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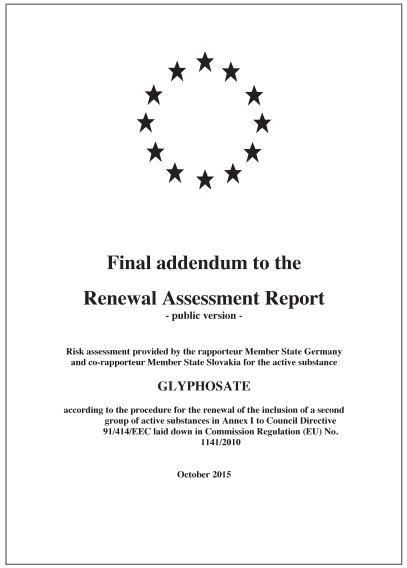
Detailed Expert Report on Plagiarism and superordinated Copy Paste in the Renewal Assessment Report (RAR) on Glyphosate



Final addendum to the

Renewal Assessment Report

- public version -

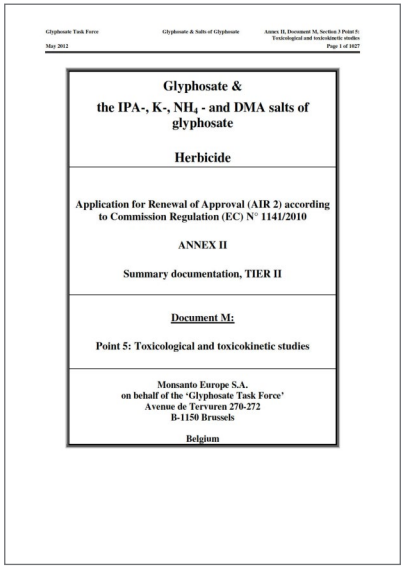
Risk assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia for the active substance

GLYPHOSATE

according to the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91/414/EEC laid down in Commission Regulation (EU) No. 1141/2010

October 2015

VS.



Glyphosate Task Force — Glyphosate & Salts of Glyphosate — Annex II, Document M, Section 3 Point 5: Toxicological and toxicokinetic studies — May 2012 — Page 1 of 1027

Glyphosate &

the IPA-, K-, NH_4 - and DMA salts of glyphosate

Herbicide

Application for Renewal of Approval (AIR 2) according to Commission Regulation (EC) N° 1141/2010

ANNEX II

Summary documentation, TIER II

Document M:

Point 5: Toxicological and toxicokinetic studies

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Table of contents

Colouring, technical terms, abbreviations and acronyms

Colouring

Colouring of "benign" copy paste in this expert report

Colouring of plagiarism (= "malign" copy paste) in this expert report

Colouring of "benign" copy paste and plagiarism (= "malign" copy paste) alltogether

Technical terms

Copy paste

We define copy paste as a technical act of marking text segments, copying them and pasting them into another file. This practice is per se neutral and can be either "benign" (for example if one puts the copy pasted text afterwards manually into quotation marks and adds a reference) or "malign" (if one pretends authorship for the copied text that in fact originates from another author).

Plagiarism

Plagiarism is the "malign" form of copy paste. Plagiarism is nearly always connected with cheating and deception of the reader. We define plagiarism in accordance with the "Principles of 'Good Scientific Practice'" of the BfR. The definition reads as follows: "Unauthorised use under the pretence of authorship".[1] This means that the real author is concealed and the reader gets a wrong impression about the authorship. The reader falsely attributes sentences, phrasings, data, statistics, synopses, etc. to an indicated or supposed author, when in fact they were collected, arranged, and written by another author. The international gold standard of scientific citation practice is the guideline of the American Psychological Association – APA. The APA states: "The key element of this principle is that authors do not present the work of another as if it were their own work. This can extend to ideas as well as written words."[2] And the recommendation is clear: "Quotation marks should be used to indicate the exact words of another."[3]

Scientific misconduct

Plagiarism is one variant of scientific misconduct. Others include ghostwriting, unethical authorship (false attribution to authors who did not in fact contribute to a paper), and the manipulation or even fabrication of data and results.[4] ("Questionable research practices" [QRPs] is a new term describing the 'grey zone' between scientific misconduct and merely 'bad practice': for example, biasing results for the client.)

Industry studies

Toxicological studies that have been commissioned or conducted by the pesticide manufacturers in order to demonstrate that their substance meets the criteria for approval. Industry studies are usually carried out according to good laboratory practice (GLP)[5] and follow narrow test guidelines (OECD Guidelines). With a few exceptions, these industry studies are not publicly available.

Published literature

Mostly peer-reviewed scientific studies from the public domain. Since June 2011, the pesticide regulation (EC) No 1107/2009 obliges the EU authorities to consider published studies for pesticide risk assessment in addition to the industry studies.[6] Published literature always has to conform to the principles of "Good

Scientific Practice" (GSP, "gute wissenschaftliche Praxis", GWP in German), a term that became widespread in Europe's scientific community in the early nineties.[7]

Klimisch evaluation

The Klimisch evaluation is named after Hans-Joachim Klimisch, a scientific employee at the chemical company BASF, who in 1997 published together with colleagues a systematic approach to assessing the quality of toxicological and ecotoxicological data.[8] Klimisch and colleagues proposed the following categories for evaluating the reliability of studies:

- Klimisch score 1: reliable without restriction
- Klimisch score 2: reliable with restriction
- Klimisch score 3: not reliable
- Klimisch score 4: not assignable

Criticism of the Klimisch criteria is based on the fact that in order to achieve the highest score, "reliable without restrictions", the study must be carried out according to GLP (Good Laboratory Practice) standards, a criterion designed to prevent scientific fraud in industry studies. As a result, only industry studies, but not published studies (which are usually not carried out as GLP studies), can be scored as "reliable without restriction".

Abbreviations and acronyms

BfR: Federal Institute for Risk Assessment (in German: Bundesinstitut für Risikobewertung)

EFSA: European Food Safety Authority

GLP: Good Laboratory Practice

GTF: Glyphosate Task Force

IARC: International Agency for Research on Cancer

PEST: European Parliament's Special Committee on the Union's authorisation procedure for pesticides

RAR: Renewal Assessment Report

RMS: Rapporteur Member State

UBA: Federal Environment Agency (in German: Umweltbundesamt)

Executive summary

Introduction

The classification of glyphosate as a probable human carcinogen in March 2015 by the World Health Organisation's cancer agency IARC triggered a public debate on why this body's verdict was at odds with the European Union's "clean bill of health" for the chemical. The question arose at to whether relevant parts of the risk assessment of glyphosate were not actually written by scientists working for Germany's Federal Institute for Risk Assessment (BfR), but by the European Glyphosate Task Force (GTF) – the coalition of pesticide companies submitting the application. This suspicion could not be satisfactorily cleared up during the hearings of the European Parliament's Special Committee on the Union's authorisation procedure for pesticides (PEST). Therefore in response, a group of parliamentarians with different political affiliations commissioned the present study.

Method

Using the software WCopyfind, the study authors Stefan Weber and Helmut Burtscher-Schaden compared the assessment of health risks by the BfR and the assessment of published studies on environmental risks by the German Environment Agency (UBA) with the corresponding chapters in the application of the Glyphosate Task Force. In a second step, the parts of the text identified as copy pasted were evaluated in detail as to whether they fulfil the criteria of plagiarism. Plagiarism can be defined as the wrongful appropriation by an author or authors of other authors' content without acknowledgement of the true source and under the pretext of self-authorship.

Results

The study authors identified different approaches of the BfR, depending on whether the authority was dealing with the manufacturers' own unpublished studies, referred to as "industry studies", or studies that were carried out by academic, private or governmental researchers, independently from the manufacturers, referred to as "published studies".

Plagiarism was discovered exclusively in the chapters dealing with the assessment of published studies on health risks related to glyphosate. **In these chapters, 50.1% of the content was identified as plagiarism (= "malign" copy paste).** This includes whole paragraphs and entire pages of running text describing the design and outcome of the studies and assessing their relevance and reliability. Among other things, each of the 58 so-called Klimisch evaluations of published studies in the BfR's assessment report were copy pasted from the application for approval and presented as the assessments of the authorities. As a result of the BfR's verbatim adoption of the industry applicants' Klimisch evaluations, the authority failed to classify even a single published study on glyphosate and/or its commercial formulations as relevant or reliable. This also applies to the epidemiological studies on non-Hodgkin lymphoma, which, according to the IARC experts, raise suspicions that glyphosate causes cancer in humans. **In addition to the 50.1% plagiarized text, 22.7% copy pasted content that was not classified as plagiarism was identified (= "benign" copy paste), resulting in a total of 72.8% copy paste (= "malign" and "benign" altogether) in the chapters on published studies.**

In the chapters on industry studies, the total proportion of copy paste is even higher, at 81.4%. However, this type of copy paste was not classified as plagiarism, as the BfR had explained its copy paste approach for the evaluation of industry studies in its „general introduction". The BfR also explained that the

copy of the GTF's assessment was followed by clearly distinguished comments from the authority. These descriptions of the BfR's approach to assessing industry studies were confirmed by the study authors' analysis. However, the descriptions of the BfR's approach to assessing published studies could not be confirmed. On the contrary, here, the study authors' analysis revealed – and this is one of their most remarkable findings – that even the BfR's description and explanation of the approach to assessing the published literature had been plagiarised from the GTF application. The BfR had thus copied Monsanto's explanation of Monsanto's approach in evaluating the published literature, yet had presented it as the approach of the authority. This is a striking example of deception regarding true authorship.

A different picture emerged from the examination of the evaluation of published studies on environmental risks posed by glyphosate. **In this part of the assessment report, which was not the responsibility of the BfR but of the UBA, copy paste and plagiarism could only be detected in traces – 2.5% and 0.1% respectively.**

Conclusion

The study authors' analyses, in particular their detailed analysis of the chapters on carcinogenicity, suggest that the BfR's practice of copy paste and plagiarism is at odds with an independent, objective, and transparent assessment of the risks, and that this practice influenced the authority's conclusions on glyphosate's safety. In addition, the study authors found clear evidence of BfR's deliberate pretence of an independent assessment, whereas in reality the authority was only echoing the industry applicants' assessment.

1. Chronology of the controversy over copy paste and plagiarism

When the Federal Institute for Risk Assessment (BfR) declared in March 2015 that glyphosate was not carcinogenic,[9] thus contradicting the International Agency for the Research on Cancer (IARC),[10] it opened a discussion that continues to this day about the causes of the stark contradiction in the assessments of these two public health organisations.

In May 2015, an article in the British newspaper *The Guardian* suggested that the underlying reason for the discrepancy could be that much of the BfR's evaluation of glyphosate "was not actually written by scientists working for the German Federal Institute for Risk Assessment (BfR), but rather by the European Glyphosate Task Force, a consortium of agrochemical firms."[11] But soon afterwards, the responsible German Federal Ministry of Agriculture issued a clear denial. In a written response to a request from the Greens in the German Bundestag (Parliament), the Ministry of Agriculture stated that the assessment report, in particular the relevant chapters on the scientific literature, "contained only assessments written by BfR staff".[12]

After this statement, accusations of copy paste disappeared from the public debate for more than two years until they were raised again in autumn 2017: In his book *The Glyphosate Files*,[13] Helmut Burtscher-Schaden claimed that "manifest misrepresentations of epidemiological studies" had been transferred from the GTF's application to the BfR's assessment report by means of copy paste. As a result, all epidemiological cancer studies that reported an increased incidence of non-Hodgkin lymphoma in farmers working with glyphosate-based herbicides were rejected as „unreliable" by the authorities, according to the author.

In mid-September 2017, the copy paste topic made it onto the front pages of newspapers throughout the EU, with some of them reporting in detail that the EU authorities had taken descriptions, interpretations, and assessments of key studies verbatim from the GTF application, while systematically deleting or omitting references to the real authors. An article in the German newspaper *Süddeutsche Zeitung* pointed out that even renowned scientists were wrong-footed by the BfR's copy paste practice, when it stated: "Professor Eberhard Greiser, former head of the largest epidemiological research institute in Germany at the time, had accused the BfR of 'scientific falsification'. Reason: The alleged deficiencies of the studies mentioned in the official report did not exist from Greiser's point of view. His written elaboration[14] for the committee, which is still available on the website of the Bundestag, quoted the passages that literally come from the dossier of the industry. Greiser, too, had taken for an official judgment what in reality was industry opinion."[15] The question of plagiarism and intent to deceive was raised.

In written statements, the BfR[16] and the European Food Safety Agency (EFSA),[17] which had peer-reviewed and adopted the BfR's report, rejected any accusations of plagiarism or scientific misconduct. The BfR called the accusations "another attempt to discredit the reliability of scientific institutions which were tasked with assessing the health hazards of pesticides such as glyphosate",[18] whilst the EFSA called them "the latest in a series of efforts to discredit the scientific process behind the EU assessment of glyphosate".[19] The BfR argued that it was "common and recognized practice for regulatory authorities to also integrate relevant passages taken from submitted documents into their assessment reports after critical review".[20] The EFSA backed up this argument by stating: "If the RMS agrees with a particular summary or evaluation it may incorporate the text directly into the draft assessment report."[21] The BfR stressed that its assessment of glyphosate was carried out "in accordance with legal requirements" and that "the same procedure had been used throughout the EU for all other more than 450 pesticide active substances approved to date". This would also apply for the other German authorities involved in the current evaluation of glyphosate, the Julius Kühn Institute (JKI) and the German Environment Agency (UBA).[22]

The Austrian environmental organisation Global 2000 commissioned the plagiarism expert Stefan Weber to assess the copy paste practice applied by the BfR and the EFSA with regard to three subchapters, which represent the evaluation of only the published scientific literature on the carcinogenicity, genotoxicity and reporoductive toxicity of glyphosate. Weber's expert opinion, which identified "plagiarism" and "significant scientific misconduct" in the sections on published literature, was published on 5 October 2017.[23]

At the "Monsanto Hearing" in the European Parliament on October 11, Jose Tarazona, the head of the EFSA pesticide unit, defended the EFSA and the BfR against "allegations of copy and paste and plagiarism", stating that these allegations came from "people that do not understand the process".[24] Tarazona explained that in the assessment report, the assessment of the company is "obviously copy pasted from the company – because it is the assessment of the company" but one could also see "the assessment by the member states": "For every single study that has been considered relevant you can see […] the conclusion by industry […] and the comment from the Rapporteur Member State" . In order to illustrate this, Tarazona picked two examples from the assessment report, where the "conclusion by the notifiers" was followed and contradicted by a separate "Rapporteur Member State comment",[25] written in italics. According to Tarazona, this clearly indicated that the BfR made its own independent assessment of every relevant study.

Tarazona's argument was picked up by the journalist Kolja Rudzio of the German weekly newspaper *Die Zeit* to denounce Stefan Weber's accusation of plagiarism as unfounded. In the series *Fact or Fake*, Kolja Rudzio explained that the copied representations of the industry studies were followed by a "deviating comment of the authority, written in italics". Therefore, it would be "completely clear for the reader, which originates from whom", and it was "not true that local officials secretly and unquestioningly copy from the documents of the agricultural companies".[26]

The BfR's exoneration from the accusation of plagiarism by the renowned weekly newspaper was taken up by other media and gave the authority some relief. But in December 2017, Tarazona's argument that every single relevant study was followed by a "Rapporteur Member State comment" was contradicted in the German television magazine *FAKT*. The journalist Andreas Rummel confronted Jose Tarazona on camera with print outs of the almost entirely copy pasted chapter on published studies on Genotoxicity. Tarazona was not able to show examples of "comments" or any other genuine assessment from the BfR in this chapter. He said: "I believe there is some misunderstanding concerning copy and paste in the assessments. The relevant aspects, the authorities' conclusions, are in Volume 1 of the assessment report. And there is no copy and paste in Volume 1." However, the german public service broadcaster *ARD* checked this and reported that this claim was false. There would be pages of copy and paste also in Volume 1.[27]

In May 2018, the president of the BfR, Andreas Hensel, was invited to the European Parliament's Special Committee on the EU authorisation procedure for pesticides (PEST Committee). In his written answer to a question from the Committee concerning the type and frequency of the copy paste practice and its influence on the assessment's independence, Hensel put forward a new argument: "The evaluation reports are not reports originally intended for publication by the author BfR, but documents between authorities for use in a (European) administrative procedure. Therefore, the standards to be applied are those of the administration, thus differing from those for scientific publications or e.g. PhD theses."[28] The accusation of scientific misconduct was again rejected by the BfR.

Finally, in December 2018, the German broadcaster *Bayerischer Rundfunk* published a data analysis for a total of 25 applications for renewal of pesticide active substances (other than glyphosate) in the EU under the title, „Pesticides: How EU authorities copied from industry".[29] In 15 out of 25 risk assessments carried out by different European authorities, the research team of *Bayerischer Rundfunk* identified copy paste from the manufacturers' applications without reference to

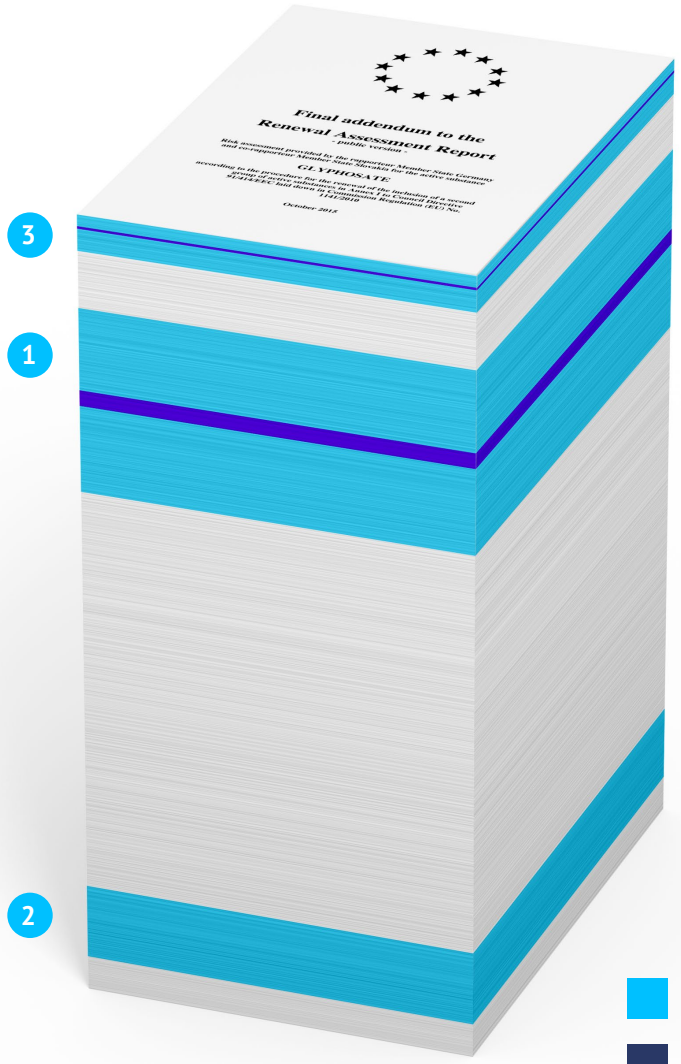
the source. In answer to BR's request, EFSA states: „The Authority's task is to review the manufacturer's self-assessment and not to rewrite everything."

Taken together, in the opinion of some members of the PEST Committee, the authorities were neither able to satisfyingly demonstrate that the risk assessment of glyphosate was carried out independently and transparently, nor to dispel the suspicion of plagiarism. On the other hand, the allegation of plagiarism was based only on a brief exploratory analysis of three selected subchapters, which together accounted for less than 2.5% of the total report. Therefore, several Members of the European Parliament's PEST committee from three different political groups[30] commissioned the plagiarism expert Stefan Weber and biochemist Helmut Burtscher-Schaden, together with a small team of experts, to conduct a comprehensive analysis of the BfR's assessment of the health risks of glyphosate, with regard to copy paste and plagiarism and its possible impact on the independence, objectivity and transparency of the EU's approval process of glyphosate.

2. Subject, methodology, and research question

The research topics of this copy paste and plagiarism study are the following parts of the 4,322-page document, "Final addendum to the Renewal Assessment Report" on Glyphosate, hereinafter referred to as the "**RAR**". Chronological order of the analysed chapters in this expert report:

1. **Volume 3 B.6 Toxicology and metabolism** (1,004 pages): Assessment of glyphosate health effects, based on industry studies and peer-reviewed published literature. Responsible authority: BfR (Federal Institute for Risk Assessment, Germany)
2. **Volume 3 B.9 (Appendix) Evaluation of peer-reviewed literature regarding ecotoxicity** (406 pages): Assessment of environmental effects, based on peer-reviewed literature. Responsible authority: UBA (German Environment Agency)
3. **Volume 1 Report and Proposed Decision** (196 pages): Summary of the evaluations in Volume 3 and overall assessment.



Subchapter Volume 1: "2.6.6 Summary of long-term toxicity and carcinogenicity" pp. 67-80

Subchapter Volume 3: "B.6.5 Long-term toxicity and carcinogenicity" pp. 955-1,040

Examined pages

Detail analysis of examined pages

Using the software WCopyfind, the above three sections of the **RAR** were compared electronically with the following published parts of the glyphosate dossier that was submitted by the Glyphosate Task Force (GTF) for the renewal of the application, hereinafter referred to as "**GTF application**":

- **AII_Doc M TIER II_Section 3_Sanitized_Nov2013** (PDF, 1,027 pages)
- **AII_Doc M TIER II_Section 6_Sanitized_Nov2013** (PDF, 651 pages)
- **Application_Sanitized_Nov2013** (PDF, 101 pages)
- **AII-III_Doc N_Overall_Assessment_Sanitized_Nov2013** (PDF, 85 pages)

In a second step, the text passages identified as copied from the GTF application were subjected to a qualitative text analysis in order to distinguish between copy paste that is not to be classified as plagiarism ("benign" copy paste) and copy paste that must be classified as plagiarism ("malign" copy paste).

Finally, the respective chapters on glyphosate carcinogenicity in Volume 3 B.6 ("Long-term toxicity and carcinogenicity") and Volume 1 ("Summary of long-term toxicity and carcinogenicity") were subjected to a detailed analysis.

This expert report, the examined documents as well as the raw data of this analysis (all classified text segments) can be downloaded from this website:

https://bit.ly/Copy-Paste-Glyphosate

Special research questions posed to the study authors were:

1) Did copy paste and plagiarism influence the BfR's clean bill of health for glyphosate?
2) Is the contradiction between the assessment of glyphosate by the WHO Cancer Research Agency IARC and the EU authorities (also) a consequence of the authorities' copy paste and plagiarism practice?
3) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the arguments raised by the BfR, the EFSA, and the German Ministry of Agriculture in order to refute the first accusations of plagiarism?
4) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the statement by the head of the pesticides unit at the EFSA that there is no copy paste in Volume 1 of the RAR?
5) In our opinion, what might be the reasons for the BfR's approach, based on our experience and expertise in the field of plagiarism? And is there evidence of deliberate deception of the reader?
6) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the legally required[31] independence, objectivity, and transparency of the glyphosate evaluation?

The answers are given in this expert report in chapter 4.1, pp. 52-54.

Samples of all tables with copy pasted and plagiarised texts were checked by two internationally acknowledged peer reviewers, Jonathan Bailey and Gerhard Dannemann.

3. Results

3.1 Analysis of Volume 3 B.6 – Toxicology and metabolism

Volume 3 B.6 of the RAR is attributed to the German Federal Institute for Risk Assessment (BfR). It contains 1,005 pages and deals with industry studies, as well as with published literature on the possible toxicological effects of glyphosate. For each domain listed in Volume 3 B.6 (ranging from eye irritation to carcinogenicity), first the industry studies are presented and assessed, then studies from the published literature are presented and assessed individually. The approach to each type of study is different. Whenever the BfR presents an industry study, it is followed by a "*Comment by the RMS*" or an "*RMS Comment*" in italics. The RMS (**R**apporteur **M**ember **S**tate Germany) is represented by the responsible authority, in this case the BfR.

Whenever a study from published literature is presented, such a distinction in formatting is missing. Individually discussed studies from published literature are instead followed by Klimisch evaluations and so-called "Additional comments". These comments are presented in the same typeface as the study summaries themselves. An intensive use of copy paste techniques as well as plagiarism was detected here.

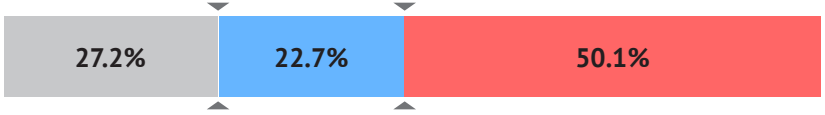
When industry studies are presented, the share of copy paste within the total text presenting industry studies in Volume 3 B.6 is 81.4%. However, these text passages copied from the GTF application were not considered plagiarisms, as the BfR announced that it had adopted the GTF's presentations of its own studies in its introductory statement, as will be discussed in the following chapters in more detail.

Figure 3.1-1: Share of genuine content, „benign" copy pasted content and plagiarised content (= „malign" copy pasted content) in the presentation of industry studies

(No plagiarised content identified)

This is different when published studies are presented. The share of copy paste within the total text presenting published literature in Volume 3 B.6 is **72.8%**.

Figure 3.1-2: Share of genuine content, „benign" copy pasted content and plagiarised content (= „malign" copy pasted content) in the presentation of published literature



Furthermore, the share of plagiarism within the total text presenting published literature is **50.1%**, whilst the share of genuine, correctly presented content is only **27.2%**, consisting mainly of contributions that were only integrated into the report after the public consultation (colour-highlighted by the BfR).

3.1.1 General findings

Figure 3.1.1-1 Overview of shares of "benign" and "malign" copy pasted and plagiarised („malign" copy pasted) content, differentiated in industry studies and published literature

Topic	Number of characters*	Share of characters* within the total adjusted Vol. 3 B.6	Share of "benign" and "malign" copy paste in characters*	Share of "benign" and "malign" copy paste in %	Share of plagiarism in characters*	Share of plagiarism in %
Industry studies	1,564,952	66.7%	1,274,105	**81.4%**	0	0%
Published literature	482,094	20.6%	350,800	**72.8%**	241,331***	**50.1%**
Neither nor**	297,530	12.7%	5,359	1.8%	4,117	1.4%

* Including blanks

** Other content than industry studies nor published studies: e.g. table of contents, introductory remarks, list of references, and other annexes

*** The following text categories were not classified as plagiarism (even if they were integrated within larger passages of plagiarised content): Copy pasted abstracts from published literature with source citations; "*Quoted from article" and copy pasted citations of responses/discussions in the context of assessments of published literature.

The amount of plagiarism is striking. The BfR plagiarised from the GTF:

1) The "General introduction and explanation of the approach taken by RMS" – see 3.1.1.1
2) 58 Klimisch evaluations originally carried out and commented on by the GTF. All were copied verbatim and with the same grading as GTF – following summaries of single published studies – see 3.1.1.2
3) 22 paragraphs following these Klimisch evaluations with the heading "Additional comments". Original authors indicated in the GTF application were repeatedly deleted by the BfR – see 3.1.1.3
4) Paragraphs and entire pages of running text, describing the design and outcome of published studies and assessing their relevance and reliablility
5) Tables and literature synopses.

In comparison to last year's exploratory and selective expert report, text plagiarism was not only found in the three subchapters B.6.4.8, B.6.5.3, and B.6.6.12, but also in the subchapters B.6.7.1, B.6.8.4, B.6.9.4, B.6.9.7, and B.6.9.8.

That means that the full analysis of Volume 3 B.6 has confirmed the earlier findings and identified a clear plagiarism practice in eight sub-chapters where published studies on glyphosate health risks are discussed and assessed with regard to their relevance and reliability. Although the BfR claims the authorship for these assessments, a comparison with the GTF application reveals that these are the assessments of the GTF.

Chapters afflicted by plagiarism are:

Number	Heading
B.6.4.8	Published data (released since 2000)
B.6.5.3	Published data on carcinogenicity (released since 2000)
B.6.6.12	Published data on reproductive toxicity (released since 2000)
B.6.7.1	Published data on neurotoxicity
B.6.8.4	Further published data (released since 2000) (further toxicological studies)
B.6.9.4	Clinical signs and symptoms of poisoning and details of clinical tests
B.6.9.7	Expected effects and duration of poisoning as a function of the type, level and duration of exposure or ingestion
B.6.9.8	Expected effects and duration of poisoning as a function of varying time periods between exposure or ingestion and commencement of treatment

3.1.1.1 Faking authorship, Part 1 – Plagiarism of the "General introduction and explanation of the approach taken by RMS"

The BfR precedes "Volume 3 B.6 – Toxicology and metabolism" with an introduction entitled, "General introduction and explanation of the approach taken by RMS". The title clearly states that the BfR is describing here the approach taken by the Rapporteur Member State (RMS), in other words, the approach of the German authority BfR itself. It is therefore all the more astonishing that most parts of this "explanation of the approach taken by RMS" are plagiarised from the GTF application.

The plagiarised part in this introduction is the description of the methodology of the assessment of the published literature (in the following facsimile highlighted in red). The non-plagiarised parts consist of a short introductory statement, followed by a description of the assessment of the industry studies, as well as text passages that were only inserted later, when the RAR was revised in January 2015 (highlighted in yellow by the BfR).

The BfR therefore not only plagiarised the assessments of published studies in the corresponding subchapters of Volume 3 B.6, but also the description of the approach to these evaluations. The fact that the evaluations and the review of the scientific literature was actually carried out by Monsanto can only be recognised by the reader if he compares the corresponding text in the GTF application (right-hand column ORIGINAL) with the introduction in the RAR (left-hand column PLAGIARISM). Only then does it become obvious that it was Monsanto that had authored the literature review and assessed the relevance and reliability of the published studies.

Interestingly, the references to Monsanto's authorship were repeatedly omitted. This is seen as a clear case of deception about the true authorship.

Legend for all following facsimiles:

Text marked light red: Plagiarised text ("malign" copy pasted text)

Text marked light blue: "benign" copy pasted text

For the reader's ease of reference, the corresponding parts of the original texts of the GTF are also marked.

Left: RAR by the RMS Right: Application by the GTF

Markings already made by the RMS

The yellow and cyan highlighter colouring in the RAR stems from the authorities themselves and marks text additions in revised versions.

Yellow highlighter: Additions of the first revised version (29-01-2015)

Cyan highlighter: Additions of the second revised version (31-03-2015)

Please note: In all facsimiles shown here, the original colour highlighters are slightly lightened for ease of reading.

A note on the citation of page numbers in this expert report: The main chapters of the original RAR were numbered solely. The page numbers on the header always refer to this pagination. For ease of reference in this expert report, we always cite the page numbers of the **entire** RAR (as a single PDF with 4,322 pages).

In the GTF Application (**AII_Doc M TIER II_Section 3_Sanitized_Nov2013**), the page numbers on the headers and the page numbers of the PDF are identical (in total 1,027 pages).

Facsimiles 3.1.1-1 and 3.1.1-2: "General introduction and explanation of the approach taken by RMS" vs. "Literature review" of the GTF

PLAGIARISM – RAR, RMS, pp. 513-515

B.6 Toxicology and metabolism

General introduction and explanation of the approach taken by RMS

This health evaluation of glyphosate is based on the following sources:

- *Toxicological and ADME studies that were submitted by the GTF for this re-evaluation.*
- *Toxicological studies and ADME studies that had been reported in the previous DAR (1998, ASB2010-10302) already and, thus, were part of previous EU evaluation. However, they were subject to re-assessment by the RMS according to current quality standards and were used only when regarded as acceptable or at least supplementary. In very few cases, NOAELs/LOAELs were revised. Unacceptable (old or new) studies were usually deleted with justifications given in the respective sections of Volume 3. In exceptional cases, such studies are still mentioned, i.e., if they were formerly taken into consideration for, e.g., ADI setting.*
- *Scientific publications and other relevant information that were submitted either by the GTF or by third parties or of which the RMS was aware before. It must be emphasised that a large part of the publications was on formulations different from the representative one and, thus, is of limited value for the toxicological evaluation of the active ingredient. With rather few exceptions in the areas of genotoxicity and human data, mainly scientific literature published since 2000 was assessed.*

Due to the large numer of submitted toxicological studies, the RMS was not able to report the original studies in detail and an alternative approach was taken instead. The study descriptions and assessments as provided by GTF were amended by deletion of redundant parts (such as the so-called "executive summaries") and new enumeration of tables. Obvious errors were corrected. Each new study was commented by the RMS. These remarks are clearly distinguished from the original submission by a caption, are always written in italics and may be found on the bottom of the individual study summaries.

Furthermore, in Volume 3, assessment was performed on the individual study level. Overall evaluation of the diverse toxicological endpoints was transferred into Volume 1 (section 2.6).

The technical databases that have been used for the literature search include: Web of Science[SM], BIOSIS Previews®, CAB Abstracts® (CABI), MEDLINE®, and CA Plus (Chemical Abstracts Plus). The searches were made on glyphosate acid, glyphosate salts (including isopropyl amine, potassium, ammonium, and methylamine), and AMPA, and their related chemical names and CAS numbers. Searches based on these search terms were also found suitable to identify publications that consider glyphosate and surfactants (such as polyoxyethylenealkylamines, or POEA) in the context of glyphosate formulations.

Additional publications cited in a recent document prepared by the NGO "Earth Open Source" (Antoniou M, et al., 2011, ASB2011-7202) *have also been included in the literature review.*

The peer-reviewed publications identified for inclusion during the literature search were reviewed and classified into one of the categories listed below.

- ***Category 0 publications**: These are publications in which glyphosate is only mentioned as an example substance or is discussed/studied in a context that is not*

ORIGINAL – Application, GTF, pp. 731-732

Part 2. LITERATURE REVIEW

Monsanto Company has been conducting routine surveillance of technical literature for glyphosate-related publications in a structured fashion since early 1997. During the period from 1997 to the present time, the search process and the literature databases used have been modified as new resources and technology became readily available. The technical databases that are used for the search include: Web of Science[SM], BIOSIS Previews®, CAB Abstracts® (CABI), MEDLINE®, and CA Plus (Chemical Abstracts Plus). The searches are done on glyphosate acid, glyphosate salts (including isopropyl amine, potassium, ammonium, and methylamine), and AMPA, and their related chemical names and CAS numbers. Searches based on these search terms will also identify publications that consider glyphosate and surfactants, (such as polyoxyethylenealkylamines, or POEA), in the context of glyphosate formulations.

Starting from the ongoing Monsanto literature database, all the peer-reviewed publications covering the time period from 2001 through 2011 that relate to the four key disciplines addressing exposure and hazard (toxicology, ecotoxicology, residues and environmental fate) were assessed within the appropriate discipline for inclusion in the literature review for the submission. Some publications address more than one discipline, and are included in each relevant discipline. More recent publications have continued to be reviewed up to shortly before submission, and selected publications have been included.

At the request of the Bundesambt für Verbraucherschutz und Lebensmittelsicherheit (BVL), additional publications cited in a recent document prepared by Earth Open Source[10] have also been included in the literature review. Many of the cited peer-reviewed publications were already included, but others were not within the scope of this literature review, primarily because the publication date was prior to 2001. The additional peer-reviewed publications have been included and are discussed within the appropriate discipline.

The peer-reviewed publications identified for inclusion during the literature search were reviewed within each discipline and classified into one of the categories listed below.

- **Category 0 publications**: These are publications in which glyphosate is only mentioned as an example substance or is discussed/studied in a context that is not relevant or related to any of the regulatory sections or the exposure/hazard assessments within this submission; the publication is therefore outside of the scope of this submission.
- **Category 1 publications**: These are publications which discuss glyphosate in a context relevant or related to the regulatory dossier sections and the conclusions fall within the conclusions of the exposure/hazard assessment. The publication is submitted with minimal or no comment or discussion.
- **Category 2 publications**: These are publications which discuss glyphosate in a context relevant or related to the regulatory dossier sections and have conclusions that call into question the endpoints/conclusions in the exposure/hazard assessment. Additionally, Category 2 also includes publications with conclusions that support the risk/hazard assessment, and may be included in discussion of other relevant publications. For selected Category 2 publications, an OECD Tier-II type summary is provided in addition to a reliability assessment (Klimisch rating, see Klimisch et al. 1997); limited comments and critical remarks are provided, as appropriate.
- **Category 3 publications**: These are publications that discuss glyphosate in a context relevant or related to (1) non-regulatory endpoints that need to be addressed as per new Regulation (EC) 1107/2009; or (2) in a context relevant to sensitive allegations that have emerged or could emerge in the media; or (3) in a context relevant to the regulatory dossier sections and have conclusions

[10] Earth Open Source report. 2011. Roundup and birth defects: Is the public being kept in the dark? Authored by Antoniou M, Habib MEEM, Howard CV, Jennings RC, Leifert C, Nodari RO, C Robinson, Fagan J. Available from: http://www.earthopensource.org/files/pdfs/Roundup-and-birth-defects/RoundupandBirthDefectsv5.pdf

Facsimiles 3.1.1-1 and 3.1.1-2: "General introduction and explanation of the approach taken by RMS" vs. "Literature review" of the GTF

PLAGIARISM – RAR, RMS, pp. 513-515

relevant or related to any of the regulatory sections or the exposure/hazard assessments within this submission; the publication is therefore outside of the scope of this submission.

- ***Category 1 publications**: These are publications which discuss glyphosate in a context relevant or related to the regulatory dossier sections and the conclusions fall within the conclusions of the exposure/hazard assessment. The publication is submitted with minimal or no comment or discussion.*
- ***Category 2 publications**: These are publications which discuss glyphosate in a context relevant or related to the regulatory dossier sections and have conclusions that call into question the endpoints/conclusions in the exposure/hazard assessment. Additionally, Category 2 also includes publications with conclusions that support the risk/hazard assessment, and may be included in discussion of other relevant publications. For selected Category 2 publications, an OECD Tier-II type summary is provided in addition to a reliability assessment (Klimisch rating, see Klimisch et al. 1997, ASB2010-14388); limited comments and critical remarks are provided, as appropriate.*
- ***Category 3 publications**: These are publications that discuss glyphosate in a context relevant or related to (1) non-regulatory endpoints that need to be addressed as per new Regulation (EC) 1107/2009; or (2) in a context relevant to sensitive allegations that have emerged or could emerge in the media; or (3) in a context relevant to the regulatory dossier sections and have conclusions that are in disagreement with endpoints/conclusions in the exposure/hazard assessment (although the experimental design seems relevant at first glance). An OECD Tier-II type summary is provided and a Klimisch rating assigned, and supplemented with critical review and discussion.*
- ***Category 'E' publications**: These are peer-reviewed publications that were cited in the Earth Open Source document. This category includes publications that were already captured by the literature search and are addressed within the appropriate discipline, as well as publications that were out of scope of the search (primarily as a result of being published prior to 2001). Publications already captured in the literature search were assigned a Category 1, 2 or 3 rating (as appropriate) in addition to a Category 'E' rating. An OECD Tier-II type summary has been prepared and a Klimisch rating assigned for each of the Category E publications. All Category 'E' publications are reviewed within the appropriate discipline, with most of the reviews provided within the toxicology dossier under Section IIA 5.10.*

A full description of the literature search methodology was provided by the GTF in a separate document (Carr and Bleeke, 2012, ASB2012-11583).
Five separate publication subject areas are addressed in the literature review.

1. *Developmental and Reproductive Toxicity (DART) and Endocrine Disruption (ED)*
2. *Neurotoxicity*
3. *Carcinogenicity*
4. *Genotoxicity*
5. *Category E and other publications*

ORIGINAL – Application, GTF, pp. 731-732

that are in disagreement with endpoints/conclusions in the exposure/hazard assessment (although the experimental design seems relevant at first glance). An OECD Tier-II type summary is provided and a Klimisch rating assigned, and supplemented with critical review and discussion.

- **Category 'E' publications**: These are peer-reviewed publications that were cited in the Earth Open Source document. This category includes publications that were already captured by the literature search and are addressed within the appropriate discipline, as well as publications that were out of scope of the search (primarily as a result of being published prior to 2001). Publications already captured in the literature search were assigned a Category 1, 2 or 3 rating (as appropriate) in addition to a Category 'E' rating. An OECD Tier-II type summary has been prepared and a Klimisch rating assigned for each of the Category E publications. All Category 'E' publications are reviewed within the appropriate discipline, with most of the reviews provided within the toxicology dossier under Section IIA 5.10.

Approximately 2000 peer-reviewed publications from the Monsanto technical literature database were assessed, and of those about 1000 were assigned a Category 1, 2 or 3 and selected for inclusion in the submission.

A full description of the literature search methodology is provided in a separate document (Carr and Bleeke, 2012).

The publications selected for inclusion are listed in Document L for each respective section, under the Annex point for 'Other/Special Studies': Point IIA 5.10 (Toxicology), Point IIA 6.10 (Metabolism and Residue), Point IIA 7.13 (Environmental Fate), and Point IIA 8.16 (Ecotoxicology). Under each point, the list of Other/Special Studies is presented in three tables:

- Table 1 lists other relevant studies conducted by the Glyphosate Task Force or member companies in support of the submission, that do not fit within any other dossier points .
- Table 2 lists all the relevant peer-reviewed publications from the literature that were selected for inclusion in the submission.
- Table 3 lists the publications and other documents that are cited within the discussion of the literature. These include documents such as government or company reports; publications that are included in the literature review under another section of the dossier; and publications that are outside the scope of the literature review.

Five separate publication subject areas are addressed in the literature review below.

1. Developmental and Reproductive Toxicology (DART) and Endocrine Disruption (ED)
2. Neurotoxicity
3. Carcinogenicity
4. Genotoxicity
5. Category E and other publications

Publications are presented in Tier II style summaries followed by Klimisch ratings then responses/comments on the paper. Results reported and discussed in the peer reviewed open literature review do not affect the conclusions drawn in the core glyphosate dossier.

Facsimiles 3.1.1-1 and 3.1.1-2: "General introduction and explanation of the approach taken by RMS" vs. "Literature review" of the GTF

PLAGIARISM – RAR, RMS, pp. 513-515

The publications on subject areas 1-4 are presented in the chapters on Genotoxicity, Long term toxicicity and carcinogenicity, Reproductive Toxicity and Neurotoxicity of the report. Furthermore, publications are presented in the chapters "Further toxicological studies" and "Medical data".
Important publications are presented in summaries as quoted from the articles followed by Klimisch ratings and by RMS comments on the paper.

In the process of public consultation after the submission of the first draft of this RAR PAN-Europe, PAN-Germany and PAN-UK conducted a PubMed literature search on the keywords 'glyphosate' and 'toxicity' and stated they got significant differences in comparison conducted by the notifier. The GTF repeated the PubMed search on June 11, 2014, using the same keywords (Glyphosate Task Force 2014, ASB2014-9624).

Overall, a total of 504 articles were identified in the search. Of those, 349 were from the time period of 2001 to 2012, and thus were considered relevant to the glyphosate submission, and were further evaluated as to whether or not they were included in either the original literature search, included in the May 2012 submission, or as part of the ongoing update of the search, as of the time of June 11 PubMed search. There were 266 reviewed for the submission (222 were included), with an additional 34 reviewed after the submission (29 selected for submission). Of the 49 remaining articles, 43 were considered to be not relevant based on the subject of the article (the majority were either on GM crops, efficacy or weed resistance). The remaining 6 were added to the literature review, and of those 4 were considered to be relevant and were selected for submission in the update.

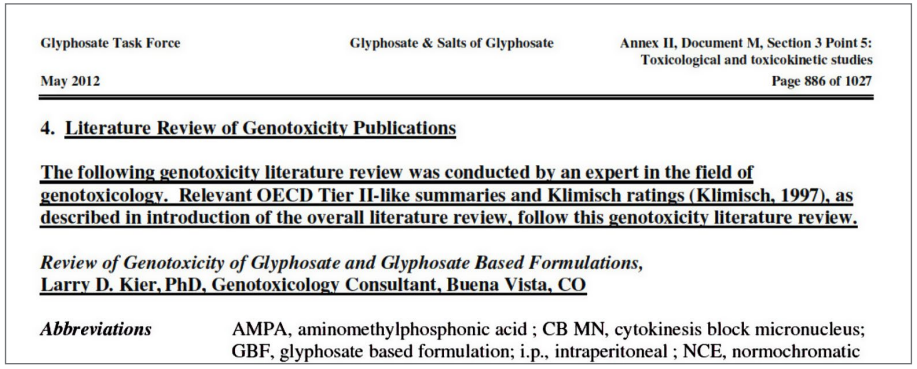
Thus, of the 349 articles identified in the search, only 4 were determined to be relevant and were not already identified in the GTF literature search process.

3.1.1.2 Faking authorship, Part 2 – Plagiarism in the subchapters on published literature

A striking example of plagiarism of the assessment of published literature is represented by the chapter on published studies on genotoxicity, a molecular mechanism of carcinogenicity and reproductive toxicity (RAR, pp. 909- 954). This 46-page chapter covers about 70 independent published studies dealing with a potential DNA-damaging mechanism of glyphosate (genotoxicity) and is almost entirely copy pasted from Monsantos literature review.

Concealment of the true authorship

No reference was made to the fact that the study descriptions and evaluations were taken verbatim from the GTF application. On the contrary, the reference to Larry D. Kier as author of the „literature review" in the GTF application was omitted by the BfR when the authority copied the GTF's review. This we regard as a clear case of deception about the authorship:



Glyphosate Task Force | Glyphosate & Salts of Glyphosate | Annex II, Document M, Section 3 Point 5: Toxicological and toxicokinetic studies
May 2012 | Page 886 of 1027

4. Literature Review of Genotoxicity Publications

The following genotoxicity literature review was conducted by an expert in the field of genotoxicology. Relevant OECD Tier II-like summaries and Klimisch ratings (Klimisch, 1997), as described in introduction of the overall literature review, follow this genotoxicity literature review.

Review of Genotoxicity of Glyphosate and Glyphosate Based Formulations,
Larry D. Kier, PhD, Genotoxicology Consultant, Buena Vista, CO

Abbreviations AMPA, aminomethylphosphonic acid ; CB MN, cytokinesis block micronucleus; GBF, glyphosate based formulation; i.p., intraperitoneal ; NCE, normochromatic

Facsimile 3.1.1-3: GTF-Application, All_Doc M TIER II_Section 3_Sanitized_Nov2013, p. 886

Verbatim appropriation of 58 Klimisch evaluations

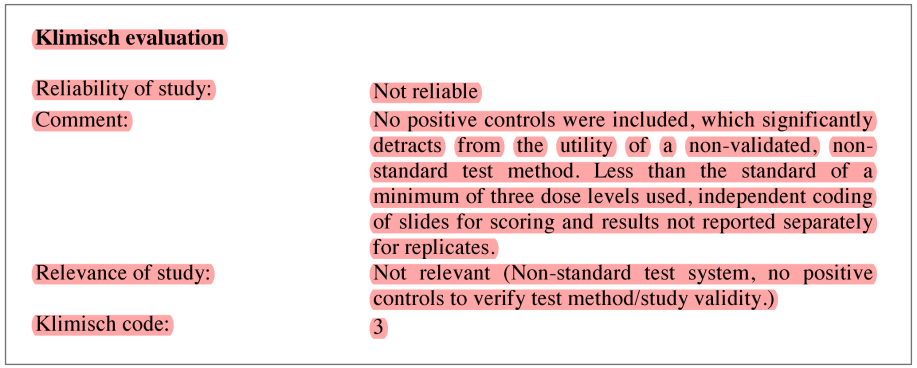
16 of the 72 studies listed and described in the RAR's subchapter on published studies on genotoxicity are subject to a Klimisch evaluation. In its "General introduction and explanation of the approach taken by RMS" the BfR writes:

> *Important publications are presented in summaries as quoted from the articles followed by Klimisch ratings and by RMS comments on the paper.*

Facsimile 3.1.1-4: RAR Vol. 3 B.6, General introduction and explanation of the approach taken by RMS, p. 515

However, the original author of these 16 Klimisch evaluations in the BfR's subchapter on published studies on genotoxicity was not the Rapporteur Member State (RMS). The evaluations are copied word-for-word from the GTF application, in common with almost the entire subchapter (approximately 94%). Moreover, contrary to what the BfR stated in its "general introduction", here, the Klimisch evaluations are not followed by "RMS comments on the paper". In this subchapter on genotoxicity, the Klimisch evaluations are presented as the "last word". This is different in other chapters – for example, the chapters on carcinogenicity, reproductive toxicity, and neurotoxicity.

All together, 58 Klimisch evaluations could be found in the different subchapters of the RAR. Each of the 58 Klimisch evaluations was appropriated from the GTF application with exactly the same grading and the same remarks. As an example, the Klimisch evaluation in the RAR of the paper "*European eel (Anguilla Anguilla) genotoxic and pro-oxidant responses following short-term exposure to Roundup® – a glyphosate-based herbicide*" by Guilherme et al. (2010) is presented below:

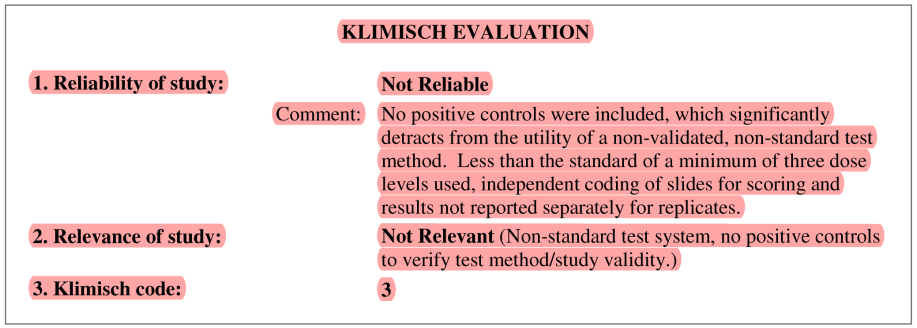


Klimisch evaluation

Reliability of study:	Not reliable
Comment:	No positive controls were included, which significantly detracts from the utility of a non-validated, non-standard test method. Less than the standard of a minimum of three dose levels used, independent coding of slides for scoring and results not reported separately for replicates.
Relevance of study:	Not relevant (Non-standard test system, no positive controls to verify test method/study validity.)
Klimisch code:	3

Facsimile 3.1.1-5: RAR Vol. 3.B.6.4.8, Published data (released since 2000), p. 945

As with all the 57 other Klimisch evaluations, the scoring and justifications is identical with the Klimisch evaluation in the GTF application:



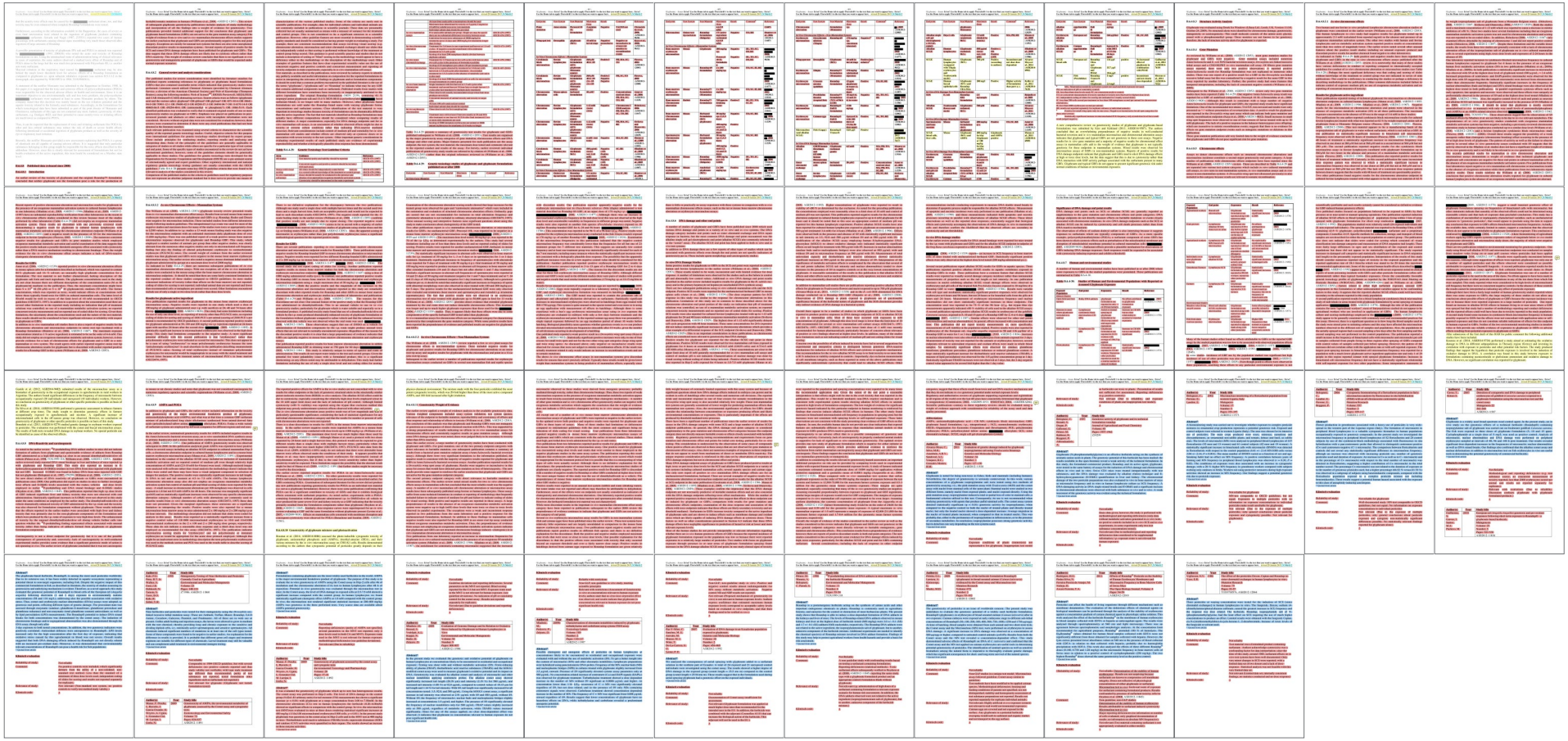
KLIMISCH EVALUATION

1. Reliability of study:		**Not Reliable**
	Comment:	No positive controls were included, which significantly detracts from the utility of a non-validated, non-standard test method. Less than the standard of a minimum of three dose levels used, independent coding of slides for scoring and results not reported separately for replicates.
2. Relevance of study:		**Not Relevant** (Non-standard test system, no positive controls to verify test method/study validity.)
3. Klimisch code:		3

Facsimile 3.1.1-6: GTF-Application, All_Doc M TIER II_Section 3_Sanitized_Nov2013, p. 932

Facsimile 3.1.1-7 on the following page, which presents the entire subchapter on published studies on genotoxicity, illustrates that not only all 16 Klimisch evaluations were copy pasted, but the entire body of the text, except for the yellow marked passages (referring to studies published after application by GTF). A total of 94% of the subchapter was appropriated from the GTF application:

Facsimile 3.1.1-7: RAR "Published data (released since 2000)" on Genotoxicity, pp. 909-954



Verbatim appropriation of comments and explanations from the GTF

The (original) Klimisch ratings in the GTF application are often followed by "responses/comments on the paper", as indicated in Monsanto's description of the methodology of the literature review:

> Publications are presented in Tier II style summaries followed by Klimisch ratings then responses/comments on the paper.

Facsimile 3.1.1-8: GTF application, All_Doc M TIER II_Section 3_Sanitized_Nov2013, p. 732

In its plagiarised "General introduction and explanation of the approach taken by RMS", the BfR has changed this sentence and claimed that the Klimisch ratings are "followed by RMS comments on the paper":

> *Important publications are presented in summaries as quoted from the articles followed by Klimisch ratings and by RMS comments on the paper.*

Facsimile 3.1.1-9: RAR Vol. 3 B.6, General introduction and explanation of the approach taken by RMS, p. 515

However, our analysis revealed that also the comments that followed these Klimisch ratings in the RAR were not written by the RMS, but copied from the GTF application, sometimes with slight modifications in wording. Comments that in the application were marked „GTF response", or with the name of an author, are frequently referred to as „additional comments" in the RAR.

In 22 instances out of 30 in the total Volume 3 B.6, these comments for which the RMS claimed authorship in its "General introduction" were plagiarised from the GTF application and refered to as "additional comments" in the RAR. The remaining eight cases where the BfR did not make any changes to the author references mentioned in the GTF application were not considered plagiarisms, but counted as ("benign") copy pasted content.

This is again a very problematic case of plagiarism, because the judgments of the industry applicants (for example, "[...] the results of this study are not convincing") were appropriated 1:1 by the RMS. In many cases, the original author is indicated in the application, yet is dropped by the RMS in the RAR, with the result that the reader again is deceived about the real authorship. The following example, taken from the chapter on published studies on carcinogenicity, shows how the paragraph "Additional comments" was plagiarised from a paragraph headed, "Response 3 Monsanto Review by John Acquavella, PhD and Donna Farmer, PhD": In the BfR's assessment report, the indication of the authorship of John Acquavella and Donna Farmer was replaced by the neutral phrase „additional comments". But the reader must assume that these additional comments are the comments of the BfR, since the BfR had explained in the "General introduction" that Klimisch ratings are followed by "RMS comments on the paper":

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

Facsimile 3.1.1-10: RAR B6.5.3, Published data on carcinogenicity (released since 2000), p. 533

The reader can only find out that this is not true by comparing the authority's report with the GTF's application for approval:

KLIMISCH EVALUATION

1. 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.
2. 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.
3. Klimisch code:		**3**

[...]

Response 3 – Monsanto Review by John Acquavella, PhD and Donna Farmer, PhD

Executive Summary

Hardell and Erikkson 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.

Facsimile 3.1.1-11: GTF application, All_Doc M TIER II_Section 3_Sanitized_Nov2013, p. 851 and p. 854

3.1.1.3 "Benign" copy pasting of summaries of industry studies

The descriptions of industry studies were generally copied from the application (following the structure: General remarks; Materials and methods; and Results and discussion). After "Results and discussion", in every case, a "Conclusion by the Notifiers" follows. Thus it is not clear a priori that all information before/above the "Conclusion by the Notifiers" is also copied verbatim from the application. Nevertheless, this type of copy paste was not classified as plagiarism by the authors of this report. This is because the BfR has described this practice as the "approach taken by RMS" to assess the studies from industry:

> *Due to the large numer of submitted toxicological studies, the RMS was not able to report the original studies in detail and an alternative approach was taken instead. The study descriptions and assessments as provided by GTF were amended by deletion of redundant parts (such as the so-called "executive summaries") and new enumeration of tables. Obvious errors were corrected. Each new study was commented by the RMS. These remarks are clearly distinguished from the original submission by a caption, are always written in italics and may be found on the bottom of the individual study summaries.*

Facsimile 3.1.1-12: RAR, general introduction, p. 513

The BfR has followed this practice in every subchapter in which industry studies are described and assessed. After the "Conclusion by the Notifiers", the evaluation of the RMS follows, with headings like "Comments by RMS" or "RMS comments", and printed in italics. The reason we call this "benign" copy paste is because there is no false pretence of authorship. However, this does not mean that such an approach by a supervisory authority is not problematic, as will be shown in the following example of BfR's cancer assessment.

3.1.2 Example analysis of the chapter "B.6.5 Long-term toxicity and carcinogenicity"

The chapter on "Long term toxicity and carcinogenicity" is divided into a first part on industry studies and a second part on published literature, both dealing with the carcinogenic potential of glyphosate.

At the head of this chapter, the BfR states with regard to the industry studies: "*For higher efficiency of the review and for the sake of transparency, the descriptions of methods and study results in the GTF dossier were virtually not amended and even the conclusions were kept as provided. However, each study that is described in detail was commented by RMS. These remarks on bottom of each study description are clearly distinguished from the original submission by a caption and are always written in italics.*"(p. 955).

With regard to published studies, the BfR states: "*In chapter B.6.5.3 publications on glyphosate and carcinogenicity are presented. These publications include a number of epidemiology studies which are focused on pesticide exposure and associated health outcomes.*"

These claims are in line with what the BfR has already stated in its (for the most part) plagiarised "*General introduction and explanation of the approach taken by RMS*" of Volume 3 B.6.

3.1.2.1 BfR's assessment of industry studies on carcinogenicity

Twelve long-term carcinogenicity studies with rodents (rats and mice), are presented, discussed and assessed in this subchapter (pp. 955-1,040) in line with the above described approach taken by the RMS. Using the example of BfR's presentation and assessment of the most recent cancer study with mice (Nufarm, 2009), we show in the following that also „benign" copy paste can lead to the uncritical adoption of false representations.

As can be seen below in Facsimiles 3.1.2-1 and 3.1.2-2 (pp. 32-33), in its application, the GTF stated about this mouse study that "*there were no treatment-related histopathological findings observed in any dose group of either sex*" (1, right column) and therefore concluded that "*Glyphosate technical is not carcinogenic in mice*" (2, right column).

In line with the approach taken by the RMS, the BfR has copied these claims of the GTF (3 and 4, left column).

The BfR also agreed with these claims in its RMS comment, at least initially.[32] As a result, in the interim version of the RAR that was subjected to public consultation in April 2014, the BfR stated, "*Indeed, there was no evidence for carcinogenicity*" (5, left column), and furthermore, "*there was no increase in malignant lymphoma*"(6, left column).

But in its revised version from March 31, 2015, finalized shortly after IARC's cancer classification of glyphosate, the BfR had to correct these statements. The authority crossed out the earlier statement that "*there was no increase in malignant lymphoma*" and wrote now that there was "*a weak increase in malignant lymphoma*" (7, left column) and that the "*actual numbers of affected animals were 0, 1, 2, and 5 in the control, low, mid and high dose groups*", (8, left column) but that the "*difference was not statistically significant*" (9, left column).

Five months later, in an Addendum to the RAR, the BfR also corrected this statement, stating finally that "*re-valuation of the incidences of malignant lymphoma [...] showed statistically significant increases with dose*".[33]

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

similar experiment, the incidence in males was lower (5.5%) but, this time, accounted for 36.3% in females. This latter information may be considered the first published evidence of a remarkable sex difference in the frequency of this tumour type and a higher vulnerability of female mice as it was nearly consistently reported thereafter.
More than 10 years later, Sher (1974, Z22020) published a review on spontaneous tumour incidences in various non-inbred mouse strains, based on scientific articles that had been released between 1960 and 1974. For Swiss random-bred strains, lymphomas and leukemias were mentioned to occur as the most common tumours. However, again, extremely variable incidences ranging from 0 to 21.4% were reported in long term studies for untreated males, depending on strain and source. In female Swiss mice, the incidences varied even between 0 and 36.4%. The maximum incidence had been noted in minimally inbred Carworth CF-1 mice (not related to Swiss mouse strains) with 53% in females.
Roe and Tucker (1974, ASB2015-2534) reported an incidence of 22.5 to 27.5% of (not further specified) lymphoreticular neoplasms in male Swiss mice (n=80) if fed ad libitum but a much lower tumour rate when diet was restricted.
Tucker (1979, Z83266) found 18% of male Swiss albino mice (Alderley Part strain) and 28% of the females with lymphoma, nearly all of them malignant. Her analysis was based on 50 males and 50 females fed ad libitum from weaning for their lifespan with the last, very few surviving animals killed after 3 years.
A large colony of (minimally inbred)"Swiss-derived" Icr:Ha(ICR) mouse had a 15% incidence of lymphoma in total with an approximate 2:1 ratio between females and males (precise percentages not given). In addition, 5% of the mice had developed leukemia (Eaton et al., 1980, ASB2015-2537). Only lung tumours occurred more frequently (23%). With regard to Swiss mice in general, the authors emphasised that "... differences occur between colonies and even within a colony with the passage of time so that contradictory results may be obtained using 'Swiss' stock from different sources. For example, the incidence of spontaneous neoplasia, although seldom reported in detail, varies with source and age."
According to a more recent article (Taddesse-Heath et al., 2000, ASB2015-2535), a much higher incidence of hematopoietic neoplasia of 58% was observed in a colony of CFW Swiss mice in the USA. Lymphoma (mostly of B-cell origin) accounted for 85% of these cases giving a total incidence of nearly 50%. The authors ascribed these tumours mainly to "infectious expression of murine leukemia viruses". It is not known to which extent such a latent infection might have contributed to lymphoma incidences reported earlier or even in the studies described in this RAR. A possible etiologic role of oncogenic viruses had been suspected by Roe and Tucker (1974, ASB2015-2534) yet who complained that many scientists performing long-term studies would often ignore this problem.

2nd new long-term study in mice ([redacted] 2009)

Reference: IIA, 5.5.3/02
Report: [redacted] (2009b), Glyphosate technical: Dietary Carcinogenicity Study in the Mouse
[redacted]
SPL Project No.: 2060-0011
Data owner: Nufarm
Date: 2009-04-22
not published, ASB2012-11492
Guidelines: OECD 451 (1981), JMAFF guideline 2-1-15 (2005), US-EPA

ORIGINAL – Application, GTF, pp. 511-516

Table 5.5-48: Incidences of lamlignant lymphoma and comparison with historical control

			Dietary concentration of glyphosate (ppm)							
			Males				Females			
	♂	♀	0	100	1000	10000	0	100	1000	10000
Dead & moribund										
Number examined	75	77	22	20	22	27	16	16	20	20
Number affected	20	49	9	12	13	13	9	10	13	12
Percentage affected	26.7	63.6	41.0	60.0+	59.0+	48.0	56.0	63.0	65.0	60.0
Mean %	26	61.8	--	--	--	--	--	--	--	--
Range %	0-44	0-100	--	--	--	--	--	--	--	--
			--	--	--	--	--	--	--	--
Terminal sacrifice										
Number examined	175	175	28	3028	23	34	34	30	30	28
Number affected	26	50	1	3	3	6+	9	10	6	13
Percentage affected	14.9	28.9	3.6	10.0	10.7	26.1+	26.5	29.4	20.0	43.3+
Mean %	14.8	28.8	--	--	--	--	--	--	--	--
Range %	8-24	20-43	--	--	--	--	--	--	--	--
			--	--	--	--	--	--	--	--
All fates										
Number examined	250	250	50	50	50	50	50	50	50	50
Number affected	46	99	10	15	16	19+	18	20	19	25
Percentage affected	18.4	39.6	20.0	30.0	32.0	38.0+	36.0	40.0	38.0	50.0+
Mean %	18.4	41.6	--	--	--	--	--	--	--	--
Range %	6-30	14.58	--	--	--	--	--	--	--	--

+ significantly increased; -- not examined/determined

III. CONCLUSION

Based on mortality at the upper limit of the historical control range, the NOAEL in mice after chronic exposure to Glyphosate technical for 18 month is conservatively set at 1000 ppm, corresponding to 149.7 mg/kg bw/day for males, 151.2 mg/kg bw/day for females, and 150.5 mg/kg bw/day for both sexes combined. It is concluded that Glyphosate is not carcinogenic in mice.

Annex point	Author(s)	Year	Study title
IIA, 5.5.3/02	[redacted]	2009b	Glyphosate technical: Dietary Carcinogenicity Study in the Mouse [redacted] SPL Project No.: 2060-0011 Date: 2009-04-22 GLP: yes not published

Guideline:	OECD 451 (1981), JMAFF guideline 2-1-15 (2005), US-EPA OPPTS 870.4200 (1996)
Deviations:	None
Dates of experimental work:	2005-10-10 - 2007-11-19

Executive Summary
The carcinogenic potential of Glyphosate technical was assessed in an 18-month feeding study in male and female CD-1 mice. Groups of 51 mice per sex received daily dietary doses of 0, 500, 1,500, and 5,000 ppm Glyphosate technical (equivalent to an average intake of 84.7, 266.8 and 945.6 mg/kg bw/day). Observations covered clinical signs, body weight, food and water consumption, palpation of masses, organ

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

	OPPTS 870.4200 (1996)
Deviations:	None
GLP:	Yes
Acceptability:	*See RMS comment*

Dates of experimental work: 2005-10-10 - 2007-11-19

Materials and methods

Test material:	Glyphosate technical
Identification:	Glyphosate
Description:	White crystalline solid
Lot/Batch #:	H05H016A
Purity:	95.7 %
Stability of test compound:	Expiry: 2008-03-25
Vehicle and/ or positive control:	Diet
Test animals:	
Species:	Mouse
Strain:	CD-1, Crl:CD-1 (ICR) BR
Source:	[redacted]
Age:	Approx. 5 – 6 weeks
Sex:	Males and females
Weight at dosing:	Males: 22 – 32 g, females: 18 – 28 g
Acclimation period:	At least ten days
Diet/Food:	Rat and Mouse SQC Ground diet No. 1, Special Diet Services Limited, UK), *ad libitum*
Water:	Tap water, *ad libitum*
Housing:	Initially in groups of three per sex in polypropylene solid-floor cages.
Environmental conditions:	Temperature: 21 ± 2 °C Humidity: 55 ± 15 % Air changes: at least 15/hour 12 hours light/dark cycle

In life dates: 2005-10-10 to 2007-11-19

Animal assignment and treatment:
In a carcinogenicity feeding study groups of 51 CD-1 mice per sex received daily dietary doses of 0, 500, 1500 and 5000 ppm (equivalent to mean achieved dose levels of 0, 84.7, 266.8 and 945.6 mg/kg bw/day) Glyphosate technical in diet. Additional 12 mice per sex, designated for veterinary controls, were housed and maintained alongside treated animals. Ten animals per sex from each group were set aside for an interim kill (toxicity assessment), which was carried out on the survivors after 39 weeks of dosing. The remaining 50 mice per sex and dose-level were dosed for a maximum of 79 weeks (carcinogenicity assessment).

ORIGINAL – Application, GTF, pp. 511-516

weights, necropsy and histopathological examination. The latter involved examination of all sampled organ tissues for all control and high dosage group animals killed at termination. In addition, differential white blood cell counts were performed for animals that were killed or died in extremis and for selected animals at twelve and eighteen month of treatment. The dose-levels were chosen based on available toxicity data.
There were no treatment-related deaths or clinical signs in any of the dose-groups. In the carcinogenicity study, survival after 78 weeks of treatment was 76, 80, 76 and 69% in males and 73, 75, 75 and 78% in females in the control through high dosage groups, respectively.
There were no treatment-related effects on body weight gain or food and water consumption noted. No significant treatment-related effects were noted on differential white blood cell counts in both sexes. There were no treatment-related trends in the proportion of masses observed, number of mice affected or time to appearance of palpable masses. Gross pathology, organ weight data and histopathological examination revealed no treatment-related effects.
In conclusion, Glyphosate technical was not carcinogenic in the CD-1 mouse following continuous dietary exposure of up to 945.6 mg/kg bw/day (average for both sexes) for 18 months. The NO(A)EL for toxicity was 810 mg/kg bw/day for male mice and 1081 mg/kg bw/day for female mice, the highest dosage tested.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material:		Glyphosate technical
	Identification:	Glyphosate
	Description:	White crystalline solid
	Lot/Batch #:	H05H016A
	Purity:	95.7%
	Stability of test compound:	Expiry: 2008-03-25
2. Vehicle and/ or positive control:		Diet
3. Test animals:		
	Species:	Mouse
	Strain:	CD-1, Crl:CD-1 (ICR) BR
	Source:	Charles River (UK) Limited, Margate, Kent, UK
	Age:	Approx. 5 – 6 weeks
	Sex:	Males and females
	Weight at dosing:	Males: 22 – 32 g, females: 18 – 28 g
	Acclimation period:	At least ten days
	Diet/Food:	Rat and Mouse SQC Ground diet No. 1, Special Diet Services Limited, UK), *ad libitum*
	Water:	Tap water, *ad libitum*
	Housing:	Initially in groups of three per sex in polypropylene solid-floor cages.
	Environmental conditions:	Temperature: 21 ± 2°C Humidity: 55 ± 15% Air changes: at least 15/hour 12 hours light/dark cycle

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

Test diets were prepared prior to start of treatment and then weekly by mixing a known amount of the test substance with a small amount of basal diet and blending for 19 minutes. This pre-mix was then added to larger amount of basal diet and blended for further 30 minutes.
The stability and homogeneity of the test material in diet were determined. Samples of each dietary admixture were analysed for achieved concentration monthly for the first six months and then every three months thereafter.

Clinical observations
A check for clinical signs of toxicity, ill health and behavioural changes was made once daily on all mice and recorded weekly. Observations for morbidity, and mortality were made twice daily. Additional unscheduled examinations were performed on animals that showed ill-health.
All surviving animals were palpated weekly for size, position and appearance of new or existing masses.

Body weight
Individual body weights were recorded on Day 1 (prior to treatment) and at weekly intervals until the end of week 13 and every 4 weeks thereafter until termination. Body weights were also determined before sacrifice. Body weight data were reported only until Week 77.

Food consumption and compound intake
Food consumption was recorded once weekly for each cage group from Week 1 to Week 13 and subsequently over one week in every 4 weeks until termination. Food consumption data were reported only until Week 77. Food efficiency and compound intake was calculated from the recorded food consumption data.

Water consumption
Water intake was observed daily, for each cage group, by visual inspection of the water bottles for any overt changes.

Haematology
Blood smear samples were collected after 12 months and at termination from all animals, and from mice that were killed in extremis. Differential white cell counts were performed on all control and high-dose animals and on the animals killed in extremis.

Sacrifice and pathology
All animals that died or were killed in extremis during the conduct of the study, and all animals sacrificed at scheduled termination were subjected to a gross pathological examination. Any macroscopic findings were recorded.
The following organ weights were determined from 10 mice per sex per group: adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, spleen, and testes.
Tissue samples were taken from the following organs and preserved in buffered formalin: adrenals, aorta (thoracic), bone & bone marrow (sternum and femur (incl. stifle joint)), brain (incl. cerebrum, cerebellum and pons), caecum, colon, duodenum, epididymides, eyes (with optic nerve), gross lesions incl. palpable masses, head (incl. pharynx, nasopharynx and paranasal sinuses), heart, Harderian and lacrimal glands, ileum, jejunum, kidneys, larynx, liver and gall bladder, lungs (with bronchi), mammary gland, lymph nodes (cervical and mesenteric), muscle (skeletal), oesophagus, ovaries, pancreas, pituitary, preputial gland, prostrate, rectum, salivary glands, sciatic nerve, seminal vesicles, skin (hind limb), spinal cord

ORIGINAL – Application, GTF, pp. 511-516

B: STUDY DESIGN AND METHODS

In life dates: 2005-10-10 to 2007-11-19

Animal assignment and treatment:
In a carcinogenicity feeding study groups of 51 CD-1 mice per sex received daily dietary doses of 0, 500, 1500 and 5000 ppm (equivalent to mean achieved dose levels of 0, 84.7, 266.8 and 945.6 mg/kg bw/day) Glyphosate technical in diet. Additional 12 mice per sex, designated for veterinary controls, were housed and maintained alongside treated animals. Ten animals per sex from each group were set aside for an interim kill (toxicity assessment), which was carried out on the survivors after 39 weeks of dosing. The remaining 50 mice per sex and dose-level were dosed for a maximum of 79 weeks (carcinogenicity assessment).

Test diets were prepared prior to start of treatment and then weekly by mixing a known amount of the test substance with a small amount of basal diet and blending for 19 minutes. This pre-mix was then added to larger amount of basal diet and blended for further 30 minutes.
The stability and homogeneity of the test material in diet were determined. Samples of each dietary admixture were analysed for achieved concentration monthly for the first six months and then every three months thereafter.

Clinical observations
A check for clinical signs of toxicity, ill health and behavioural changes was made once daily on all mice and recorded weekly. Observations for morbidity, and mortality were made twice daily. Additional unscheduled examinations were performed on animals that showed ill-health.
All surviving animals were palped weekly for size, position and appearance of new or existing masses.

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Sacrifice and pathology
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The following organ weights were determined from 10 mice per sex per group: adrenals, brain, epididymides, heart, kidneys, liver, lungs, ovaries, spleen, and testes.
Tissue samples were taken from the following organs and preserved in buffered formalin: adrenals, aortic (thoracic), bone & bone marrow (sternum and femur (incl. stifle joint)), brain (incl. cerebrum, cerebellum pons), caecum, colon, duodenum, epididymides, eyes (with optic nerve), gross lesions incl. palpable

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

(cervical, mid-thoracic and lumbar), spleen, stomach, testes, thymus, thyroid/parathyroid, tongue, trachea, urinary bladder, uterus and vagina.
A detailed histopathological examination was performed on all sampled tissues of the control and high-dose animals, and on animals that died or were killed in extremis. In addition, tissues of the liver, lungs and kidneys, as well as gross macroscopic lesions and palpable masses from low and intermediate dose groups at termination were examined microscopically.

Statistics
All data were summarised in tabular form and analysed by computerised analysis using ProvantisTM Tables and Statistics Module. For each variable the of variance incorporating Student´s t-test and F-test. For each variable the most suitable transformation of data was found, the use of possible covariates checked and the homogeneity of means assessed using ANOVA or ANOVA and Bartlett´s test. The lowest treatment-related significant effects were determined using the Williams Test for parametric data or the Shirley Test for non-parametric data. If no response is found, but the data showed non-homogeneity of means, data were further analysed by a stepwise Dunnet (parametric) or Steel (non-parametric) test to determine significant differences from control. If required, pair-wise tests are performed using Students t-test (parametric) or the Mann-Whitney U test (non-parametric)
The levels of probability chosen as significant were $p < 0.01$** and $p < 0.05$*.
Histopathology data were analysed using Chi squared analysis (differences in the incidence of lesions occurring with an overall frequency of 1 or greater) and the Kruskal-Wallis one-way non-parametric analysis of variance (comparison of severity grades).
The levels of probability chosen as significant were $p < 0.001$, $p < 0.01$, $p < 0.05$, and $p < 0.1$.

Results and discussion
Analysis of dose formulations
Analyses for homogeneity and stability indicated that the dose preparations were homogeneous and stable for at least six weeks. Analyses for achieved concentration demonstrated that the mean prepared dietary admixture concentrations were within ± 5 % of the nominal concentration for all but 1 sample (500 ppm –level), which was + 10 % of the nominal concentration.
The group mean achieved doses are summarised below.

Table B.6.5-49: Group mean achieved dose levels

Dose group	Dietary concentration (ppm)	Achieved dose level (mg/kg bw/day)*				
		Males		Females		Overall mean
		Mean	Range	Mean	Range	
1 (control)	0					
2 (low)	500	71.4	33 – 104	97.9	55 – 155	84.7
3 (mid)	1500	234.2	101 – 365	299.5	176 – 466	266.8
4 (high)	5000	810	461 - 1143	1081.2	610 - 1728	945.6

* based on actual food intake and body weight data

The results show a higher test material intake for females when compared to males for each dose level. Highest intakes were achieved within the first few treatment weeks, with subsequent decline thereafter. The mean intake for each dose group (sexes combined) is therefore 84.7, 266.8 and 945.6 mg/kg bw/day for 500, 1500, and 5000 ppm, respectively.

Mortality

ORIGINAL – Application, GTF, pp. 511-516

masses, head (incl. pharynx, nasopharynx and paranasal sinuses), heart, Harderian and lacrimal glands, ileum, jejunum, kidneys, larynx, liver and gall bladder, lungs (with bronchi), mammary gland, lymph nodes (cervical and mesenteric), muscle (skeletal), oesophagus, ovaries, pancreas, pituitary, preputial gland, prostrate, rectum, salivary glands, sciatic nerve, seminal vesicles, skin (hind limb), spinal cord (cervical, mid-thoracic and lumbar), spleen, stomach, testes, thymus, thyroid/parathyroid, tongue, trachea, urinary bladder, uterus and vagina.
A detailed histopathological examination was performed on all sampled tissues of the control and high-dose animals, and on animals that died or were killed in extremis. In addition, tissues of the liver, lungs and kidneys, as well as gross macroscopic lesions and palpable masses from low and intermediate dose groups at termination were examined microscopically.

Statistics
All data were summarised in tabular form and analysed by computerised analysis using ProvantisTM Tables and Statistics Module. For each variable the of variance incorporating Student´s t-test and F-test. For each variable the most suitable transformation of data was found, the use of possible covariates checked and the homogeneity of means assessed using ANOVA or ANOVA and Bartlett´s test. The lowest treatment-related significant effects were determined using the Williams Test for parametric data or the Shirley Test for non-parametric data. If no response is found, but the data showed non-homogeneity of means, data were further analysed by a stepwise Dunnet (parametric) or Steel (non-parametric) test to determine significant differences from control. If required, pair-wise tests are performed using Students t-test (parametric) or the Mann-Whitney U test (non-parametric)
The levels of probability chosen as significant were $p < 0.01$** and $p < 0.05$*.
Histopathology data were analysed using Chi squared analysis (differences in the incidence of lesions occurring with an overall frequency of 1 or greater) and the Kruskal-Wallis one-way non-parametric analysis of variance (comparison of severity grades).
The levels of probability chosen as significant were $p < 0.001$, $p < 0.01$, $p < 0.05$, and $p < 0.1$.

II. RESULTS AND DISCUSSION

A. ANALYSIS OF DOSE FORMULATIONS
Analyses for homogeneity and stability indicated that the dose preparations were homogeneous and stable for at least six weeks. Analyses for achieved concentration demonstrated that the mean prepared dietary admixture concentrations were within ± 5% of the nominal concentration for all but 1 sample (500 ppm – level), which was + 10% of the nominal concentration.
The group mean achieved doses are summarised below.

Table 5.5-49: Group mean achieved dose levels

Dose group	Dietary concentration (ppm)	Achieved dose level (mg/kg bw/day)*				
		Males		Females		Overall mean
		Mean	Range	Mean	Range	
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2 (low)	500	71.4	33 – 104	97.9	55 – 155	84.7
3 (mid)	1500	234.2	101 – 365	299.5	176 – 466	266.8
4 (high)	5000	810	461 - 1143	1081.2	610 - 1728	945.6

* based on actual food intake and body weight data

The results show a higher test material intake for males when compared to males for each dose level. Highest intakes were achieved within the first few treatment weeks, with subsequent decline thereafter. The mean intake for each dose group is therefore 84.7, 266.8 and 945.6 mg/kg bw/day for 500, 1500, and 5000 ppm, respectively.

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

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No treatment-related effects on the deaths occurred during the study, as well as no treatment-related effects on the time of death. From three male mice that were killed in extremis, examination results suggest that the morbidity of these animals was due to fighting between cage mates.

Table B.6.5-50: Cumulated mortalities after 78-week dietary exposure to Glyphosate technical

	Dose group (ppm)			
Sex	0	500	1500	5000
Male	12 (6)	10 (8)	12 (6)	16 (6)
Female	14 (10)	13 (7)	13 (10)	11 (8)

( ): number of animals killed in extremis

The percentage of survival in each of the dose groups are summarised below.

Table B.6.5-51: Percentage survival at termination after 78-week dietary exposure to glyphosate technical

	Dose group (ppm)			
Sex	0	500	1500	5000
Male	76	80	76	69
Female	73	75	75	78

Clinical observations
There were no significant treatment-related clinical signs of toxicity observed.

There were no trends in the proportion of palpable masses observed during the study period. A significant proportion observed showed evidence for regression before the animal reached the point of death or termination. Based on the results (see Table B.6.5-52) no treatment-related effect on the development of palpable masses is seen for either sex. The slight increase in the mean number of masses per animal for high-dose females and mid-dose males was considered a coincidence. The median time to appearance of palpable masses was comparable for all dose groups of either sex.

Table B.6.5-52: Group summary of palpable masses

Dose	Total number of animals in group		Number of animals with palpable masses		Total number of masses per group		Mean number of masses per animal		Median time (weeks) to appearance of masses	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0	51	51	28	23	45	38	0.88	0.75	42.00	45.75
500	51	51	32	28	49	49	0.96	0.96	42.00	46.08
1500	51	51	39	23	60	38	1.20	0.75	42.43	44.83
5000	51	51	25	23	49	51	0.96	1.00	41.67	42.50

Body weight
There were no treatment-related effects on male and female overall body weight gain during the conduct of study.

Food consumption and compound intake

ORIGINAL – Application, GTF, pp. 511-516

B. MORTALITY
No treatment-related effects on the deaths occurred during the study, as well as no treatment-related effects on the time of death. From three male mice that were killed in extremis, examination results suggest that the morbidity of these animals was due to fighting between cage mates.

Table 5.5-50: Cumulated mortalities after 78-week dietary exposure to Glyphosate technical

	Dose group (ppm)			
Sex	0	500	1500	5000
Male	12 (6)	10 (8)	12 (6)	16 (6)
Female	14 (10)	13 (7)	13 (10)	11 (8)

( ): number of animals killed in extremis

The percentage of survival in each of the dose groups are summarised below.

Table 5.5-51: Percentage survival at termination after 78-week dietary exposure to Glyphosate technical

	Dose group (ppm)			
Sex	0	500	1500	5000
Male	76	80	76	69
Female	73	75	75	78

C. CLINICAL OBSERVATIONS
There were no significant treatment-related clinical signs of toxicity observed.

There were no trends in the proportion of palpable masses observed during the study period. A significant proportion observed showed evidence for regression before the animal reached the point of death or termination. Based on the results (see Table 5.5-52) no treatment-related effect on the development of palpable masses is seen for either sex. The slight increase in the mean number of masses per animal for high-dose females and mid-dose males was considered a coincidence. The median time to appearance of palpable masses was comparable for all dose groups of either sex.

Table 5.5-52: Group summary of palpable masses

Dose	Total number of animals in group		Number of animals with palpable masses		Total number of masses per group		Mean number of masses per animal		Median time (weeks) to appearance of masses	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0	51	51	28	23	45	38	0.88	0.75	42.00	45.75
500	51	51	32	28	49	49	0.96	0.96	42.00	46.08
1500	51	51	39	23	60	38	1.20	0.75	42.43	44.83
5000	51	51	25	23	49	51	0.96	1.00	41.67	42.50

D. BODY WEIGHT
There were no treatment-related effects on male and female overall body weight gain during the conduct of study.

E. FOOD CONSUMPTION AND COMPOUND INTAKE
There were no treatment-related effects on food consumption for either sex noted during the study.

F. WATER CONSUMPTION
There were no treatment-related effects on water consumption for either sex noted during the study.

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

There were no treatment-related effects on food consumption for either sex noted during the study.

Water consumption
There were no treatment-related effects on water consumption for either sex noted during the study.

Haematology
There were no significance differences in the proportions of white blood cell counts for either sex at both 12 and 18 month.

Necropsy
Gross pathology
There were no treatment-related macroscopic findings observed for any mice sacrificed at termination or mice that died or were killed in extremis during the study period.

Organ weights
There were no treatment-related findings observed in organ weights or relative organ weights.

Histopathology
There were no treatment-related histopathological findings observed in any dose group of either sex.

Conclusion by the Notifiers
Based on the study results the NOEL and NOAEL in mice after chronic exposure to Glyphosate technical for 18 month is 810 mg/kg bw/day for males, and 1081 mg/kg bw/day for females. It is concluded that Glyphosate technical is not carcinogenic in mice.

RMS comments
The study is considered acceptable and setting of the NOAEL at the highest dose level of 5000 ppm (eqivalent to 810 mg/kg bw/day in males and 1081 mg/kg bw/day in females) is supported. Indeed, there was no evidence for carcinogenicity up to this dose level and the very comprehensive ranges of tissues that were examined histologically does not suggest an increase in any non-neoplastic pathological lesion. In an amendment to the study report ([redacted] 2011, ASB2014-9149) it was clarified that there was also no increase in (bilateral) testicular atrophy between the control and the high dose group, correcting a misleading statement in the original report. As further confirmed again by [redacted] (2011, ASB2014-9150) in a response to a "question" (not mentioned, by whom it was raised) the latter one was an artefact due to incorrect data management. Apparently, there had been no appropriate differentiation between the two testes of the animals when effects were reported.
Survival and growth of the animals were not affected. However, the dose levels choosen, although sufficiently high for a study of this type, were much lower than in other long-term studies with glyphosate in mice.
It was noted that histological examination of salivary glands covered submaxillary, sublingual and parotid glands. However, no lesions similar to those found by [redacted] (1992, TOX9551954, see B.6.3.2) in another mouse strain following administration of glyphosate ober 90 days at higher doses were reported.
~~There was no increase in malignant lymphoma.~~

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ORIGINAL – Application, GTF, pp. 511-516

G. HAEMATOLOGY
There were no significance differences in the proportions of white blood cell counts for either sex at both 12 and 18 month.

H. NECROPSY
Gross pathology
There were no treatment-related macroscopic findings observed for any mice sacrificed at termination or mice that died or were killed in extremis during the study period.

Organ weights
There were no treatment-related findings observed in organ weights or relative organ weights.

Histopathology
There were no treatment-related histopathological findings observed in any dose group of either sex.

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III. CONCLUSION

Based on the study results the NOEL and NOAEL in mice after chronic exposure to Glyphosate technical for 18 month is 810 mg/kg bw/day for males, and 1081 mg/kg bw/day for females. It is concluded that Glyphosate technical is not carcinogenic in mice.

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Annex point	Author(s)	Year	Study title
IIA, 5.5.3/03	[redacted]	1997	HR-001: 18-Month Oral Oncogenicity Study in Mice. [redacted] Data owner: Arysta LifeScience Study No.: IET 94-0151 Date: 1997-06-18 GLP: yes not published
Guideline:			Japan MAFF Guidelines 59 NohSan No.4200, 1985 U.S. EPA FIFRA Guidelines Subdivision F, 1984 OECD 451 (1981).
Deviations:			None
Dates of experimental work:			1995-02-21 to 1996-09-06

Executive Summary
In order to evaluate the oncogenic potential of HR-001 in mice, the test substance was administered to SPF ICR mice –Crj:CD-1) by incorporating it into a basal diet at a concentration of 0, 1600, 8000 or 40000 ppm for a period of 18 months (78 weeks). During the treatment period, all animals were observed for clinical signs and measured body weights as well as food consumption. At week 21, urinalysis was carried out on 20 males from all groups. Differential leukocytes counts were determined on the blood smears from 10 males and 10 females of all groups at week 52 and after 78 weeks of treatment, organ weight analysis was conducted on 10 males and 10 females which were served to the determination of differential leukocytes counts. All animals of both sexes were subjected to necropsy and histopathological examinations.

- 40,000 ppm groups In clinical observations, the incidence of pale-coloured skin was increased in males. In addition, loose stool was observed in all cages beginning at week 21 in males and at week 20 in females. Retarded growth was persistently observed during treatment period showing

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

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There was a weak increase in malignant lymphoma incidence in male mice at the top dose level. The actual numbers of affected animals were 0, 1, 2, and 5 in the control, low, mid and high dose groups (n=51 in each of them). In females, the respective figures were 11/51, 8/51, 10/51 and, again, 11/51. Thus, no evidence of any change in lymphoma frequency was seen in female mice in this study. Even in males, the difference was not statistically significant but a possible effect might be suspected and should be clarified because of the increase in malignant lymphoma in the study by [redacted] (2001, ASB2012-11491, "1st new study", see above) and because of a weakly higher incidence in the study by [redacted] (1997, ASB2012-11493, "3d new study", see below). On request of the RMS, the GTF submitted historical control data for malignant lymphoma from the performing laboratory ([redacted] 2015; ASB2015-2531) but, unfortunately, only after the PRAS 125 meeting that was held in February, 2015. Therefore, the following data was not subject to peer review by the regulatory agencies of the MS.

Nine long-term studies were included which had been conducted in the same mouse strain between 2000 and 2010. The study duration was 104 weeks and, thus, longer than in the study that was under evaluation here. In total, 768 control mice (sexes not distinguished) had been examined. Malignant lymphoma was found in 63 animals, i.e., in 8.2%. (In the submitted document, 12.63% was mentioned but this must be wrong if the whole number of animals under examination is taken into consideration.) In line with that figure, the mean study incidence for this tumour type was 7.51% with a standard deviation of 6.61 pointing to a large variation. In the individual studies, the lymphoma rates ranged from 0 to 32%. Based on this data, the incidences of malignant lymphoma in all groups in the study with glyphosate by [redacted] (2009, ASB2012-11492) were within the historical control and the incidence of slightly below 10% in top dose males (even if compared to 0% in the concurrent control) was of no concern. However, the quality and regulatory value of the historical control data is very much compromised by the fact that the sexes were not considered separately. Moreover, the data were apparently not all obtained from the same laboratory but, instead, also from other testing facilities of the Harlan group in Europe. At least, this information may be considered as indicative for the high variability in lymphoma incidence in the mouse strain used.

There are more sources to support, based on historical control data, remarkable differences in the occurrence of malignant lymphoma in CD-1 mice. According to information obtained from the "Registry of Industrial Toxicology Animal-data" (RITA) database (Fraunhofer ITEM Institute, Hannover, Germany; http://reni.item.fraunhofer.de/reni,) and made available to the RMS only very recently by the GTF, male CD-1 mice had a mean incidence of 3.4% (of 470 animals in total) in the control groups from nine 18-/19-month long-term studies performed between 1994 and 1998. In the individual studies, incidences ranged from 0 up to 12%. In female mice, the mean control incidence was much higher (16.9% in a total of 350 examined animals). In line with that, actual study incidences in female mice varied between 4 and 32% (Anonym, 2015, ASB2015-2532).
For the Crl:CD1 (ICR) mouse [i.e., the strain that was used by [redacted] (2009, ASB2012-11492), in their glyphosate study], Giknis and Clifford (2010, ASB2015-2529) reported data from a total of 13 (males) or 14 studies (females) with a duration between 78 and 104 weeks that had been performed between 2002 and 2006 by [redacted]. (Also this data was submitted by GTF following PRAS 125 meeting.) In males, malignant lymphoma was more rarely seen than in females since tumours of this type were found in the control groups in 8 out of 13 studies only with a minimum study incidence of 1/75 and a maximum one of 5/49 closely resembling that one at the top dose level of the [redacted] (2009, ASB2012-11492) study with glyphosate. In female CD-1 mice, malignant lymphoma was

Facsimiles 3.1.2-1 and 3.1.2-2: "Benign" copy pasting of data from an industry study

COPY PASTE – RAR, RMS, pp. 1,023-1,030

observed in all but one of the 14 studies, even though with an extremely variable study incidence ranging from 2/60 up to 22/50.
Based on their retrospective analysis of 20 long-term studies for carcinogenicity (Huntingdon Life Sciences, U.K., 1990-2002) Son and Gopinath (2004, ASB2015-2533) described lymphoma as the most common tumour in young control CD-1 mice. This result was based on an analysis of premature deaths in these studies. In a total of 101 fatalities occurring up to week 50 of treatment in all these studies among male animals, lymphoma was found in 23 cases. In the 190 males which died between weeks 50 and 80 before scheduled termination, 36 were diagnosed with lymphoma. Among females, there were 68 premature deaths up to week 50 of which 19 had lymphoma suggesting a slightly higher rate than in males (28% vs. 23%). Between weeks 50 and 80, there were 211 deaths and, among them, 61 with lymphoma (ca 29% vs. 19% in males). It was noted that lymphoma incidence in the Huntingdon colony was similar in females as in the ICR mouse (Giknes and Clifford, 2010, ASB2015-2529) or in CD-1 mice included in the RITA database (Anonym, 2015, ASB2015-2532) whereas a more frequent occurrence of this tumour type was noted in males. However, this might be due to a different focus of the analysis. In the RITA database and in the review from [redacted] all animals on study were considered. In contrast, Son and Gopinath (2004, ASB2015-2533) looked only at the premature deaths to which malignant lymphoma might have contributed to a rather large extent.

3d new long-term study in mice ([redacted] 1997)

Reference: IIA, 5.5.3/03
Report: [redacted] (1997)
HR-001: 18-Month Oral Oncogenicity Study in Mice.
[redacted]
Data owner: Arysta LifeScience
Study No.: [redacted] 94-0151
Date: 1997-06-18
Not published, ASB2012-11493
Guidelines: Japan MAFF Guidelines 59 NohSan No.4200, 1985
U.S. EPA FIFRA Guidelines Subdivision F, 1984
OECD 451 (1981).
Deviations: None
GLP: yes
Acceptability: *See RMS comment*

Dates of experimental work: 1995-02-21 to 1996-09-06

Materials and methods

Test material:	Glyphosate technical	
Identification:	HR-001	
Description:	Solid crystals	
Lot/Batch #:	T-941209	T-950308
Purity:	97.56 %	94.61 %
Stability of test compound:	Not mentioned in the report	

3.1.2.2 BfR's assessment of published studies on carcinogenicity

The subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)" deals with epidemiological studies on cancer (in particular non-Hodgkin lymphoma) – studies which, according to the IARC experts, raise suspicions that glyphosate causes cancer in humans.[34]

A detailed running text (literature overview) was plagiarised verbatim. The only changes concern the referencing system. The same applies to the selection of studies that are described individually. And again, the Klimisch evaluations were plagiarised with the same scores and the same interpretations. Comments by the applicants following these Klimisch evaluations in many cases were labelled "Additional comments".

In the GTF application, every single study that reports an increased risk for non-Hodgkin lymphoma with glyphosate was assessed as "not reliable" (Klimisch Score 3). By copying every single evaluation from the GTF, the BfR has dismissed all of the epidemiological studies that report an increased risk in humans for cancer with glyphosate.

In September 2015, the renowned German epidemiologist Eberhard Greiser stated in an expert assessment[35] for the German Bundestag that the BfR's explanations for why all those studies were supposedly unreliable are obvious misrepresentations of those studies; it would have been easy to check their truthfulness, and the authorities should have done so. Dr Greiser at the time had accused the BfR of an "obvious falsification of study contents" – apparently not realizing that the "obvious falsification of study contents" actually was produced by GTF, and that BfR had only copied it.

Facsimile 3.1.2-3: "Benign" copy paste and plagiarism (= "malign" copy paste) in the subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)"

RAR, RMS, pp. 1,040-1,063

Table B.6.5-60: ***Incidence of malignant lymphoma at terminal sacrifice in the study by [redacted] (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 [redacted] (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 [redacted] (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 exosure 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 attapcable 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, lending 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, chlorothalanil 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 oand 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 dificulty 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 at 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 heterogenous 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 limitions 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.

Facsimile 3.1.2-3: "Benign" copy paste and plagiarism (= "malign" copy paste) in the subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)"

RAR, RMS, pp. 1,040-1,063

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, an breast cancer were integrated. Glyphosate was reported to be the most commonly used in conventional pesticide active ingedient 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*a* 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 an 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 ≥ 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 associaton 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 glpyphosate/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 adequaetely 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 send 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 assciation 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,

Facsimile 3.1.2-3: "Benign" copy paste and plagiarism (= "malign" copy paste) in the subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)"

RAR, RMS, pp. 1,040-1,063

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 Healt 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. Immunodefective 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.
ConclusionS. 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. Kricker, 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

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RAR, RMS, pp. 1,040-1,063

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.

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RAR, RMS, pp. 1,040-1,063

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

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RAR, RMS, pp. 1,040-1,063

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 (ASB2012-11606)	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 (ASB2012-11838)	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 (ASB2012-11839)	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 (ASB2012-11883)	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 (ASB2011-364)	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

Facsimile 3.1.2-3: "Benign" copy paste and plagiarism (= "malign" copy paste) in the subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)"

RAR, RMS, pp. 1,040-1,063

Author Year	Exposure Evaluated	Subgroup Description	No. of Exposed Cases	No. of Exposed Controls	OR	95% CI	Variables Included in Statistical Model
Nordstrom et al. 1998 (TOX1999-687)	Exposure to specific herbicides, insecticides, and fungicides	Glyphosate	4	5	3.1	0.8-12	Age and country (matching factors)
Eriksson et al. 2008 (ASB2012-11614)	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

Facsimile 3.1.2-3: "Benign" copy paste and plagiarism (= "malign" copy paste) in the subchapter "B.6.5.3 Published data on carcinogenicity (released since 2000)"

RAR, RMS, pp. 1,040-1,063

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

even higher than required in guideline 453. Therefore, the study is considered to be relevant. No carcinogenic effects have been registered in the study.

B.6.6 Reproductive toxicity (Annex IIA 5.6)

Introduction into this chapter by the RMS
For higher efficiency of the review and for the sake of transparency, the descriptions of methods and study results in the GTF dossier were virtually not amended and even the conclusions were kept as provided. However, each study that is described in detail was commented by RMS. These remarks on bottom of each study description are clearly distinguished from the original submission by a caption and are always written in italics. In addition, redundant parts (in particular the so-called "executive summaries") have been deleted and the structure of the original submission was significantly changed to make it more transparent and comprehensible.

The overall assessment of reproductive toxicity of glyphosate by the RMS is provided in Volume 1 (2.6.6) of the present RAR.

Comments by the GTF on the first draft of the RAR (July 1013) have been partly included in the present report. Responses by RMS to GTF are written in italcs and given below. This approach was taken to avoid doubling of comments/responses at a later timepoint.

B.6.6.1 Two generation reproductive toxicity in the rat

The reproductive toxicity of glyphosate was tested in a variety of multi-generation studies in rats. For the previous EU evaluation, a total of 8 studies in rats had been submitted of which four were still considered acceptable or, in case of a single one-generation study, at least supplementary upon re-evaluation. The studies by [redacted] (1981, TOX9552385), by [redacted] (1985, TOX9650161) and by [redacted] (both 1988, TOX9551832 and TOX9551965), however, were deleted from current evaluation due to major deficiencies and/or because the dose levels were much too low and therefore one could not expect the occurrence of any toxic effects.
Three new studies were provided in the GTF dossier and were submitted either for the first time for this evaluation or had been subject to JMPR evaluation (JMPR, 2004, ASB2008-6266) yet.

Reference:	IIA, 5.6.1/01
Report:	[redacted] (2007) Glyphosate technical: Dietary Two Generation Reproduction Study in the Rat [redacted] Data owner: Nufarm SPL project no.: 2060/0013 Date:2007-10-31 (amended 2008-04-08 and 2008-08-08) not published ASB2012-11494
Guidelines:	OECD 416 (2001), JMAFF 2-1-17 (2001), US-EPA OPPTS

3.2 Analysis of Volume 3, Annex B.9 – Evaluation of peer-reviewed literature regarding ecotoxicity

Volume 3 B.9 of the RAR is attributed to the German Environment Agency (UBA). The chapter contains 405 pages (403 + ii). It deals exclusively with published, peer-reviewed literature on the possible dangers of glyphosate for the environment. Our task was to see if the Umweltbundesamt (UBA) also worked with copy paste techniques or committed plagiarism.

We found that the Umweltbundesamt (UBA) worked according to the standards of Good Scientific Practice. The amount of copy pasted texts or paragraphs that can be classified as plagiarism in Volume 3 B.9 is insignificant.

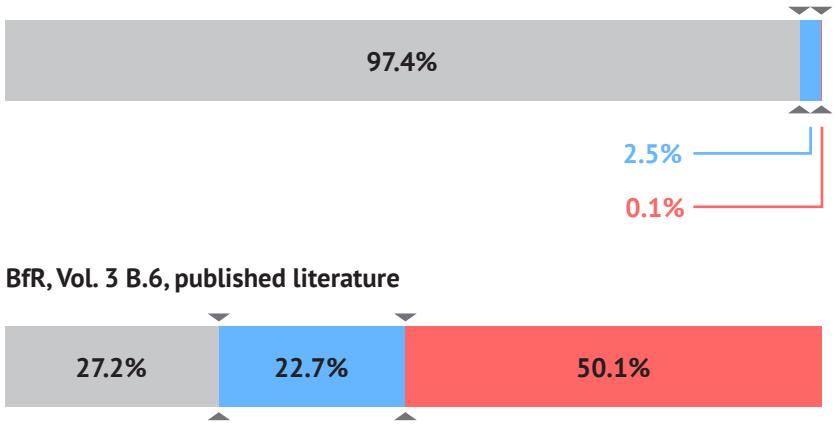
In contrast with the BfR, the UBA describes its "methodology of the literature research" (p. 3,731) completely in its own words, without relying upon the formulations of the GTF. The UBA describes the "procedures of sighting and classifying" in detail (pp. 3,732). The UBA even contrasts the "analysis of reliability and relevance of peer-reviewed literature" as executed by the notifier, the GTF (pp. 3,733) with its own approach (pp. 3,735). The UBA presents a so-called "UBA score" (UBA1, UBA2, and UBA3) to represent its own evaluation (pp. 3,735). The presentation of published studies follows a rigid template (pp. 3,736):

Biological Relevance	
1 Is an appropriate test species/ life-stage(s) studied?	Communities of naturally occurring bird species in field monitoring studies have been assessed over 2-4 years, which could be ecologically highly relevant.
2 Is the magnitude of effects of significance to cause a (population) relevant effect?	Since the methodology was not described in detail for each of the studies the statistical significance could not be judged. The studies were conducted on population level and could therefore considered relevant on this particular level of organisation
3 Is the ecotoxicological manifestation level appropriate for the assessment?	Population changes over time is amongst the highest possible levels of manifestation
Environmental Relevance	
1 Is the substance tested representative and relevant for the substance being assessed?	The test substances were not uniform and not described in more detail than the mere mentioning of 'glyphosate' as the test substance.
2 Do the tested concentrations relate to predicted environmental concentrations?	Yes, because recommended field rates have been tested.
3 Have parameters influencing the endpoints been considered adequately?	-/-
Concluding weight of evidence/proposed action	The paper deals with the impact of the Anglo-Saxon practice of managing the vegetation for purposes of enhancing forest and other crop yields. This includes especially the control of roadside vegetation and intends the maintenance of ecological processes in terrestrial ecosystems. However, the review shows the transiency and indirectness of effects of Glyphosate treatments on the biodiversity of birds, most probably mediated by ephemeral changes of the (shrub) vegetation.
Type of information (Critical, supporting, low weight)	**Supporting information**
Consideration/concluding score	**UBA2**

Facsimile 3.2-1: Template by the UBA with the concluding UBA score, RAR, RMS, p. 3,743

The approach is categorically different to that of the BfR. The amount of text segments appearing in both documents, the application of the GTF and the RAR, is 2.5%. We compare this amount with a 72.8% copy paste share in the BfR's evaluation of published literature in Volume 3 B.6. Out of this 2.5%, 0.1% can be classified as plagiarism. Once again, we compare this amount with a 50.1% plagiarism share in the BfR's evaluation of published literature in Volume 3 B.6.

Figure 3.2-2: "Benign" copy paste and plagiarism (= "malign" copy paste) shares of the BfR compared to the UBA



The share of plagiarism totals 1,646 characters, including blanks. In one case, a brief introduction appears in both compared documents. In another case, an old literature reference provided by the GTF ("Abel and Skidmore, 1975") was obviously dropped by the UBA. These are minor incidences of plagiarism. Copy pasted text segments mainly appeared in instances in which the UBA took abstracts and study findings verbatim from the evaluated papers, which also appear in the application. We classify this as "benign" copy paste practice.

We conclude that in contrast to the BfR, the UBA did not commit significant plagiarism.

3.3 Analysis of Volume 1 – Report and proposed decision

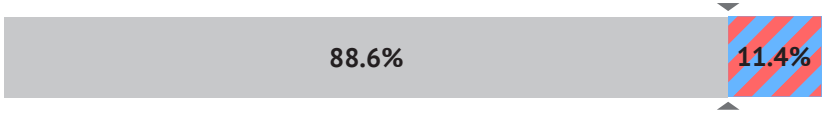
Volume 1 is the core of the RAR and reads as a summary of the chapters that follow. The chapter contains 195 pages (190 + v). Our task was to see if Volume 1 is free of copy pasted texts and plagiarism. This is what Jose Tarazona, head of the pesticides department at the EFSA, claimed on German TV in 2017: "There is no copy and paste in Volume 1."[36]

However, we can confirm the analysis of ARD journalist Andreas Rummel, that Tarazona's statement is wrong: The amount of copy pasted text in Volume 1 compared to the application is 11.4%. Furthermore, plagiarism was detected in subchapter 2.6.6 of Volume 1, which is attributed to the BfR.

3.3.1 General findings

There are 470,786 characters, including blanks, in Volume 1 of the RAR. The share of copy paste, including plagiarism (out of the entire Volume 1) is 53,704 characters, including blanks – that's 11.4%. Copy paste sometimes occurred when the central findings of the same literature were cited indirectly. In these cases, the concordances could also stem from abstracts used by both the applicant and the RMS. These incidences could be classified as "benign". "Malign" copy paste or plagiarism could be detected almost exclusively – with the exception of a handful of other paragraphs – in chapter 2.6.6. This is why an in-depth analysis of that chapter follows.

Figure 3.3.1-1: "Benign" and "malign" copy paste share in Vol. 1



3.3.2 Detailed analysis of the subchapter "2.6.6 Summary of long-term toxicity and carcinogenicity"

Plagiarism as a clear case of scientific misconduct in Volume 1 was found almost exclusively in the paragraphs attributed to the BfR. Especially in the subchapter 2.6.6, the summary of published literature on the carcinogenicity of glyphosate-based formulations has been grossly plagiarised. The BfR only made minimal editorial changes, changed some formulations in detail, and adapted the citation. There is no hint to the reader that this text mainly relies upon the applicant. The following facsimile comparison provides proof:

Facsimiles 3.3.1-2 and 3.3.1-3: "Published data" from the subchapter "2.6.6 Summary of long-term toxicity and carcinogenicity" of the RAR compared to the "Literature review of carcinogenicity publications" from GTF

PLAGIARISM – RAR, RMS, pp. 75-79

In the Pesticides Peer Review 125 expert meeting (February 2015), it was agreed that there is no need to propose classification and labelling of glyphosate for carcinogenicity.

Another, non-neoplastic but presumably treatment-related effect found by [redacted] (2001, ASB2012-11491) was a more frequent occurrence of cystic glands of the stomach in male mice at all dose levels. However, there were no clear dose response and no evidence of an increase in severity of this lesion of which the clinical relevance is equivocal. Again, this finding was not reported in any other study in mice. Thus, based on the higher malignant lymphoma incidence, the mid dose level of 1000 ppm (*ca* 151 mg/kg bw/day) was considered the NOAEL. This figure was virtually the same as established by [redacted] (1983, TOX9552381) even though effects at higher dose levels were different.

In the third, previously not evaluated study in mice by [redacted] (1997, ASB2012-11493), the NOAEL was 153 mg/kg bw/day (1600 ppm), based on effects of glyphosate administration on body weight gain, food consumption and efficiency in female mice at the next higher dose level of 8000 ppm (equivalent to 787 mg/kg bw/day). At the extremely high dose of 40000 ppm (equivalent to 4348/4116 mg/kg bw/day in males and females, respectively) additional signs of toxicity included loose stools, caecum distention and increased absolute and relative caecum weight (without corollary histopathological findings), a higher incidence of anal prolapses and erosion/ulceration of the anus in male mice and some minor changes such as a decrease in urinary pH, lymphocytosis in females and few external signs (loss of tactile hair, pale-colored skin).

Based on the studies by [redacted] (1997, ASB2012-11493), [redacted] (2001, ASB2012-11491) and [redacted] (1983, TOX9552381), the overall NOAEL for long-term toxicity in the mouse can be set at 150 mg/kg bw/day. The overall LOAEL was around 800 mg/kg bw/day since first effects were observed at 787 mg/kg bw/day in females by Sugimoto (1997, ASB2012-11493) and at 814 mg/kg bw/day by [redacted] (1983, TOX9552381) in males. As in rats, the nature of high dose effects in mice was different in the various studies, depending on laboratory, strain, dose selection and, perhaps, purity/impurity profile of the test material.

Studies with formulations/Published data

Epidemiology

1 A number of epidemiology studies over the last decade have focused on pesticide exposure and associated health outcomes. Publications vary in the scope of their conclusions regarding either pesticides in general, certain 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 speculative if exposure cannot be confirmed and quantified.

2 The largest epidemiological study of pesticide exposure and health outcomes in the United States was the Agricultural Health Study (AHS) that also adressed and included glyphosate.

ORIGINAL – Application, GTF, pp. 847-849

3. Literature Review of Carcinogenicity Publications

Over the 40 year product history of glyphosate based herbicides, regulatory expert and other authoritative review panels have evaluated multiple data sets to evaluated glyphosate safety, including potential for carcinogenicity. These multiple reviews over the decades have consistently drawn the same conclusion; glyphosate is not carcinogenic. These conclusions include those of the U.S. Environmental Protection Agency in 1993 and 1997 (Category E, evidence of non-carcinogenicity for humans -- based on the lack of convincing evidence of carcinogenicity in adequate studies); the European Commission's Health and Consumer Protection Directorate-General in 2002 (no evidence of carcinogenicity); the U.S. Forest Service (based on standard animal bioassays for carcinogenic activity *in vivo*, there is no basis for asserting that glyphosate is likely to pose a substantial risk); Canadian regulators (no evidence that glyphosate causes cancer); the World Health Organization and Food and Agriculture Organization of the United Nations in 2004 (long-term studies of toxicity and carcinogenicity were conducted in mice and rats. In the study of carcinogenicity in mice, no toxic effects were observed at up to the highest dose tested (1000 mg/kg bw per day), and there was no evidence of carcinogenicity).

1 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.

7 One publication (George et al., 2009) utilized 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 for a positive control/comparator after exposure to a tumor initiator, 7, 12-dimethylbenz[a]anthracene. Proteomics were later applied to extrapolate a basis for glyphosate formulation tumor promotion. This study is discussed in more detail 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; 2005), 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 current EU glyphosate acceptable operator exosure Level (AOEL). The highest systemic dose, skewed well above the geometric mean, was 0.004 mg/kg/day, which is 1.95% of current EU glyphosate AOEL and 1.3% of the current EU glyphosate attapcable daily intake (ADI). Not surprisingly, even lower systemic doses were determined for spouses and children, 0.00004 mg/kg and 0.0008 mg/kg, respectively. Interestingly, the current European ADI is based on the NOAEL (highest dose tested) in an old 2-year rat carcinogenicity study; 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.

2 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) 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) 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) reported an association between NHL and glyphosate use. McDuffie et al. (2001) reported a non-significant positive association between self-

Facsimiles 3.3.1-2 and 3.3.1-3: "Published data" from the subchapter "2.6.6 Summary of long-term toxicity and carcinogenicity" of the RAR compared to the "Literature review of carcinogenicity publications" from GTF

PLAGIARISM – RAR, RMS, pp. 75-79

Dozens of publications have resulted from data generated in this study of approximately 57,000 enrolled farmers (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 leukaemia, 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) had reported an association between NHL and glyphosate use. Likewise, McDuffie *et al*. (2001, ASB2011-364) mentioned a non-significant positive association between self-reported glyphosate exposure and NHL in a Canadian study. Blair *et al*. (2009, ASB2012-11566), in contrast, 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 making reference to a "suggested association" between glyphosate use and multiple myeloma suggested by De Roos *et al*. (2005, ASB2012-11605). However, in this paper, no significant increase in relative risk for multiple myeloma was demonstrated. Both papers by De Roos *et al*. will be discussed in more detail below. Interestingly, a subsequent AHS review paper for the President's Cancer Panel (Freeman, 2009, ASB2012-11623) specifically referenced De Roos *et al*. (2005 ASB2012-11605) to provide no evidence of cancers of any type to be associated with glyphosate.

3 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 about higher positive associations observed for proxy respondents with glyphosate and several other pesticides. They suggested perhaps more accurate reporting of proxies for cases and underreporting by proxies for controls.

4 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, chlorothalonil and "others". No association was noted for paternal exposures, but elevated incidence of leukaemias was associated with maternal exposures to "other pesticides" during pregnancy.

Some further epidemiological studies have 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)

ORIGINAL – Application, GTF, pp. 847-849

reported glyphosate exposure and NHL in a Canadian study. Blair et al. (2009) 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), 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) specifically references De Roos (2005) as providing no observed incidents of cancers of any type being associated with glyphosate.

3 Lee et al. (2005) 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, lending to lower reported incidents in the control group.

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

- Alavanja et al. (2003) reported on prostate cancer associations with specific pesticide exposures in the AHS; glyphosate did not demonstrate a significant exposure-response association with prostate cancer.
- Multigener et al, (2008) 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).
- 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).
- Lee et al. (2004) reported a lack of association between glyphosate use and stomach and esophageal adenocarcinomas.
- Carreon et al. (2005) reported epidemiological data on gliomas and farm pesticide exposure in women; glyphosate had no association with gliomas.
- Engel et al. (2005) reported AHS data on breast cancer incidence among farmers' wives, with no association between breast cancer and glyphosate.
- Flower et al (2004) reported AHS data on parental use of specific pesticides*a* and subsequent childhood cancer risk among 17,280 children, with no association between childhood cancer and glyphosate.
- Andreotti et al. (2009) reported AHS data where glyphosate was not associated with pancreatic cancer.
- Landgren et al. (2009) reported AHS data on monoclonal gammopathy of undetermined significance (MGUS), showing no association with glyphosate use.
- Karunanayake et al. (2011) reported a lack of association between glyphosate and Hodgkin's lymphoma.
- Pahwa et al. (2012) reported a lack of association between glyphosate and multiple myeloma.

6 In summarizing AHS publications, Weichenthal et al. (2010) 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.

4 Monge et al (2007) 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, chlorothalanil and "others". No association was noted for paternal exposures, but elevated leukaemias were associated with maternal exposures to "other pesticides" during

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PLAGIARISM – RAR, RMS, pp. 75-79

with data from a previously submitted publication from Nordström *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 found with a heterogenous category of "other herbicides" and not for glyphosate. No information is given about exposure duration, exposure concentration, as well as medical history, lifestyle factors (*e.g*., smoking, use of prescribed drugs *etc*.). In all, the above mentioned limitations of the publication of Hardell and Eriksson (1999, ASB2012-11838) are also applicable to the publication by 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, 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, NHL, leukemia, multiple myeloma, and breast cancer were integrated. Glyphosate was reported to be the most commonly used conventional pesticide active ingedient worldwide. However, the only association between the use of glyphosate and cancer burden mentioned in this review was the observation of Eriksson *et al*. (2008, ASB2012-11614, see above).

5

The following epidemiological studies did not reveal an 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 in 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.

ORIGINAL – Application, GTF, pp. 847-849

pregnancy. Similarly, glyphosate is captured under "other pesticides" being associated with NHL by Fritschi et al. (2005) and therefore should not be interpreted as an association with glyphosate.

Non-Hodgkin's Lymphoma (NHL)

Non-Hodgkin's lymphoma is not a specific disease, but rather a grouping of all lymphoma types, other than Hodgkin's lymphoma. This is a large group of different cancers of the immune system including Burkitt lymphoma, diffuse large B-cell lymphoma (NLPHL), follicular lymphoma, immunoblastic large cell lymphoma, precursor B-lymphoblastic lymphoma, mantle cell lymphoma, mycosis fungoides, anaplastic large cell lymphoma, and precursor T-lymphoblastic lymphoma (National Cancer Institute, http://cancer.gov/cancertopics/wyntk/non-hodgkin-lymphoma.pdf). Risk factors associated with NHL include weakened immune system (such as from an inherited condition or certain drugs used after an organ transplant), infections (Epstein-Barr virus, EBV; Human immunodeficiency virus, HIV; *Helicobacter pylori* bacteria; Human T-cell leukemia/lymphoma virus, HTLV-1; Hepatitis C virus; age). There are many different types of Non-Hodgkin's lymphomas, which are different lymphomas arising from different pathogeneses, and as such, should not be clustered together as a single disease with a common etiology for epidemiological investigation. When clustered together in epidemiological studies, further investigation to identify both the specific type of lymphoma and any underlying risk factors associated with individual reports of HNL is necessary.

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PLAGIARISM – RAR, RMS, pp. 75-79

- 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 an glyphosate was reported.
- Kachuri *et al*. (2013, ASB2014-8030) investigated an 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 ≥ 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-Zaemey and Heyworth (2013, 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 no 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 associaton 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 a comprehensive review of the AHS publications and data, Weichenthal *et al*. (2010, ASB2012-12048) noted that increased rates in the following cancers were not associated with

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PLAGIARISM – RAR, RMS, pp. 75-79

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 assciations indicating a causal relationship between total cancer (in adults or in children) or any site-specific cancer and exposure to glyphosate.

Toxicological studies with formulations in laboratory animals

Chruscielska *et al*. (2000, ASB2013-9829) published the results of a combined long-term toxicity and carcinogenicity study in rats. The active substance glyphosate (apparently manufactured in Poland and fomulated as a 13.85 % solution of the ammonium salt in water) was used in the study that was performed mainly according to OECD guideline 453. The number of animals per dose group and sex (85 animals) was even higher than required. The highest dose level of the glyphosate salt was 2700 ppm. Study duration was 2 years. No carcinogenic effects have been found in the study. However, apart from tables with cancer incidences, no raw data has been reported and the whole report was very brief.

7

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.

More recently, a two-year study in rats was published by 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 glpyphosate/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 adequaetely 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

4. Possible motives for, and impact of, the copy paste and plagiarism practices and future recommendations

4.1 Answering special research questions

Based on our copy paste and plagiarism analysis, the „special research questions posed to the study authors" (p. 13 in this expert report) can be answered as follows:

1) Did copy paste and plagiarism influence the BfR's clean bill of health for glyphosate?

The answer is yes. It is obvious that BfR's uncritical adoption of incorrect, incomplete or biased information from applicants by means of copy paste influenced the basis of its assessment. This became very clear in the case of both published and industry studies on glyphosate's carcinogenicity.

Published epidemiological studies on non-Hodgkin lymphoma that, according to IARC experts, raise suspicions that glyphosate causes cancer in humans, were dismissed as "not reliable" by the BfR, on the basis of the GTF's Klimisch evaluations. However, the justifications of the GTF for the alleged lack of reliability of these studies, which were also copied by the BfR, do not stand up to scientific scrutiny.[37] [38]

In the case of industry cancer studies with mice, the BfR based its initial evaluation on incorrect statistical evaluations provided by the GTF. As a consequence, the BfR used the same two industry cancer studies with mice, in which the IARC experts had identified "sufficient evidence for the carcinogenicity of glyphosate in animal experiments", as evidence for the lack of a carcinogenic potential. This became clear in the BfR's Addendum to the RAR, where the "statistical analysis by IARC was confirmed and extended" by the BfR and the authority had to admit that its re-evaluation of the industry mice studies confirmed statistically significant increases of tumours with dose in no less than eight cases, of which seven had been overlooked because the authority had initially "relied on the statistical evaluations provided [by the applicant] with the study reports".[39] Such serious failures of the responsible authorities are certainly favoured by their copy paste practice, if not made possible in the first place.

2) Is the contradiction between the assessment of glyphosate by the WHO Cancer Research Agency IARC and the EU authorities (also) a consequence of the authorities' copy paste and plagiarism practice?

With regard to the cancer assessment in Vol. 3.B.6 and Vol. 1 of the RAR (which are the subjects of this expert report on plagiarism), the answer is a clear yes. The IARC based its cancer classification on "limited evidence in humans", sufficient evidence in animals" and "strong evidence for genotoxicity" as a possible molecular mechanisms for the carcinogenicity of glyphosate. The GTF, however, classified published studies that link glyphosate to genotoxicity and an increased risk of non-Hodgkin lymphoma in humans as "not reliable". The GTF also reported four out of five industry carcinogenicity studies with mice as lacking statistically significant increase of tumours in glyphosate-treated animals, after having failed to apply the statistical test recommended in the OECD test guidelines. The BfR appropriated the flawed GTF evaluation with its copy paste approach. The authority's contradiction to IARC's cancer assessment can thus clearly be traced back to this.

3) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the arguments raised by the BfR, the EFSA, and the German Ministry of Agriculture in order to refute the first accusations of plagiarism?

The first known official statement on the accusation that the BfR had copied relevant parts of its assessment from the application came from the German Ministry of Agriculture in July 2015. This statement was clearly misleading. In particular, the claim that "the relevant chapters on the scientific literature contained only assessments written by BfR staff"[40] was false. As far as the BfR and the EFSA are concerned, it is striking that these authorities have never responded seriously to a specific allegation of plagiarism, let alone refuted any of them. Instead their strategy seems to have been to divert attention from the core of the plagiarism allegations. The clearest example of this was provided by Jose Tarazona at the "Monsanto Hearing",[41] when he responded to allegations of plagiarism that refer exclusively to chapters on published studies, with examples picked only from chapters on industry studies.

This report has shown that the distinction between "benign" copy paste and "malign" plagiarism is crucial. Copy paste seems to be widespread practice by European audit authorities in evaluating applications of producers of pesticides, as investigations of the German broadcaster *Bayerischer Rundfunk* have revealed.[42] It is open to discussion whether this practice is conducive to the independence, objectivity, and transparency of the authorities' assessments of the scientific evidence. But there can be no doubt that the "malign" form of copy paste, called plagiarism, is something categorically different and is always incompatible with scientific standards. This is why the BfR for example is committed to the principles of "Good Scientific Practice" (GSP).[43] The authors of this study hope that the public and political discourse will from now on focus on the new findings of this expert report.

4) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the statement by the head of the pesticides unit at the EFSA that there is no copy paste in Volume 1 of the RAR?

This statement is wrong. There seem to be two possible reasons for it: Stating a lie or a lack of knowledge (wrong briefing from the team).

5) In our opinion, what might be the reasons for the BfR's approach, based on our experience and expertise in the field of plagiarism? And is there evidence of deliberate deception of the reader?

It is not possible to look into someone's mind and therefore we do not know what motivated the responsible BfR staff to take this problematic approach. In principle, however, plagiarism can usually be traced back to one of the following two motives, or a combination of both:

1) Plagiarism makes it possible to achieve a desired result, which could otherwise only be achieved with significantly greater use of time and resources.

2) Plagiarism makes it possible to achieve a result that would otherwise not have been achievable at all, due to a lack of the necessary skills.

Given the huge amount of industry studies (in the Monsanto Hearing, Jose Tarazona spoke of "several hundred thousand" pages), the rapid progress of science, and the broad thematic range of published studies of possible relevance for the assessment, both the above explanations seem plausible.

In our opinion, the question of whether the BfR intended to deceive the reader must be answered with a clear "yes". Clear indications of deception were found. Most striking was the finding that what the BfR described as the "approach taken by the RMS" was actually copy pasted from the GTF application and was the approach taken by Monsanto scientists.

6) What conclusions can be drawn from this copy paste and plagiarism analysis with regard to the legally required[44] independence, objectivity, and transparency of the glyphosate evaluation?

With regard to the assessment performed by the BfR, the institute's word-for-word adoption of the manufacturers' assessments ("Klimisch evaluation") of published studies in every single case can be only regarded as the opposite of independence. Because independence is a prerequisite for objectivity, the BfR's assessment also lacks objectivity. Last but not least, the systematic omission of references to the real author via selective deletions can only be interpreted as deliberate concealment of the origin of the text. It goes without saying that this is the opposite of what we would expect from a transparent assessment.

However, with regard to the assessment performed by the UBA, the present analysis provided no evidence to cast doubt on the independence of the evaluation.

4.2 Suggestions for improvement: Recommendations for more transparency

Concerning the assessment of unpublished industry studies ("benign", but in this form also avoidable copy paste):

- The reader of the RAR must always be able to differentiate between text and data from the applicant and text and data from the RMS. A "negative indication" (RMS comments in italics) should be avoided. It is always more transparent and clearer to mark the external contributions instead of one's own. Therefore, text segments and data directly appropriated (copy pasted) by the RMS from the text of the applicant should be clearly indicated, for example, in the same way as text paragraphs which are added in later revisions of the RAR are clearly indicated by highlighter colour markings.
- Verbatim appropriated text segments under the heading "Conclusion of the Notifiers" should be put in quotation marks or otherwise optically marked (e.g. printed in italics or marked as quotations by means of the design/layout).

Concerning the evaluation of published literature ("malign" copy paste = plagiarism):

- All citations must be made according to the principles of Good Scientific Practice (GSP).
- The audit authority must explicitly declare its mode of citation and strictly adhere to it – without any exception that could undermine the distinction between one's own and others' intellectual property.
- Even if the auditing authority fully agrees with judgments given by the applicant and draws exactly the same conclusions, the authority must still be obliged to mark externally sourced text.
- Plagiarism of literature reviews and literature synopses of the applicant by the RMS should be strictly avoided as it constitutes a clear case of scientific misconduct.
- Plagiarism of Klimisch evaluations following study summaries, "Additional comments", and other texts constitute a similar, sometimes even more problematic, case of scientific misconduct, because of the appropriation of value judgments, which should be strictly avoided.

5. List of references and explanatory notes

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32 Interestingly, the conclusion that there is no increase in malignant lymphoma in the study of Nufarm 2009, has been "contradicted" in Volume 1 of the version of the RAR of 18 December 2013. An increase of malignant lymphoma of 0, 1, 2, 5, tumors in the control-, low-, medium-, and high dose groups was already discussed then. However, this increase was wrongly classified by the BfR as not statistically significant. Subsequently, this false finding was used by the BfR as an argument to dismiss the significant increase in malignant lymphoma in another study (Adama, 2001) as a random result. Finally, the BfR dismissed statistically significant increases of malignant lympoma in three studies, of kidney tumors in three studies, and of haemangiosarcoma in two studies as random results. See also: Clausing P, Robinson C, Burtscher-Schaden H: Pesticides and public health: an analysis of the regulatory approach to assessing the carcinogenicity of glyphosate in the European Union, Epidemiol Community Health 2018; 72:668–672; https://jech.bmj.com/content/jech/72/8/668.full.pdf (accessed 10.01.2019)

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