	Size	Total
Records identified by searching in the databases		
PubMed	9	
Google Scholar	0	
Web of Science	0	
Additional records identified from other sources	2	11
2. Clean-up of search (Screening)		
Records removed after verifying duplication	0	
Records excluded by title	2	
Records excluded due to other reasons	2	
(Articles outside the inclusion criteria)		
3. Eligibility		
Articles evaluated for eligibility		7
Articles excluded for various reasons		
- Language	0	
- Data access barriers	0	
4. Included		
Articles included in the meta-analysis		7

Flow Diagram of the article selection process. Adopted from PRISMA 2009 (Liberati et al., 2009; Moher et al., 2009).

The study of (L. Hardell & Eriksson, 1999) published (4/404) positive cases and (3/741) positive controls but was not considered for a re-analyses. The data of this study are extremely self-contradictory. The index of unfairness is IOU = -0.64 and highly unfair. At the same time, the exclusion relationship between GS and NHL is positive (p (EXCL) = 0,99650655, X^2 (EXCL) =0,04 and X^2 (EXCL) =2,29) while equally the conditio per quam relationship is significant too (p (IMP) =0,997379913. X^2 (IMP) =0,01. X^2 (IMP) =1,29). This is a contradiction. Mathematically, it is not possible **GS excludes NHL** and at the same time that **if GS then NHL**.

Leon et al. (Leon et al., 2019) investigated the relationship of ever use of glyphosate and non-Hodgkin lymphoid malignancies (NHL) in a pooled analysis of three large agricultural worker cohorts of 316 270 farmers. A control group has not been provided. During follow-up, 2430 NHL cases were diagnosed while 1131 of these cases ever used glyphosate. Besides of a missing control group, a fair study design assumed, it is possible to calculate the significance of a conditio sine qua non relationship between GS and NHL as X^2(SINE) = ((2430-1131)*(2430-1131))/2430 = 694,41, a highly significant result. In other words, the study of Leon et al. has provided striking evidence that GS is not a necessary condition of NHL. In other words, it is possible to suffer from NHL without GS. According to Leon et al. (Leon et al., 2019) the Null-hypothesis: without GS no NHL must be rejected. The consequence is, that the use of GS must imply that people will suffer from NHL, which is not the case either.

2.2.2 Statistical Analysis

The causal relationship k (I. Barukčić, 1989, 1997, 2016a, 2016b, 2017, 2018a, 2019c; K. Barukčić & Barukčić, 2016; Hessen, 1928; Korch, 1965) is defined *at every single event* (I. Barukčić, 2016a, 2018b, 2018a, 2019c; K. Barukčić & Barukčić, 2016; K. Barukčić, Barukčić, & Barukčić, 2018) , *at every single Bernoulli trial (Uspensky, 1937, p. 45) t* and was used to proof the data for a causal relationship while the significance was tested by *the hypergeometric distribution* (HGD) and sometimes by the chi-square distribution (Karl Pearson, 1900) too. The *conditio sine qua non* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) was used to proof the hypothesis, *without* (I. Barukčić, 2019d) HCMV infection *no* AS. The *conditio per quam* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (IMP) was used to proof the hypothesis, *if* (I. Barukčić, 2019d) HCMV infection *then* AS. The *necessary and sufficient condition* (I. Barukčić, 2018d, 1989, 1997, 2017, 2018a, 2018b, 2019c; K. Barukčić & Barukčić, 2016, 2016) relationship (SINE) can be used to proof the hypothesis, (*without* HCMV infection *no* AS) **and** (*if* HCMV infection *then* AS). The *index of unfairness*

(I. Barukčić, 2019b) and *the index of independence* (I. Barukčić, 2019a) was used to control publication bias. All statistical analyses were performed with Microsoft® Excel® for Mac® version 16.2 (181208) software (© 2018, Microsoft GmbH, Munich, Germany). The level of significance was set to 0.05.

3. Results

Theorem 3.1. (Glyphosate is neither a cause nor the cause of Non-Hodgkin Lymphoma.)

McDuffie et al. (McDuffie et al., 2001) conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma.

Claim.

Null Hypothesis:

Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma. In other words, $k = 0$.

Alternative Hypothesis:

Glyphosate is either the cause or a cause of Non-Hodgkin Lymphoma. In other words, $k > 0$.

Proof.

McDuffie et al. investigated the relationship between exposure to glyphosate of humans with respect to the development of Non-Hodgkin Lymphoma. The data as obtained by McDuffie et al. (McDuffie et al., 2001) are view by **table 7**.

Table 7

The study of McDuffie et al., 2001.

Country: **Canada**		Non-Hodgkin Lymphoma YES	NO		
Glyphosate	YES	51	133	**184**	
	NO	466	1373	1839	
		517	1506	**2023**	**PMID: 11700263**

Statistical analysis

Causal relationship k =	**0,016**	95 % CI (k) :	-0,034	to	0,065
P value (k | HGD) =	**0,78755**	Chi Sq.(k) =	0,497		
p(IOI) =	**0,165**	**p(IOU) =**	**0,653**	**p(IOU) + p(IOI) =**	**0,818**
p (SINE) =	**0,770**	X^2(SINE|Bt) =	420,031	X^2(SINE|<u>A</u>t) =	118,084
P likely (SINE)=	0,794	P Value (SINE)=	0,206		
p (IMP) =	**0,934**	X^2(IMP| At)) =	96,136	X^2(IMP|<u>B</u>t) =	11,746
P likely (IMP) =	0,936	P Value (IMP) =	0,064		
p (SINE ^ IMP) =	**0,704**	X^2(SINE^IMP|At) =	431,777	X^2(SINE^IMP|Bt) =	431,777
p likely (SINE^IMP)=	0,744	p Value (SINE^IMP)=	0,256		
p (EXCL) =	**0,975**	X^2(EXCL| At)=	14,136	X^2(EXCL|Bt)=	5,031
P (Likely EXCL)=	0,975	P Value (EXCL)=	0,025		
Odds ratio (OR) =	1,130	95 % CI (OR) :	0,805	to	1,587

The index of independence of the study of McDuffie et al. is p(IOI) = 0,165 and is not only of restricted value to consider these data for the re-analysis of causal relationship and the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,653 and do indicate potentially biased data. Altogether, the data as published by the study of McDuffie et al. are more or less not absolutely biased. The relative frequency of **the conditio sine qua non relationship** (SINE) between GS and NHL is p (SINE) = 0,770. Thus far, the approximate P Value (I. Barukčić, 2019e) can be calculated as P Value (SINE) = 0,206. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 2023) yields the following result, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated $X^2(SINE|B_t)$ is $X^2(SINE|B_t)$ = (((466)*(466)/517) + 0 = 420,031. Secondly. The same data demand that the calculated $X^2(SINE|\underline{A}_t)$ is $X^2(SINE|\underline{A}_t)$ = (((466)*(466))/1839)+0= 118,084. The data of the study of McDuffie et al. do not support the hypothesis that GS is a necessary condition of NHL. Furthermore, mathematically a positive causal relationship, even if not significant, does not contradict formally the hypothesis of a conditio sine qua non relationship. According to the data of the study of McDuffie et al. it is possible to suffer from NHL without having any contact with GS. The relative frequency of **the conditio per quam relationship** (IMP) between GS and NHL is p (IMP) = 0,934. The approximate P Value (I. Barukčić, 2019e) can be calculated as P Value (IMP) = 0,064. The significance of these data tested by the Chi-square goodness of fit test (sample size n =2023) yield the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated $X^2(IMP|A_t)$ is $X^2(IMP|A_t)$ = (((133)*(133))/ 184) + 0 = 96,136. Secondly. The same data demand that the calculated $X^2(IMP|Not\ B_t)$ is $X^2(IMP|Not\ B_t)$ =(((133)*(133))/1506) + 0 = 11,746. The data of the study of McDuffie et al. do not support the hypothesis that GS is a sufficient condition of NHL. Furthermore, mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio per quam relationship. Based on the data of the study of McDuffie et al. it is necessary to conclude the following: People who have contact with GS will not suffer from NHL due to Glyphosate. Contrary to expectation, the use of GS or a contact with GS can have protective effects against NHL. In this case we expect a significant **negative** causal relationship k and a significant exclusion relationship. The relative frequency of **the exclusion relationship** (EXCL) between GS and NHL is p (EXCL) = 0,975. The approximate P Value can be calculated as P Value (EXCL) = 0,025 and is significant. In other words, GS excludes NHL and protects against NHL. The index of independence of the study of McDuffie et al. is p(IOI) = 0,165 with the consequence that the data can be used for these purposes. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 2023) yields the following result while the X^2

critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((51)*(51))/ 184) + 0 = 14,136. Secondly. The same data demand that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((51)*(51))/ 517) + 0 = 5,031. Based on the Chi square distribution, the data of the study of McDuffie et al. do not support the hypothesis that GS excludes NHL. Furthermore, the causal relationship is positive. However, mathematically it is not possible to obtain a positive causal relationship and at the same time a significant exclusion relationship. Therefore, the conclusion is not justified that the study of McDuffie et al. supports the hypothesis that GS excludes NHL. The causal relationship k is k = 0,016 and positive while the approximate 95% confidence interval of the causal relationship k is between -0,034 and 0,065. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,78755 and not significant. Conclusion. There is no positive cause-effect relationship between GS and NHL. Thus far, according to the data of McDuffie et al., Glyphosate is neither a cause nor the cause of Non-Hodgkin Lymphoma.

Quod erat demonstrandum.

Theorem 3.2. (Glyphosate is neither a cause nor the cause of Non-Hodgkin Lymphoma.)

Hardell, Eriksson, & Nordstrom (Lennart Hardell, Eriksson, & Nordstrom, 2002) investigated the importance of glyphosate and other factors in the etiology of NHL by a pooled analysis performed on two case-control studies. Hardell, Eriksson, & Nordstrom reported that they were not able to find an association between glyphosate and non-Hodgkin lymphoma.

Claim.

Null Hypothesis:

Glyphosate is not a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

The data as obtained by Hardell, Eriksson, & Nordstrom (Hardell, Eriksson, & Nordstrom, 2002) are viewed by **table 8**.

Table 8

The study of Hardell, Eriksson, & Nordstrom et al., 2002.

Country: **Sweden**		Non-Hodgkin Lymphoma YES	NO		
Glyphosate	YES	8	8	**16**	
	NO	507	1133	1640	
		515	1141	**1656**	**PMID: 12148884**

Statistical analysis

Causal relationship k =	**0,040**	95 % CI (k) :	-0,015	to	0,095
P value (k | HGD) =	**0,96830**	Chi Sq.(k) =	2,694		
p(IOI) =	**0,301**	**p(IOU) =**	**0,679**	**p(IOU) + p(IOI) =**	**0,981**
p (SINE) =	**0,694**	X^2(SINE|Bt) =	499,124	X^2(SINE|At) =	156,737
P likely (SINE)=	0,736	P Value (SINE)=	0,264		
p (IMP) =	**0,995**	X^2(IMP| At)) =	4,000	**X^2(IMP|Bt) =**	**0,056**
P likely (IMP) =	0,995	P Value (IMP) =	0,005		
p (SINE ^ IMP) =	**0,689**	X^2(SINE^IMP|At) =	499,180	X^2(SINE^IMP|Bt) =	499,180
p likely (SINE^IMP)=	0,733	p Value (SINE^IMP)=	0,267		
p (EXCL) =	**0,995**	X^2(EXCL| At)=	4,000	**X^2(EXCL|Bt)=**	**0,124**
P (Likely EXCL)=	0,995	P Value (EXCL)=	0,005		
Odds ratio (OR) =	2,235	95 % CI (OR) :	0,834	to	5,988

The index of independence of the study of Hardell, Eriksson, & Nordstrom et al. is p(IOI) = 0,301 and of some but restricted value to consider these data for the re-analysis for causal relationship and the re-analysis of the exclusion relationship. In contrast to IOI, the *index of unfairness* (I. Barukčić, 2019b) of this study is p(IOU) = 0,679 and indicates potentially biased data. Altogether, the data as published by the study of Hardell, Eriksson, & Nordstrom et al. are with great care and more or less of use for a re-analysis. The relative frequency of the **conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,694. The approximate P Value can be calculated as P Value (SINE) = 0,264, the relationship is not significant. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 1656) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((507)*(507))/ 515) + 0 = 499,124. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((507)*(507))/ 1640) + 0 = 156,737 while the cause effect relationship is positive! The data of the study of Hardell, Eriksson, & Nordstrom et al. do not support the hypothesis that GS is a necessary condition of NHL. According to the data of the study of Hardell, Eriksson, & Nordstrom et al. it is possible to suffer from NHL without any contact to GS. The relative frequency of **the conditio per quam relationship** between GS and NHL is p (IMP) = 0,995. The approximate P Value can be calculated as P Value (IMP) = 0,005. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 1656) yield the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((8)*(8))/16) + 0 = 4,000 and not significant. Secondly. The same data demand that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) = (((8)*(8))/1141) + 0 = 0,056, a significant result while the cause effect relationship is positive, but not significant.The data of the study of Hardell, Eriksson, & Nordstrom et al. do support both: GS is a sufficient condition of NHL and the same data demand too that GS is not a sufficient condition of NHL which is a **contradiction**! The data of the study of Hardell, Eriksson, & Nordstrom et al. are more or less biased as indicated by an p(IOI) = 0,301 and cannot be used for these purposes. Can the use of GS have any protective effects against NHL? In this case we expect a significant negative causal relationship k and a significant **exclusion relationship**. The relative frequency of the exclusion relationship between GS and NHL is p (EXCL) = 0,995. The approximate P Value can be calculated as P Value (EXCL) = 0,005. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 1656) yield the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((8)*(8))/16) + 0 = 4,000, a non-significant. Secondly. The same data demand too that the calculated $X^2(EXCL|Bt)$ is $X^2(EXCL|Bt) = (((8)*(8))/515\ ) + 0 = 0{,}124$, a significant result. The data of the study of Hardell, Eriksson, & Nordstrom et al. support both: GS excludes NHL and the same data demand too that GS do not exclude NHL which is a **contradiction**! Furthermore, the causal relationship k is not negative. In toto, the data of the study of Hardell, Eriksson, & Nordstrom et al. are self-contradictory, biased and cannot be used for these purposes. The causal relationship k is k = 0,040 and positive while the approximate 95% coincidence interval of the causal relationship k is between -0,015 and 0,095. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,96830 and not significant. Conclusion. There is no positive cause-effect relationship between GS and NHL. Thus far, according to the data of the study of Hardell, Eriksson, & Nordstrom et al., Glyphosate is neither a cause nor the cause of Non-Hodgkin Lymphoma.

Quod erat demonstrandum.

Theorem 3.3. (Glyphosate is not a cause of Non-Hodgkin Lymphoma.)

De Roos et al. (A. J. De Roos et al., 2003) examined whether an increased rate of non-Hodgkin's lymphoma (NHL) observed among farmers (Cantor, 1982) is due to pesticide exposures in farming. The term pesticide denotes a wide variety of chemicals used to destroy weeds (herbicides), insects (insecticides), and mold (fungicides).

Claim.

Null Hypothesis:

Glyphosate is not a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

De Roos et al. investigated the potential health effects of glyphosate in humans with respect of the development of Non-Hodgkin Lymphoma. The data as obtained by De Roos et al. (De Roos et al., 2003) are view by **table 9**.

Table **9**

The study of **De Roos et al.** **,** **2003** **.**

		Non-Hodgkin Lymphoma			
Country: **USA**		YES	NO		
Glyphosate	YES	36	61	**97**	
	NO	614	1932	2546	
		650	1993	**2643**	**PMID: 12937207**

Statistical analysis

Causal relationship k =	**0,057**	95 % CI (k) :	0,013	to	0,100
P value (k | HGD) =	**0,99824**	Chi Sq.(k) =	8,511		
p(IOI) =	**0,209**	**p(IOU) =**	**0,717**	**p(IOU) + p(IOI) =**	**0,927**
p (SINE) =	**0,768**	X^2(SINE|Bt) =	579,994	X^2(SINE|At) =	148,074
P likely (SINE)=	0,793	P Value (SINE)=	0,207		
p (IMP) =	**0,977**	X^2(IMP| At)) =	38,361	**X^2(IMP|Bt) =**	**1,867**
P likely (IMP) =	0,977	P Value (IMP) =	0,023		
p (SINE ^ IMP) =	**0,745**	X^2(SINE^IMP|At) =	581,861	X^2(SINE^IMP|Bt) =	581,861
p likely (SINE^IMP)=	0,775	p Value (SINE^IMP)=	0,225		
p (EXCL) =	**0,986**	X^2(EXCL| At)=	13,361	**X^2(EXCL|Bt)=**	**1,994**
P (Likely EXCL)=	0,986	P Value (EXCL)=	0,014		
Odds ratio (OR) =	1,857	95 % CI (OR) :	1,218	to	2,831

The index of independence of the study of De Roos et al. (A. J. De Roos et al., 2003) is p(IOI) = 0,209 and is not only of restricted value to consider these data for the re-analysis for causal relationship and for the re-analysis of the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,717 and indicates potentially biased data. Altogether, the data as published by the study of De Roos et al. are more or less potentially biased. The relative frequency of the **conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,768. The approximate P Value can be calculated as P Value (SINE) = 0,207. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 2643) yields the following result while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) =

3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((614)*(614))/ 650) + 0 = 579,994. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((614)*(614))/2546) + 0 = 148,074 . The data of the study of De Roos et al. do not support the hypothesis that GS is a necessary condition of NHL! However, mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio sine qua non relationship. The relative frequency of the conditio per quam relationship between GS and NHL is p (IMP) = 0,977. The approximate P Value can be calculated as P Value (IMP) = 0,023. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 2643) yield the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((61)*(61))/97) + 0 =38,361, a non-significant. Secondly. The same data demand that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) = (((61)*(61))/ 1993) + 0 = 1,867, a significant result . The data of the study of De Roos et al. support both: GS is a sufficient condition of NHL and the same data demand too that GS is not a sufficient condition of NHL which is **a contradiction**! However, mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio per quam relationship. The data of the study of De Roos et al. are biased and cannot be used for these purposes. Theoretically, GS may be effective against NHL. In this case we expect a significant negative causal relationship k and a significant exclusion relationship. The relative frequency of the **exclusion relationship** between GS and NHL is p (EXCL) = 0,986. The approximate P Value can be calculated as P Value (EXCL) = 0,014 and is significant. However, the significance of these data can be tested by the Chi-square goodness of fit test (sample size n = 2643) too and yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((36)*(36))/97) + 0 = 13,361, a non-significant result. Secondly. The same data demand too that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((36)*(36))/650) + 0 = 1,994, a significant result. In point of fact, the data of the study of De Roos et al. support in the same respect both: GS excludes NHL and the same data demand too that GS do not exclude NHL which is a contradiction while the causal relationship k is positive! The data of the study of De Roos et al. are biased and cannot be used for these purposes. The causal relationship k is k = 0,057 and positive while the approximate 95% coincidence interval of the causal relationship k is between 0,013 and 0,100. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,99824 and not significant. Formally, according to the data of De Roos et al. it is not possible to conclude that glyphosate is at least a cause of Non-Hodgkin Lymphoma.

Quod erat demonstrandum.

Theorem 3.4. (Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma.)

De Roos et al. (Anneclaire J. De Roos et al., 2005) evaluated the associations between the exposure to the broad-spectrum herbicide glyphosate and cancer incidence in a prospective cohort study of 57,311 applicators in the U.S.

Claim.

Null Hypothesis:

Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is either the cause or a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

De Roos et al. investigated the potential health effects of glyphosate in humans with respect of the development of Non-Hodgkin Lymphoma. The data as obtained by De Roos et al. (De Roos et al., 2005) are view by **table 10**.

Table **10**

The study of **De Roos et al.** **,** **2005** **.**

Country: USA		Non-Hodgkin Lymphoma YES	NO	
Glyphosate	YES	71	40964	**41035**
	NO	21	13259	13280
		92	54223	**54315**

PMID: 15626647

Statistical analysis

Causal relationship k =	**0,002**	95 % CI (k) :	-0,008	to	0,011
P value (k | HGD) =	**0,68001**	Chi Sq.(k) =	0,132		
p(IOI) =	**0,754**	**p(IOU) =**	**0,243**	**p(IOU) + p(IOI) =**	**0,997**
p (SINE) =	**1,000**	X²(SINE|Bt) =	4,793	**X²(SINE|At) =**	**0,033**
P likely (SINE)=	1,000	P Value (SINE)=	0,000		
p (IMP) =	**0,246**	X²(IMP| At)) =	40893,123	X²(IMP|Bt) =	30947,187
P likely (IMP) =	0,470	P Value (IMP) =	0,530		
p (SINE ^ IMP) =	**0,245**	X²(SINE^IMP|At) =	30951,980	X²(SINE^IMP|Bt) =	30951,980
p likely (SINE^IMP)=	0,470	p Value (SINE^IMP)=	0,530		
p (EXCL) =	**0,999**	**X²(EXCL| At)=**	**0,123**	X²(EXCL|Bt)=	54,793
P (Likely EXCL)=	0,999	P Value (EXCL)=	0,001		
Odds ratio (OR) =	1,094	95 % CI (OR) :	0,672	to	1,781

The index of independence of the study of De Roos et al. (Anneclaire J. De Roos et al., 2005) is p(IOI) = 0,754 and is more or less of none value to consider these data for the re-analysis for causal relationship k and for the re analysis of the exclusion relationship EXCL. The index of unfairness of this study is p(IOU) = 0,243 and indicates that the date are may be of some even if limited value to analyze the same data for conditions or risk factors. Altogether, the data as published by the study of De Roos et al. are more or less biased and can be considered with great care. The relative frequency of **the conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,999613. The approximate P Value can be calculated as P Value (SINE)

= 0,000387, a highly significant result. Based on this test statistics, without GS not NHL. However, the significance of these data tested by the Chi-square goodness of fit test (sample size n =54315) yields the following result, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((21)*(21))/ 92) + 0 = 4,793 and not significant. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((21)*(21))/ 13280) + 0 = 0,033, a significant result. Thus far, the data of this study of De Roos et al. support both: GS is a necessary condition of NHL and the same data demand too that GS is not a necessary condition of NHL which is **a contradiction**! This result cannot be considered as significant even if the causal relationship is positive. Whether a Chi-square goodness of fit test should be applied to such a sample size, is not the point of issue in this respect. The data this study of De Roos et al. are biased and of no use for these purposes. The relative frequency of the conditio per quam relationship between GS and NHL is p (IMP) = 0,246. The approximate P Value can be calculated as P Value (IMP) = 0,530, a non-significant result. In other words, the use or the contact with GS does not imply NHL. The significance of these data tested by the Chi-square goodness of fit test (sample size n =54315) yields the following result while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data of this study of De Roos et al. demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((40964)*(40964))/ 41035) + 0 = 40893,123, a non-significant result. Secondly. The same data demand that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) =(((40964)*(40964))/54223) + 0 = 30947,187, a non-significant result. The data of the study of De Roos et al. do not support the hypothesis that GS is a sufficient condition of NHL. However, it is necessary to obtain a significant sufficient condition to, to be able to establish a significant cause effect relationship. Contrary to expectation, the data of this study of De Roos et al. support the hypothesis too that GS protects against NHL. The relative frequency of **the exclusion relationship** between GS and NHL is p (EXCL) = 0,999. The approximate P Value can be calculated as P Value (EXCL) = 0,001, As proofed before, without GS no NHL and equally GS excludes NHL, which is a **contradiction**. The data of this study of De Roos et al. are just self-contradictory and of very limited value. In the same respect, the cause-effect relationship is not negative while the index of independence of the study of De Roos et al. (Anneclaire J. De Roos et al., 2005) is p(IOI) = 0,754 and far away from 0. Therefore, the conclusion GS excludes NHL is not justified even if supported by the data. The significance of these data tested by the Chi-square goodness of fit test (sample size n =54315) yields the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((71)*(71))/ 41035) + 0 = 0,123, a significant result. Secondly. The same data demand that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((71)*(71))/ 92) + 0 = 54,793, a non-significant result. The data of the study of De Roos et al. support both: GS excludes NHL and the same data demand too that GS does not exclude NHL which is **a contradiction**! The data of the study of De Roos et al. are biased and cannot be used for these purposes. The causal relationship k is k = 0,002 and positive while the approximate 95% coincidence interval of the causal relationship k is between -0,008 and 0,011. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,68001, p(IOI) = 0,754 and not significant. The data of De Roos et al., do not provide any valuable contribution with respect to the causal relationship between glyphosate and Non-Hodgkin Lymphoma. The null-hypothesis has not been rejected. There is no causal relationship between glyphosate and Non-Hodgkin Lymphoma according to this data of De Roos et al.

Quod erat demonstrandum.

Theorem 3.5. (Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma.)

Eriksson et al. (Eriksson, Hardell, Carlberg, & Akerman, 2008) evaluated the associations between the exposure to the broad-spectrum herbicide glyphosate and cancer incidence in a prospective cohort study of 57,311 applicators in the U.S.

Claim.

Null Hypothesis:

Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is either the cause or a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

Eriksson et al. (Eriksson, Hardell, Carlberg, & Akerman, 2008) investigated the potential health effects of glyphosate in humans with respect of the development of Non-Hodgkin Lymphoma. The data as obtained by Eriksson et al. (Eriksson, Hardell, Carlberg, & Akerman, 2008) are view by **table 11**.

Table		**11.**			
The study of		**Eriksson et al.** ,		**2008** .	
Country: **Sweden**		Non-Hodgkin Lymphoma YES	NO		
Glyphosate	YES	29	18	**47**	
	NO	881	998	1879	
		910	1016	**1926**	**PMID: 18623080**

Statistical analysis

Causal relationship k =	**0,046**	95 % CI (k) :	-0,005	to	0,097
P value (k | HGD) =	**0,98466**	Chi Sq.(k) =	4,038		
p(IOI) =	**0,448**	**p(IOU) =**	**0,503**	**p(IOU) + p(IOI) =**	**0,951**
p (SINE) =	**0,543**	X^2(SINE|Bt) =	852,924	X^2(SINE|At) =	413,071
P likely (SINE)=	0,633	P Value (SINE)=	0,367		
p (IMP) =	**0,991**	X^2(IMP| At)) =	6,894	**X^2(IMP|Bt) =**	**0,319**
P likely (IMP) =	0,991	P Value (IMP) =	0,009		
p (SINE ^ IMP) =	**0,533**	X^2(SINE^IMP|At) =	853,243	X^2(SINE^IMP|Bt) =	853,243
p likely (SINE^IMP)=	0,627	p Value (SINE^IMP)=	0,373		
p (EXCL) =	**0,985**	X^2(EXCL| At)=	17,894	**X^2(EXCL|Bt)=**	**0,924**
P (Likely EXCL)=	0,985	P Value (EXCL)=	0,015		
Odds ratio (OR) =	1,825	95 % CI (OR) :	1,007	to	3,309

The index of independence of the study of Eriksson et al. (Eriksson, Hardell, Carlberg, & Akerman, 2008) is p(IOI) = 0,448 and is only of restricted value to consider these data for the re-analysis for causal relationship and for the re-analysis of the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,503 and do not indicate potentially biased data. Altogether, the data as published by the study of Eriksson et al. are potentially biased. The relative frequency of **the conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,542575. The approximate P Value can be calculated as P Value (SINE) = 0,367089. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 1926) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((881)*(881))/910) + 0 = 852,924. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((881)*(881))/1879) + 0 = 413,071 while the causal relationship is positive but not significant. However, the data are only of limited value and more or less of no use for these purposes. The relative frequency of **the conditio per quam relationship** between GS and NHL is p (IMP) = 0,991. The approximate P Value can be calculated as P Value (IMP) = 0,009, a significant result. In other words, *if* contact with GS *then* NHL. However, the significance of these data tested by the Chi-square goodness of fit test (sample size n = 1926) too and yields the following result, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((18)*(18))/ 47) + 0 = 6,894, a non-significant result. Secondly. The same data demand too that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) = (((18)*(18))/1016) + 0 = 0,319, a significant result. The data of the study of Eriksson et al. support both: GS is a sufficient condition of NHL and the same data demand too that GS is not a sufficient condition of NHL which is **a contradiction!** Furthermore, mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio per quam relationship. The data of the study of Eriksson et al. are biased and cannot be used for these purposes. Again, and contrary to expectation, the use of GS can have protective effects against NHL. In this case we expect a significant negative causal relationship k which is not given and a significant exclusion relationship. The relative frequency of **the**

exclusion relationship between GS and NHL is p (EXCL) = 0,985. The approximate P Value can be calculated as P Value (EXCL) = 0,015. The significance of these data tested by the Chi-square goodness of fit test (sample size n = 1926) yields the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((29)*(29))/47) + 0 = 17,894. Secondly. The same data demand that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((29)*(29))/910) + 0 = 0,924, a significant result while the sample size of n = 1926 allows the use of the Chi-square distribution. The data of the study of Eriksson et al. support both: GS excludes NHL and the same data demand too that GS does not exclude NHL which is **a contradiction**! The data of the study of Eriksson et al. are biased and cannot be used for these purposes as already indicated by an is p(IOI) = 0,448. The causal relationship k is k = 0,046 and positive while the approximate 95% coincidence interval of the causal relationship k is between -0,005 and 0,097. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,98466 and not significant. In other words, glyphosate is neither a necessary condition nor a sufficient condition for the development of Non-Hodgkin Lymphoma. Furthermore, the data of Eriksson et al., glyphosate were not able to provide evidence that GS is either the cause or a cause of Non-Hodgkin Lymphoma.

Quod erat demonstrandum.

Theorem 3.6. (Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma.)

Orsi et al. (Orsi et al., 2009) conducted a hospital-based case-control study in France between 2000 and 2004 to investigate the relationship between occupational exposure to pesticides and the risk of lymphoid neoplasms in men.

Claim.

Null Hypothesis:

Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is either the cause or a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

The study of Orsi et al. (Orsi et al., 2009) investigated the potential health effects of glyphosate in humans with respect of the development of Non-Hodgkin Lymphoma. The data as obtained by Orsi et al. (Orsi et al., 2009) are view by **table 12**.

Table 12

The study of Orsi et al., 2009.

Country: **France**		Non-Hodgkin Lymphoma YES	NO		
Glyphosate	YES	12	24	**36**	
	NO	232	412	644	
		244	436	**680**	**PMID: 19017688**

Statistical analysis

Causal relationship k =	**-0,013**	95 % CI (k) :	-0,098	to	0,073
P value (k | HGD) =	**0,44676**	Chi Sq.(k) =	0,107		
p(IOI) =	**0,306**	**p(IOU) =**	**0,588**	**p(IOU) + p(IOI) =**	**0,894**
p (SINE) =	**0,659**	X²(SINE|Bt) =	220,590	X²(SINE|At) =	83,578
P likely (SINE)=	0,711	P Value (SINE)=	0,289		
p (IMP) =	**0,965**	X²(IMP| At)) =	16,000	X²(IMP|Bt) =	1,321
P likely (IMP) =	0,965	P Value (IMP) =	0,035		
p (SINE ^ IMP) =	**0,624**	X²(SINE^IMP|At) =	221,911	X²(SINE^IMP|Bt) =	221,911
p likely (SINE^IMP)=	0,686	p Value (SINE^IMP)=	0,314		
p (EXCL) =	**0,982**	X²(EXCL| At)=	4,000	X²(EXCL|Bt)=	0,590
P (Likely EXCL)=	0,983	P Value (EXCL)=	0,017		
Odds ratio (OR) =	0,888	95 % CI (OR) :	0,436	to	1,809

The index of independence of the study of Orsi et al. (Orsi et al., 2009) is p(IOI) = 0,306 and is of some and equally restricted value to consider these data for the re-analysis for causal relationship and for the re-analysis of the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,588 and indicate to some extent potentially biased data. Altogether, the data as published by the study of Orsi et al. are more or less not potentially biased. The relative frequency of **the conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,658824. The approximate P Value can be calculated as P Value (SINE) = 0,289067. The significance of these data tested by the Chi-square goodness of fit test (sample size n =680) yields the following results, while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((232)*(232))/244) + 0 = 220,590. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((232)*(232))/644) + 0 = 83,578. The data of the study of Orsi et al. do not support the hypothesis that GS is a necessary condition of NHL! Furthermore, mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio sine qua non relationship. The relative frequency of **the conditio per quam relationship** between GS and NHL is p (IMP) = 0,965.The approximate P Value can be calculated as P Value (IMP) = 0,035, a significant result. The significance of these data tested by the Chi-square goodness of fit test (sample size n =680) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((24)*(24))/36) + 0 =16,000, a non-significant result. Secondly. The same data demand that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) = (((24)*(24))/ 436) + 0 =1,321, a significant result.The data of the study of Orsi et al. support both: GS is a sufficient condition of NHL and the same data demand too that GS is not a sufficient condition of NHL which is not **a contradiction**! Furthermore, mathematically a **negative** causal relationship, even if not significant, does contradict the hypothesis of a conditio per quam relationship. The data of the study of Orsi et al. are biased and cannot be used for these purposes. The data of the study of Orsi et al. support the hypothesis that the use of GS has protective effects against NHL. In this case we expect a significant negative causal relationship k, which is given and a significant exclusion relationship, which is given too. The relative frequency of **the exclusion relationship** between GS and NHL is p (EXCL) = 0,982. The approximate P Value can be calculated as P Value (EXCL) = 0,017, a significant result. The significance of these data tested by the Chi-square goodness of fit test (sample size n =680) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((12)*(12))/36) + 0 = 4,000, a non-significant result. Secondly. The same data demand too that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((12)*(12))/244) + 0 =0,590, a significant result. In point of fact, the data of the study of Orsi et al. support the hypothesis that both: GS excludes NHL and the same data demand too that GS do not exclude NHL which is **a contradiction** while the use of the Chi-square distribution was justified (sample size n =680)! Even if the data of the study of Orsi et al. provide some evidence that GS excludes NHL such a conclusion is not justified, the data are potentially biased and cannot be used for these purposes. The causal relationship k is k = -0,013 and negative while the approximate 95% coincidence interval of the causal relationship k is between -0,098 and 0,073. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,44676 and not significant. However, mathematically it is not possible to obtain a negative causal relationship and at the same time a significant conditio per quam or a conditio sine qua non relationship. However, mathematically it is not possible to obtain a positive causal relationship and at the same time a significant exclusion relationship. The data of the study of Orsi et al. are biased and cannot be used for these purposes. Furthermore, mathematically a negative causal relationship, even if not significant, is not compatible with the hypothesis of a conditio per quam relationship as proofed before. In other words, according to the data of Orsi et al. glyphosate is neither a necessary condition for the development of Non-Hodgkin Lymphoma nor a sufficient condition. Furthermore, the Null-hypothesis above cannot be rejected. According to the data of Orsi et al., the use of glyphosate **and** Non-Hodgkin Lymphoma are not causally related.

Quod erat demonstrandum.

Theorem 3.7. (Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma.)

In the large, prospective cohort study of Andreotti et al. (Andreotti et al., 2018) the previous (De Roos et al., 2005) evaluation of glyphosate with cancer incidence was updated and again no association was apparent between glyphosate and any solid tumors including NHL and its subtypes.

Claim.

Null Hypothesis:

Glyphosate is neither the cause nor a cause of Non-Hodgkin Lymphoma. In other words, k = 0.

Alternative Hypothesis:

Glyphosate is either the cause or a cause of Non-Hodgkin Lymphoma. In other words, k >0.

Proof.

The study of Andreotti et al. investigated the potential health effects of glyphosate in humans with respect of the development of Non-Hodgkin Lymphoma. The data as obtained by De Roos et al. (De Roos et al., 2005) are view by **table 13**. The index of independence of the study of Andreotti et al. (Andreotti et al., 2018) is p(IOI) = 0,808 and is none and if at all only of restricted value to consider these data for the re-analysis of causal relationships and of the re-analysis of the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,171 and allows to some extent to analyze the data. Altogether, the data as published by the study of Andreotti et al. are more or less potentially biased. The relative frequency of **the conditio sine qua non relationship** between GS and NHL is p (SINE) = 0,997512. The approximate P Value can be calculated as P Value (SINE) =0,002485, a significant result. In other words, according to the study of Andreotti et al. *without* GS *no* NHL, while the cause effect relationship is **negative**! The significance of these data tested by the Chi-square goodness of fit test (sample size n =54251) yields the following result while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((135)*(135))/575) + 0 = 31,696, a non-significant result. Secondly. The same data demand that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((135)*(135))/9859) + 0 = 1,849, a significant result.

Table **13**

The study of **Andreotti et al.** , **2018** .

		Non-Hodgkin Lymphoma			
Country: **USA**		YES	NO		
Glyphosate	YES	440	43952	**44392**	
	NO	135	9724	9859	
		575	53676	**54251**	**PMID: 29136183**

Statistical analysis

Causal relationship k =	**-0,014**	95 % CI (k) :	-0,024	to	-0,005
P value (k | HGD) =	**0,00077**	Chi Sq.(k) =	11,000		
p(IOI) =	**0,808**	**p(IOU) =**	**0,171**	**p(IOU) + p(IOI) =**	**0,979**
p (SINE) =	**0,998**	X²(SINE|Bt) =	31,696	**X²(SINE|At) =**	**1,849**
P likely (SINE)=	0,998	P Value (SINE)=	0,002		
p (IMP) =	**0,190**	X²(IMP| At)) =	43516,361	X²(IMP|Bt) =	35989,610
P likely (IMP) =	0,445	P Value (IMP) =	0,555		
p (SINE ^ IMP) =	**0,187**	X²(SINE^IMP|At) =	36021,306	X²(SINE^IMP|Bt) =	36021,306
p likely (SINE^IMP)=	0,444	p Value (SINE^IMP)=	0,556		
p (EXCL) =	**0,992**	X²(EXCL| At)=	4,361	X²(EXCL|Bt)=	336,696
P (Likely EXCL)=	0,992	P Value (EXCL)=	0,008		
Odds ratio (OR) =	0,721	95 % CI (OR) :	0,594	to	0,876

The data of the study of Andreotti et al. support both: GS is a necessary condition of NHL and the same data demand too that GS is not a necessary condition of NHL which is **a contradiction**! Furthermore, mathematically a negative causal relationship, even if not significant, is not compatible with the hypothesis of a conditio sine qua non relationship. The data of the study of Andreotti et al. are biased and of no use for these purposes.

The relative frequency of **the conditio per quam relationship** between GS and NHL is p (IMP) = 0,190. The approximate P Value can be calculated as P Value (IMP) =0,555, a non-significant result. The significance of these data tested by the Chi-square goodness of fit test (sample size n =54251) yields the following results while the X² critical (degrees of freedom =

1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(IMP|At) is X^2(IMP|At) = (((43952)*(43952))/44392) + 0 = 43516,361, a non-significant result. Secondly. The same data demand that the calculated X^2(IMP|Not Bt) is X^2(IMP|Not Bt) = (((43952)*(43952))/53676) + 0 = 35989,610, a non-significant result. The data of the study of Andreotti et al.do not support the hypothesis that GS is a sufficient condition of NHL. Furthermore, mathematically a negative causal relationship, even if not significant, is not compatible with the hypothesis of a conditio per quam relationship. The data of the study of Andreotti et al. are biased and cannot be used for these purposes. Contrary to expectation, following the data of the study of Andreotti et al. (Andreotti et al., 2018) we must conclude that GS is an antidot against NHL. In this case we expect *a significant negative causal relationship k* and *a significant exclusion relationship* and indeed both is given. The relative frequency of **the exclusion relationship** between GS and NHL is p (EXCL) = 0,992. The approximate P Value can be calculated as P Value (EXCL) = 0,008. The significance of these data tested by the Chi-square goodness of fit test (sample size n =54251) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(EXCL|At) is X^2(EXCL|At) = (((440)*(440))/44392) + 0 = 4,361, a non-significant result. Secondly. The same data demand too that the calculated X^2(EXCL|Bt) is X^2(EXCL|Bt) = (((440)*(440))/575) + 0 = 336,696, a non-significant result. Based on the Chi-square distribution, the data of the study of Andreotti et al. do not support the hypothesis that GS excludes NHL which is **a contradiction**. The **causal relationship** k is k = -0,014 and negative, while the approximate 95% coincidence interval of the causal relationship k is between -0,024 and -0,005. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,00077 and highly significant. Thus far and formally the conclusion is imperative that **GS protects against NHL**. However, such a conclusion is fallacious too and not justified at all. Firstly. The index of unfairness of this study is p(IOU) = 0,171 and even if very low does not guarantee that the data are of any use when analyzed for an exclusion relationship. Secondly. To rely on the data when analyzing the same for an exclusion relationship we need a very low p(IOI), if possible, a p(IOI) equal to zero, which is not given. The index of independence of the study of Andreotti et al. (Andreotti et al., 2018) is p(IOI) = 0,808 with the consequence that it does not make any sense to consider the highly significant negative causal relationship between GS and NHL as given within the population. The data of the study of Andreotti et al. are biased and do not provide anything valuable on the causal relationship between GS and NHL. In other words, according to the data of Andreotti et al. glyphosate is neither a necessary condition for the development of Non-Hodgkin Lymphoma nor a sufficient condition. Furthermore, the Null-hypothesis above must be rejected. According to the data of Andreotti et al., there is no significant positive causal relationship between the use of glyphosate and Non-Hodgkin Lymphoma (k = -0,014).

Quod erat demonstrandum.

Theorem 3.8. (Without Epstein-Barr virus infection no Non-Hodgkin Lymphoma.)

Non-Hodgkin lymphomas differ in several aspects but share some features too. Epstein-Barr virus (EBV) is possibly one of these common features and has been discussed (IARC, 2012) as a cause of non-Hodgkin lymphoma (NHL). However, the role of EBV in non-Hodgkin lymphomas (NHLs) remains unclear. Teras et al. (Teras et al., 2015) examined the association between prospectively-collected plasma EBV antibodies and NHL risk in the Cancer Prevention Study-II (CPS-II) Nutrition Cohort which included 225 NHL cases and 2:1 matched controls and documented an association between EBV serostatus or antibody levels (early antigen) and risk of the three most common types of NHL (diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma).

Claim.

Null Hypothesis:

Epstein-Barr virus infection is a necessary condition of Non-Hodgkin Lymphoma.

In other words, *without* an Epstein-Barr virus infection *no* Non-Hodgkin Lymphoma.

Alternative Hypothesis:

Epstein-Barr virus infection is not a necessary condition of Non-Hodgkin Lymphoma.

In other words, a human being can suffer from Non-Hodgkin Lymphoma even if not Epstein-Barr virus positive.

Proof.

The study of Teras et al. investigated the potential role of EBV in non-Hodgkin lymphomas (NHLs). The data as obtained by Teras et al. (Teras et al., 2015) are view by **table 14**.

Table 14

The study of Teras et al., 2015.

Country: **USA**		Non-Hodgkin Lymphoma YES	NO		
EBV	YES	212	416	**628**	
	NO	13	33	46	
		225	449	**674**	**PMID: 24831943**

Statistical analysis

Causal relationship k =	**0,029**	95 % CI (k) :	-0,057	to	0,116
P value (k | HGD) =	**0,82192**	Chi Sq.(k) =	0,582		
p(IOI) =	**0,598**	p(IOU) =	0,266	**p(IOU) + p(IOI) =**	**0,864**
p (SINE) =	**0,981**	**X²(SINE|Bt) =**	**0,751**	**X²(SINE|At) =**	**3,674**
P likely (SINE)=	0,981	P Value (SINE)=	0,019		
p (IMP) =	**0,383**	X²(IMP| At)) =	275,567	X²(IMP|Bt) =	385,425
P likely (IMP) =	0,539	P Value (IMP) =	0,461		
p (SINE ^ IMP) =	**0,364**	X²(SINE^IMP|At) =	386,177	X²(SINE^IMP|Bt) =	386,177
p likely (SINE^IMP)=	0,529	p Value (SINE^IMP)=	0,471		
p (EXCL) =	**0,685**	X²(EXCL| At)=	71,567	X²(EXCL|Bt)=	199,751
P (Likely EXCL)=	0,730	P Value (EXCL)=	0,270		
Odds ratio (OR) =	1,294	95 % CI (OR) :	0,667	to	2,510

The index of independence of the study of Teras et al. (Teras et al., 2015) is p(IOI) = 0,598. The data are only of restricted value to consider these data for the re-analysis for causal relationship or for the re-analysis of the exclusion relationship. The index of unfairness of this study is p(IOU) = 0,266 and allows to some extent to analyze the data for conditions or risk factors. The relative frequency of the **conditio sine qua non relationship** between Epstein-Bar virus (EBV) and NHL is p (SINE) = 0,980712. The approximate P Value can be calculated as P Value (SINE) = 0,019103, a significant result. The significance of these data tested by the Chi-square goodness of fit test (sample size n =674) yields the following results while the X^2 critical (degrees of freedom = 1, Alpha 0,05) is X^2(critical) = 3,84145882. Firstly. The data demand that the calculated X^2(SINE|Bt) is X^2(SINE|Bt) = (((13)*(13))/ 225) + 0 = 0,751, a significant result. Secondly. The same data demand too that the calculated X^2(SINE|Not At) is X^2(SINE|Not At) = (((13)*(13))/46) + 0 = 3,674, a significant result. The data of the study of Teras et al.do support the hypothesis that **EBV is a necessary condition of NHL** while the causal relationship k is positive, but not significant. In other words, without an EBV infection no NHL. Mathematically a positive causal relationship, even if not significant, does not contradict the hypothesis of a conditio sine qua non relationship. The causal relationship k is k = 0,029 and positive while the approximate 95% coincidence interval of the causal relationship k is between -0,057 and 0,116. The left tailed P Value of the causal relationship k calculated according to the hypergeometric distribution is P Value (k | HGD) = 0,82192 and not significant. In other words, according to the data of Teras et al. (Teras et al., 2015) we cannot reject the null-hypothesis: **EBV is a necessary condition of Non-Hodgkin Lymphoma**. There is another aspect to the characterization of this relationship: *without* EBV infection *no* Non-Hodgkin Lymphoma.

Quod erat demonstrandum.

4. Discussion

NHL consists of more than 40 major subtypes and is a very heterogeneous group of malignant lymphoid tumors. **Historically, people suffered from NHL before the existence or the use of GS**. In other words, historically, it is proven that **the existence or the use of GS is not a necessary condition for the development of NHL**. Independently of this historical fact, todays data proof this hypothesis too. The National Cancer Institute (NCI) reported 2019 about 19,6 new cases of non-Hodgkin lymphoma per 100,000 men and women per year (National Cancer Institute, 2019). The data as reported by NCI are viewed by the table (**Table 15**) below.

Table 7. Percent of New U. S. Cases of Non-Hodgkin Lymphoma by Age Group according to National Cancer Institute 2019 (NCI, 2019).

Percent of New NHL U.S. Cases	1,7 %	3,6 %	5,1 %	11,8 %	21,3 %	26,0 %	20,9 %	9,6 %
Age	< 20	20-34	35-44	45-54	55-64	65-74	75-84	>84

According to National Cancer Institute, NHL can occur at any age and especially in the childhood (Sandlund, 2015). There does not appear to be any justifiable reason to assume, that very small children or even newborn children are working somehow with glyphosate frequently or at all. Therefore, no human reason can provide serious evidence of the hypothesis that *without* GS *no* NHL. **Glyphosate [N-(phosphonomethyl)glycine] has not been and is not a necessary condition for the development of Non-Hodgkin Lymphoma**. None of the studies analyzed provided clear evidence of a significant conditio sine qua non relationship (without GS no NHL) between GS and NHL. Two studies (De Roos et al., 2005; Andreotti et al., 2018) were self-contradictory (**Table 16**) on this point.

Table 8. Overview of the results achieved.

Study ID	Year	N	Case_P	Case_T	Con_P	Con_T	IOU	k	$X^2(IMP\|A_t)$	$X^2(IMP\|\underline{B}_t)$	$X^2(SINE\|B_t)$	$X^2(SINE\|\underline{A}_t)$
McDuffie et al.	2001	2023	51	517	133	1506	-0,65	+0,02	96,14	11,75	420,03	118,08
Hardell et al.	2002	1656	8	515	8	1141	-0,68	+0,04	**4,00**	**0,06**	99,12	156,74
De Roos et al.	2003	2583	36	650	61	1933	-0,71	**+0,05**	**38,36**	**1,92**	579,99	151,65
De Roos et al.	2005	54315	71	92	40964	54223	-0,24	+0,00	40893,12	30947,19	4,79	0,03
Eriksson et al.	2008	1926	29	910	18	1016	-0,50	**+0,05**	**6,89**	**0,32**	852,92	413,07
Orsi et al.	2009	680	12	244	24	436	-0,59	-0,01	**16,00**	**1,32**	220,59	83,58
Andreotti et al.	2018	54251	440	575	43952	53676	-0,17	**-0,01**	43516,36	35989,61	31,70	1,85

N = sample size. Case_P: case, positive. Case_T: number of cases. Con_P: control, positive, Con_T: number of controls.

None of the studies analyzed provide non-selfcontradictory results of a cause effect realtionship between GS and NHL. The systematic review and meta-analysis by Chang and Delzell (Chang & Delzell, 2016) examined the relationship between glyphosate exposure and among other, the risk of NHL and was not able to establish a causal relationship between glyphosate exposure and the risk of any type of lymphohematopoietic cancer (LHC) including NHL. In contrast to Chang and Delzell, the meta-analysis conducted by Zang et al. (Zhang, Rana, Taioli, Shaffer, & Sheppard, 2019) used published human studies on the relationship between exposures to GS and NHL and reported that GS exposure is associated with increased risk of NHL. However, the meta-analysis of Zang et al. is grossly flawed, one-sided and worthless in toto due to several reasons. The data of the most studies considered by Zang et al. (Zhang, Rana, Taioli, Shaffer, & Sheppard, 2019) are self-contradictory and of none or of an extremely limited value, which was ignored by the study group completely. Other possible factors which are causally related to NHL were not considered at all or even to a necessary extent. Statistical methods, far away from being able, to provide anything valuable on the point of issue, were used with the consequence that everything desirable can be proofed as correct, even pure non-sense. The inconsistency of Forest plot (I. Barukčić, 2019b) supported meta-analysis was ignored completely. The results of this systematic review and meta-analysis suggest that **EBV and not glyphosate is causally linked with a wider spectrum of NHL subtypes**. Still, this cannot be considered as the final proof of the relationship between EBV and NHL and further and better designed studies are needed to confirm and fully understand the etiology of NHL. Besides of all, as long as no better data are available, it is justified, necessary and allowed to deduce the following conclusion.

5. Conclusion

Glyphosate is neither a cause nor the cause of Non-Hodgkin Lymphoma.

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Author Contributions

The author confirms being the sole contributor of this work and has approved it for publication.

Conflict of Interest Statement

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