HEAL
HEALTH AND ENVIRONMENT ALLIANCE

HOW THE EU RISKS GREENLIGHTING A PESTICIDE LINKED TO CANCER

Zooming in on the glyphosate renewal dossier

ACKNOWLEDGEMENTS

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GLOSSARY

Biological relevance

The concept of biological relevance is used to refer to an effect of interest that is considered important and biologically meaningful and which, in risk assessment, may have consequences for human health [1]. A major challenge in biological sciences is that a statistically significant change alone is not always biologically relevant; in addition, not every biologically relevant change will necessarily be statistically significant.

Historical controls and control groups

A control group or concurrent control in animal experimental studies is a group of animals that have not been exposed to the chemical substance under investigation. It is used as a reference to compare effects observed in the exposed groups. Historical controls are unexposed animals from experiments other than the one under evaluation (concurrent control) that have taken place in the past. Historical control data are the data (i.e. tumour incidences) from unexposed animals other than the one under evaluation.

Limit dose

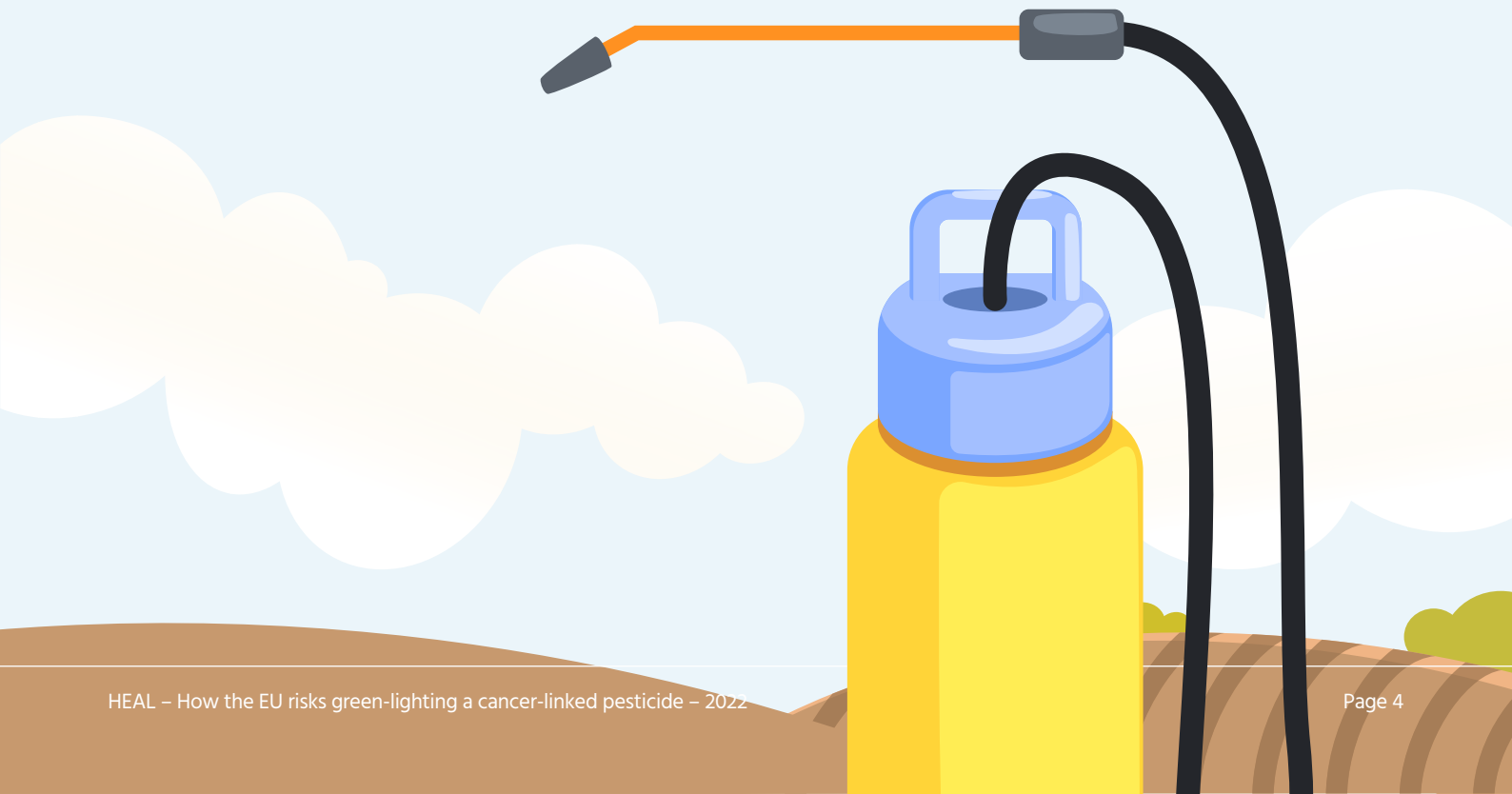
The limit dose refers to a dose at an upper limitation on testing.

One-sided test versus two-sided statistical test

The choice of whether to use a one-sided test versus two-sided statistical test should be made at the design stage rather than the analysis stage. A two-sided statistical hypothesis tests for a difference from the negative control in either direction (both increase and decrease). A one-sided comparison tests for a difference in only one pre-specified direction (increase or decrease), but as a consequence has more power. In a carcinogenicity study, the expectation is often that the change will be an increase in tumours in the treated group, so a one-sided test may be considered more appropriate, although this can be controversial. If the treatment
could also be protective (i.e. reduce tumour incidence or delay it), then a two-sided comparison may be more appropriate. Regulatory authorities may have specific opinions [2].

Pairwise comparison statistical method

A pairwise comparison is comparing whether one exposed group is statistically significantly different from the controls.



Progression to malignancy

In certain cases, a benign tumour (a lump caused by an abnormal growth of cells) may transform into a malignant tumour. Malignant tumours or carcinomas display aggressive characteristics, can invade and destroy adjacent tissues, and metastasize to distant sites, which can lead to death. The term progression to malignancy is also used for the development of cancer throughout the different phases, as it grows and spreads.

Statistical significance

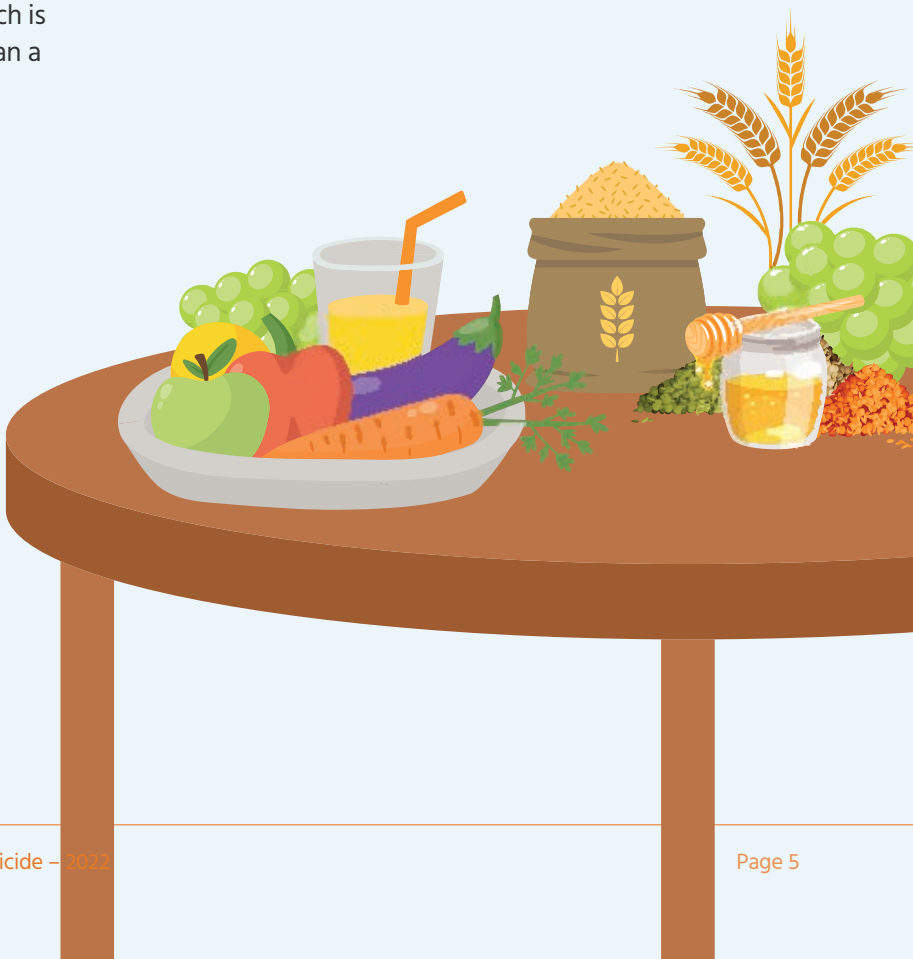
In animal experiments, where animals are exposed to various concentrations of a chemical substance, the conclusion that there is a statistically significant difference in a response (i.e. in tumour incidences) observed in the animals of (an) exposed group(s) compared to that of the control group of unexposed animals indicates that this difference is unlikely to have occurred by chance. A statistical significance therefore indicates that the tumours developed in exposed animals are linked to exposure to the chemical substance.

Trend test

In statistics, a Trend test is used to test whether there is a linear trend with a slope (steepness) greater than zero. In general, testing a trend which is a more specific hypothesis has greater power than a pairwise comparison.

Types of tumours

- Skin keratoacanthoma, a rapidly growing tumour believed to originate from within hair follicles. There is an ongoing debate whether skin keratoacanthoma is benign or malignant.
- Skin basal cell tumours, adenoma (benign) and carcinoma (malignant) are known and exist independent of each other (i.e. no progression to malignancy from skin basal cell adenoma to carcinoma).
- Hepatocellular adenoma, benign tumours of liver cells.
- Thyroid C-cell adenoma, benign tumour of the neuroendocrine cells of the thyroid.
- Malignant Lymphoma, a group of blood cancers (malignant) that arise from lymphocytes.
- Kidney tumours (tumours of renal tubule), adenoma tumours (benign) and carcinoma tumours (malignant) are known to exist. A kidney adenoma can progress to carcinoma.
- Haemangiosarcoma, a malignant tumour of vascular origin.



EXECUTIVE SUMMARY

As the discussions on a potential 15-year renewal of the EU market licence for glyphosate have started, the Health and Environment Alliance (HEAL) is seriously concerned that the EU scientific assessment on the cancer potential of this pesticide active substance dismisses important scientific findings from the existing cancer studies.

The Assessment Group on Glyphosate (AGG), formed by member states representatives from France, the Netherlands, Hungary and Sweden and acting as a joint rapporteur for the renewal dossier, recently concluded that glyphosate is not carcinogenic and therefore meets the approval criteria under EU law.

However, as presented in this report, the cancer studies provided by pesticide companies for the carcinogenicity assessment of glyphosate show the clear potential for the substance to cause cancer. On the basis of this evidence, glyphosate should in fact be classified as a substance "presumed to have carcinogenic potential for humans", and according to the EU law on pesticides, be removed from the EU market.

This report is based on the scientific analysis of Prof. Chris J. Portier - an independent expert in the design, analysis, and interpretation of environmental health data with a focus on carcinogenicity - and Dr. Peter Clausing - a toxicologist with a career in regulatory toxicology - on the carcinogenicity section of the AGG assessment report. The experts submitted their analysis to the parallel consultations organised by the European Food Safety Authority (EFSA) and the European Chemicals Agency (ECHA). Their findings were also presented at ECHA's Committee on Risk Assessment (RAC) discussions, responsible for adopting an opinion on the carcinogenicity of glyphosate.

Our analysis reveals the occurrence of clear and statistically significant tumours in ten out of 11 animal studies, which confirms the 2015 classification of glyphosate as 'probable carcinogen' by the International Agency for Research on Cancer's (IARC). These tumour incidences were reinforced by additional scientific observations such as: a comparison with background in-house data of unexposed animals; a rising trend in the number of tumours with increasing exposure to glyphosate, or the development of several tumours in the exposed animal groups. Despite these observations, all these tumours were systematically dismissed from the assessment, first by the AGG and now seemingly also by RAC members.

Overall, the glyphosate EU renewal process illustrates serious scientific shortcomings that question its scientific objectivity and fall short of adhering to European and international scientific rules and guidelines. Based on these findings, the EU authorities should take corrective measures as soon as possible in order to ensure that the procedure is carried out according to the highest scientific standards.

1 BACKGROUND

Exposure to glyphosate, Europe's most widely used herbicide, has been linked to cancer in humans by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) [3]. According to the EU Regulation on Pesticides (EC 1107/2009), pesticide active substances that have the potential to cause cancer in humans should not be approved for use in any pesticide products marketed in the EU [4]. The current EU market licence for glyphosate expires on 15 December 2022 and might be further extended due to delays in the assessment procedure. The pesticide industry has applied for a 15-year renewal, insisting that glyphosate is safe.

In December 2019, the Glyphosate Renewal Group (GRG) [5], a consortium of nine pesticide companies involved in producing glyphosate, submitted an application for renewal of the glyphosate approval to the Assessment Group on Glyphosate (the AGG) [6], a group formed by four member states' authorities (France, Hungary, the Netherlands and Sweden). Acting as a joint rapporteur, the AGG has been tasked with carrying out the scientific assessment of glyphosate, based on the studies provided by the companies in their application, along with public scientific literature.

In June 2021, following this assessment process, the AGG announced that given the available evidence "a classification of glyphosate with regard to carcinogenicity is not justified" and therefore concluded that glyphosate does not cause cancer [7].

The AGG delivered this assessment simultaneously, in the form of a combined draft Renewal Assessment Report (dRAR) and Harmonised Classification and Labelling (CLH) report (dRAR/CLH), to the European Chemicals Agency (ECHA) and to the European Food Safety Authority (EFSA). These agencies are responsible for delivering an opinion on the hazard classification of glyphosate (ECHA), and a conclusion on the peer review of the risk assessment of glyphosate (EFSA). They initiate the process by making the dRAR/CLH publicly available and launching a 60-days public consultation to collect comments from interested parties.

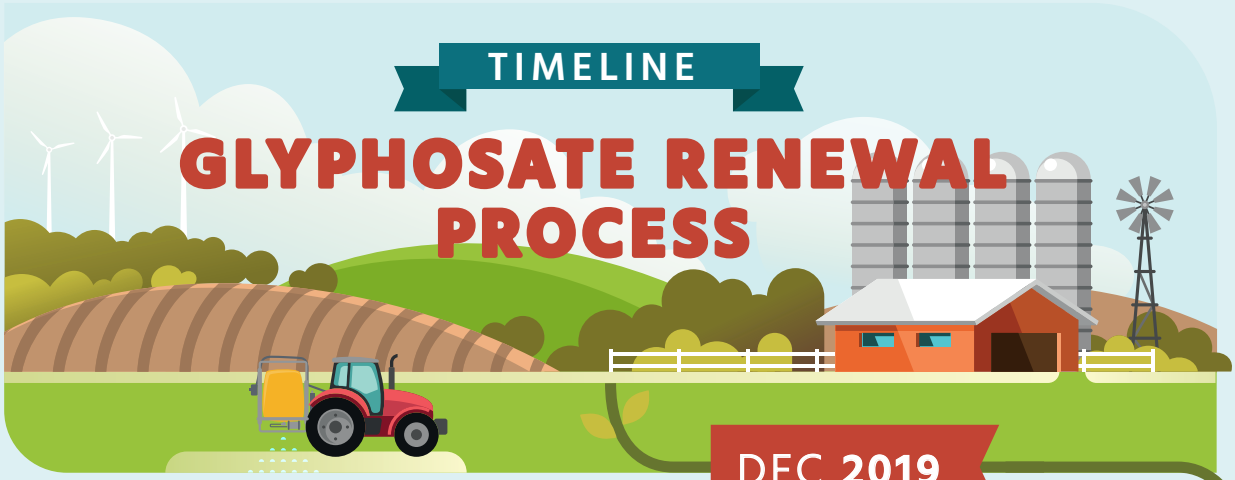
The ECHA's Risk Assessment Committee (RAC) started its discussions on the hazard classification of glyphosate in March 2022. On May 30th, the Committee announced that the available scientific evidence did not meet the criteria to classify glyphosate as a carcinogenic or mutagenic substance, thus agreeing with AGG's proposal of no classification.

Despite the available scientific evidence that glyphosate may cause cancer, the conclusions of AGG and RAC open the way for the re-authorisation of its license.

EFSA's evaluation has started and, according to the agency's recent announcement, it will be delayed by a whole year [8]. Once it is finalised, the European Commission will make a proposal on whether or not to renew glyphosate's market licence, on the basis of the conclusions of both EFSA and ECHA. A final decision will then be taken by the representatives of EU member states at the Standing Committee of Plants Animals Food and Feed (PAFF Committee).

TIMELINE

GLYPHOSATE RENEWAL PROCESS



DEC 2019

Pesticide companies send an application to renew glyphosate's market license to four Rapporteur member states (France, Hungary, the Netherlands and Sweden) forming the Assessment Group on Glyphosate (AGG). Together, they are responsible for carrying out the scientific assessment.

JUNE 2021

The AGG delivers its assessment in the form of a combined draft Renewal Assessment Report (dRAR) and Harmonised Classification and Labelling Report (dRAR/CLH) to the European Chemicals Agency (ECHA) and to the European Food Safety Authority (EFSA). **The AGG concludes that glyphosate is not carcinogenic and meets the criteria to be approved for use.**

SEPT - NOV 2021

ECHA and EFSA publish the combined dRAR/CLH report and launch parallel consultations on the initial scientific evaluation of glyphosate.

MAR - MAY 2022

ECHA's Committee for Risk Assessment (RAC) discusses the proposal for harmonised classification and labelling (CLH). On 30th May, the RAC concludes that classifying glyphosate as a carcinogen is not justified.

JULY 2023

EFSA is expected to deliver its conclusion on the peer review of the risk assessment of glyphosate.

END OF 2023

Based on ECHA's opinion and EFSA's conclusion, the European Commission presents a legislative proposal for renewal to member states at the PAFF committee.

16 DECEMBER 2023 (TBC) **GLYPHOSATE'S CURRENT LICENSE EXPIRES**

The conclusion of AGG and the RAC that glyphosate does not cause cancer contradicts the conclusion reached by IARC in 2015. Having analysed the available scientific literature and the publicly available studies performed by the companies, IARC stated that glyphosate is "probably carcinogenic for humans" [9]. Subsequently, numerous peer-reviewed scientific studies published since 2015 also support IARC's conclusion [10]. In the meantime, internal industry documents and emails known as "the Monsanto papers" came into light, following the course of US litigation cases against Monsanto. These revealed that the company had ghostwritten scientific literature to assert glyphosate's safety, run campaigns to discredit academic scientists, and hidden concerns connecting glyphosate to cancer [11]. In 2017, the combined effect of these findings and the subsequent public outrage led EU regulators to grant only a five-year glyphosate licence, instead of the 15 years requested by industry.

In 2021, Prof. Christopher J. Portier, an independent expert in the design, analysis and interpretation of environmental health data with a focus on carcinogenicity and Dr. Peter Clausing, a toxicologist with a career in regulatory toxicology and co-author of this report, scrutinised the carcinogenicity assessment section of the combined dRAR/CLH. Their comments were submitted during the public consultation on the dRAR/CLH, co-organised by ECHA and EFSA, and were presented at ECHA's RAC discussions on glyphosate [13]. **This report summarises their findings, revealing that while numerous cancer incidences were observed in the animal studies provided by the industry, these have so far been systematically dismissed by the EU authorities in their assessment.**

At the time of writing, the full ECHA opinion on the hazard classification is not yet publicly available. Therefore the analysis presented in this report is based on the assessment of the AGG. ECHA's public announcement regarding glyphosate's hazard classification suggests that the RAC fully endorses the AGG conclusions.

2 10 OUT OF 11 STUDIES SHOW TUMOUR INCIDENCES

Providing long-term animal studies is a legal requirement for the cancer assessment of chemical substances in the European Union [14]. Such studies are commonly performed on mice and rats.

For the cancer assessment of glyphosate, the herbicide producing companies provided six rat and five mouse studies that the AGG considered acceptable for the assessment. These eleven studies, an unusually high total for a scientific assessment on a pesticide active substance, are featured in the dRAR/CLH.

In their analysis, Dr. Clausing and Prof. Portier provided an overview of the eleven studies considered by the AGG. Table 1 illustrates all the tumour incidences found to be statistically significant and where these were supported by additional evidence, i.e. dose-dependence (D) and/or historical control data (HCD; H). In ten out of the 11 studies, animals developed significant tumours [graphs are presented in the appendix].

CANCER ANIMAL STUDIES
6 RAT AND 5 MOUSE STUDIES

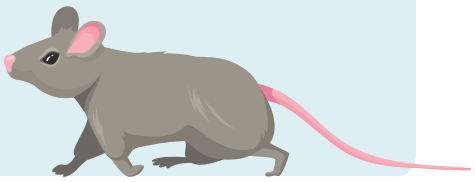
IN 10 OUT OF 11 STUDIES ANIMALS DEVELOP TUMOURS
in five rat and five mouse studies

HISTORICAL CONTROL DATA (HCD)
In three mouse and four rat studies, the tumours are supported by HCD

DOSE-RESPONSE INCREASE
in three mouse and one rat study the number of tumours increased as the glyphosate dose increased

MULTI-SITE TUMOURS
In two rat and three mouse studies, animals developed two or three different types of tumours

TUMOURS IN FEMALES
Females also developed tumours in one rat study and one mouse study



Study (rats)	Year	Strain	Skin keratoacanthoma	Skin basal cell tumour	Hepatocellular adenoma +carcinoma	Thyroid C-cell adenoma
R1	2009	Wistar	#			
R2	2001	Wistar			** # H^+	
R3	1997	SD	# H^+	** H^+		
R4	1996	Wistar				
R5	1993	SD	* # H^+			
R6	1990	SD	(*) # H^+D		** (#, H^+)	♀**H^+

Study (mice)	Year	Strain	Duration (months)	Malignant lymphoma	Kidney adenoma (+carcinoma)[b]	Haemangiosarcoma
M1	2009	Crl:CD-1	18	** # D		
M2	2001	Swiss	18	♂*(#)H^+D ♀(** #)	**(# H^+) D	
M3	1997	Crj:CD-1	18	**#H^{+a}	**H	**(#)
M4	1993	Crl:CD-1	24	*(#)		**# (H^+)
M5	1983	Crl:CD-1	24		**# D[b]	
Supportive						
M6	1999	CD-1	-	♀*(#)[c]		

Table 1. Statistically significant (p <0.05) according to: * one sided (AGG); ** two-sided (AGG); 1-sided (Portier, 2020)
Historical Control Data (HCD): H indicates tumour incidences are above HCD mean; + indicates that the interquartile range was used
Dose-response: D indicates that a significant dose-response relationship of tumour incidences was observed
Symbols in parentheses (): indicate borderline significance (p<0.09)
♂ / ♀ indicates females/males when relevant
a if corrected and the outlier is excluded (see main text)
b it contains 1 carcinoma is middle dose and 2 carcinomas in the high dose
c Study analysed by JMPR (The Joint FAO/WHO Meeting on Pesticide Residues) but not available to AGG, historical controls not available.

The tumours detected following glyphosate exposure:

Studies in rats:

- Skin keratoacanthomas - rapidly growing tumours with the potential to become malignant (cancerous) [15] - were observed in males in four studies (R1, R3, R5, R6).
- Skin basal cell tumours in males were observed in one study (R3).
- Hepatocellular adenomas combined with carcinomas were observed in males in two studies (R2, R6).
- Thyroid C-cell adenomas were observed in females in one study (R6).

Studies in mice:

- Malignant lymphomas in males were observed in four studies (M1-M4). One of these studies also found malignant lymphomas in females (M2). Malignant lymphomas were also found in females of another study which is considered, which is however only considered 'supportive', since the AGG did not have access to the full study report (M6).
- Kidney tumours (benign adenomas) were observed in males in two 18-months studies (M2, M3) and malignant tumours were observed in one 24-months study (M5). Progression from benign adenomas to malignant carcinomas could be expected in M2 and M3 studies, if the exposure period was to be extended by 6 months to 24 months, as it was the case with M5 study (24 months).
- Heamangiosarcomas were detected in males in two studies, at 18 months (M3) and 24 months (M4).

Three of these tumour incidences increased significantly in more than just one study:

- Skin keratoacanthomas in **four** of six rat studies,
- Malignant lymphomas in **four** of five mouse studies,
- Kidney tumours in **three** of five mouse studies.

In their findings, Prof. Portier and Dr. Clausing concluded that ten studies show cancer occurrence, reinforced with further evidence.

2.1 The indisputable basis for a 1B classification for carcinogenicity

In the EU, the classification of a substance as hazardous (e.g. carcinogen) is determined by Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (hereinafter referred to as the CLP Regulation), which aims to *"ensure a high level of protection of human health and the environment"*[16]. The assessment of the cancer potential of chemical substances is carried out according to CLP with the use of specific international and European agreed protocols.

INTERNATIONAL AND EU AGREED PROTOCOLS FOR CARCINOGENICITY ASSESSMENT

- The internationally accepted Test Guidelines (TG) of the Organisation for Economic Cooperation and Development (OECD) No. 451 or 453 on carcinogenicity studies (rats and mice).
- The overarching OECD Guidance Document 116 on the conduct and design of chronic toxicity and carcinogenicity studies (OECD, 2012) (referred hereafter as OECD Guidance 116) [17].
- ECHA's Guidance on the Application of the CLP Criteria (ECHA 2017) [18].

According to the CLP Regulation (Annex I, 3.6), a substance meets the criteria for classification as a category 1B carcinogen if there is sufficient evidence of carcinogenicity, i.e. a causal relationship has been established between the chemical and an increased incidence of malignant tumours or combination of malignant and benign tumours, in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times, in different laboratories or under different protocols.

Out of the 11 studies analysed by the AGG and compiled in Table 1, ten animal studies show that glyphosate caused malignant tumours or a combination of malignant and benign tumours in two species of animals (rats and mice), as well as in two or more studies of one species (for rats: R1, R3, R5, R6; for mice: M1, M2, M3, M4, M5) carried out at different times, in different laboratories or under different protocols (OECD test guidelines 451, 453, 452).

Dr. Clausing and Prof. Portier analysed the animal studies by following the EU CLP Regulation and the OECD gold standards on the carcinogenicity assessment of substances. According to their findings, there is more than enough evidence of carcinogenicity, and this evidence meets the criteria to classify glyphosate as category 1B carcinogen. The studies selected by the pesticide companies and considered by the AGG corroborate the IARC conclusion that glyphosate may cause cancer.

CATEGORY 1: Known or presumed human carcinogens

A substance is classified in category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:

- **Category 1A:** Known to have carcinogenic potential for humans, classification is largely based on human evidence,
- **Category 1B:** Presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

In addition, on a case-by-case basis, scientific judgment may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals (CLP Regulation).

2.2 Despite evidence, authorities fail to classify glyphosate as carcinogenic

While there is no ground for the AGG to reject the 1B classification, it is incomprehensible that it does not even propose a category 2 carcinogen classification. According to the CLP Regulation (Annex I, 3.6), a substance is considered a category 2 carcinogen when there is limited evidence of carcinogenicity. This classification gets triggered when the data suggest a carcinogenic effect, but is insufficient to make a definitive conclusion because (a) the evidence of carcinogenicity is restricted to a single experiment; (b) the agent increases the incidence only of benign neoplasms (tumours) or lesions of uncertain neoplastic potential; or (c) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs, among others.

Table 1 shows that (a) carcinogenic effects were not restricted to a single experiment as they were observed in more than one animal study; that (b) exposure to glyphosate increased the incidences of benign and malignant tumours; and that (c) tumours were observed in various tissues and organs. **Evidently, there is much more evidence available than required to classify glyphosate as a category 2 carcinogen (Box 1).**

CATEGORY 2: Suspected human carcinogens

The placing of a substance in category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animals (CLP Regulation).

BOX 1

Other substances have been classified as category 2 carcinogens with a lower level of evidence

By looking into the classification of other active substances approved on the EU market, it seems that some have been classified as category 2 carcinogens with less evidence than glyphosate.

For example, the active substance pyriofenone was classified as category 2 based on evidence of liver tumours observed only in one sex of one species.

Similarly, the active substance iprovalicarb was also classified as a category 2 carcinogen, based on observed tumours in one rat study. The types of tumours developed were not consistent across males and females, and tumours in males were observed only at high doses.

In the case of glyphosate, the level of evidence is higher; nevertheless the authorities have not proposed any classification, either as category 1B or category 2 carcinogen.

3 ELIMINATING EXISTING EVIDENCE

Despite the cancer incidences observed in animals exposed to glyphosate, the AGG considers the evidence as neither 'sufficient' nor 'limited' to support a classification of glyphosate in line with the CLP Regulation as carcinogenic, either for category 1B or category 2.

The following section details the flaws identified by Prof. Portier and Dr. Clausing that highlight the lack of scientific objectivity that led to this mistaken conclusion.

3.1 No consistent 'assessment strategy' or systematic approach for evaluating the evidence

A core principle in the assessment of chemicals is that the evaluation of evidence must follow a systematic approach, one that is consistent, clear and transparent (OECD, Series on Testing and Assessment No. 311). According to EFSA, the first step of the overall process when dealing with data and evidence in scientific assessment is to plan upfront a strategy for the assessment [19]. ECHA's guidance documents also highlight that the hazard classification of substances must follow a stepwise approach, where all the evidence is considered systematically (ECHA, 2017).

However, throughout the carcinogenicity assessment of glyphosate in the dRAR/CLH, the AGG has not set out such a strategy or any systematic scientific approach to follow for the review of the 11 available animal cancer studies.

As a result, **numerous incoherences were observed in the assessment of the evidence from the different studies provided in the dRAR/CLH, which led to selective dismissal of the observed tumour incidences. These are presented in the following sections.**

3.2 Use of unjustified statistical methods and the least powerful test

Statistical methods are used to decide whether an observed effect is considered "real" (significant) or whether it has happened by chance (which is 'non-significant' and hence can be dismissed from the scientific assessment). The most appropriate method depends on the type of data to be analysed (e.g. data collected in an animal study designed to investigate the potential of chemicals to cause cancer, such as weight of animals or tumour incidences). The OECD's Guidance 116 recommends to use the following statistical tests for the assessment of tumours developed in exposed animals [20]:

(a) The "Trend" tests: designed to assess a trend (i.e. an upward trend in tumours with the increase of exposure to glyphosate);

(b) The "one-sided" statistical tests: designed to specifically focus on the increase of tumour incidences instead of, for example, the two-sided tests that aim to investigate the potential of a chemical to increase as well as to reduce tumour incidences (i.e. when investigating a therapeutic effect). One-sided tests are twice as powerful, as they have higher probability of identifying the presence of an effect than two sided tests.

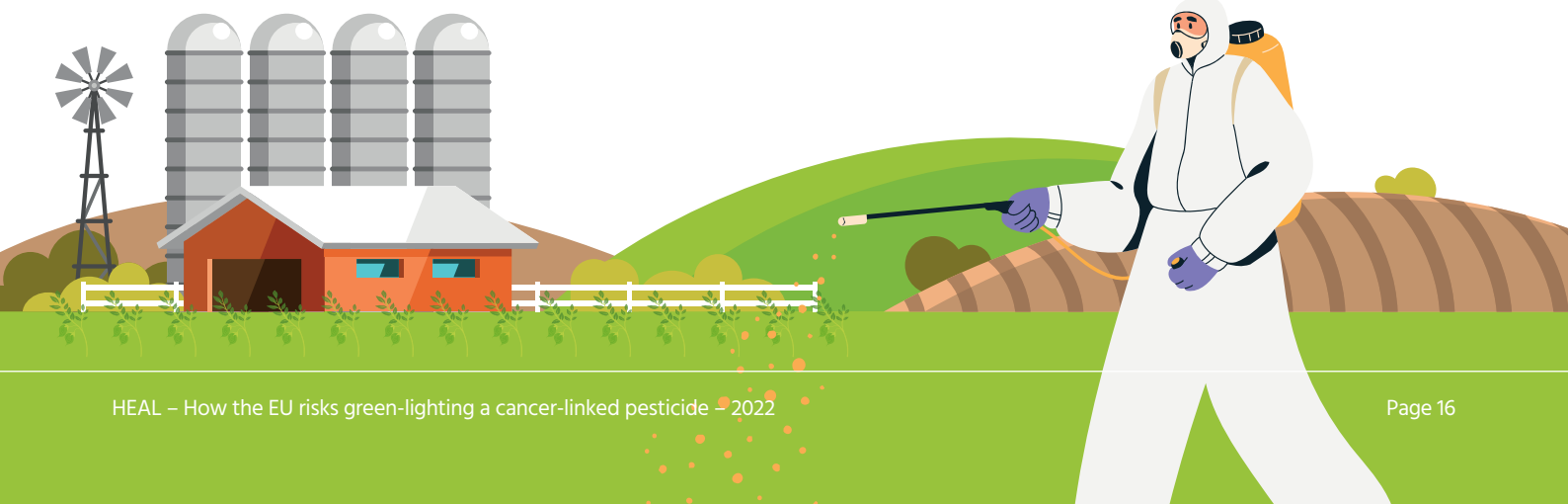
In the dRAR/CLH, the AGG has included the results for a Trend test (more powerful), both one-sided and two-sided, as well as pairwise comparison (less powerful, see glossary) statistics but without explaining its choice and why a given method would be more relevant than the other. Nevertheless, according to OECD Guidance 116, *"Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the (cancer) result."*

As summarised in Table 1, by following the recommendations of OECD Guidance 116 (points a and b) and applying them to the 11 cancer studies that form the carcinogenicity assessment of glyphosate, **the tumour incidents observed in ten of these studies were found to be statistically significant (i.e. not due to chance but due to glyphosate exposure).**

Although a statistically significant response alone may or may not be biologically relevant [21], it is highly improbable that several statistically significant responses are all due to chance. Nevertheless, in the dRAR/CLH, the AGG concludes in every case that the cancer incidences observed in the animal studies were not related to glyphosate exposure.

The AGG applies the so-called two-sided statistical test in its evaluation, without explaining the reasons supporting such an approach. According to OECD Guidance 116 (p. 133) *"a two-sided comparison may be more appropriate",* when *"the treatment could also be protective".* **However, since glyphosate is not a protective treatment against cancer, the use of the two-sided statistical test is incomprehensible.**

In any case, even when considered through the filter of a 'weaker' statistical approach and applying a two-sided test together with the trend-test, the tumour incidences in eight studies (five mouse- and three rat study) remain statistically significant (Table 1, two asterisks) and therefore still confirm the potential of glyphosate to cause cancer.



3.3 Inventing a 'limit dose'

The AGG dismisses all the observed increases of two types of tumours in mice (malignant lymphoma and kidney tumours), stating that the increases were seen at dose(s) *"above the recommended maximum dose of 1000 mg/kg bw/day according to OECD TG 453" and therefore "should be considered of very limited relevance"* due to the potential of excessive toxicity (dRAR/CLH Vol 1, p. 293).

This assertion is completely incorrect.

First of all, the mouse studies referred to in this statement were not performed under TG 453, but under a different test guideline (TG 451). TG 451 is a test guideline on carcinogenicity studies and does not consider a maximum dose of 1,000 mg/kg bw/day. The OECD TG 453 referred to by the AGG is a test guideline on combined chronic toxicity and carcinogenicity studies and the 1,000 mg/kg limit dose is exclusively mentioned for the assessment of chronic toxicity, not for carcinogenicity.

Secondly, in relation to the excessive toxicity that could be caused by high-dose exposures, OECD Guidance 116 says *"... the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%)".* However, the main concern with regard to the selection of a high dose that causes a higher depression of body weight gain is that this may obscure carcinogenic effects and not pronounce them [22].

In fact, a limit dose for carcinogenicity studies is described in OECD Guidance 116 but only for the concentration of test substance in the diet given to the animals during the testing period. Guidance 116 recommends that the dietary concentration of the test substance should not exceed 50,000 ppm (paragraph 54). The summaries of the carcinogenicity studies in the dRAR/CHL provide the concentration of glyphosate in the diet of the animals and this limit was not exceeded in any of the studies.

Therefore, referring to a "limit dose" of 1,000 mg/kg to dismiss the tumour incidences is arbitrary, as it is not scientifically justified, according to both the relevant guidance and the applicable test guideline protocols, under which these studies were performed.

3.4 Misuse of Historical Control Data

When available, historical control data (HCD) – the data from control, unexposed animals of previous studies – can strengthen or weaken the evidence of tumour incidences observed in the study under consideration [23]. If the number of tumours observed in a study are above the upper limit of the HCD range (the range between the smallest and the highest number of animals with tumours), the HCD strengthens this finding. If the tumours are below the HCD-average, and particularly below the HCD range, the HCD weakens this finding.

Yet, in all cases, as emphasised in the OECD Guidance 116, *"the concurrent control group is always the most important consideration in the testing for increased tumour rates."*

The AGG used and reported the available HCD in the dRAR/CLH. A number of these data actually reinforce the observed tumour findings in seven out of the ten animal studies (Table 1, marked with "H" or "H+" R2-R5 and M2-M4), and they strengthen the evidence that these are due to glyphosate exposure. However, while documented in the dRAR/CLH, this supporting evidence has not been taken into consideration in the overall conclusion for the individual tumour types (e.g. skin keratoacanthomas and hepatocellular adenomas and carcinomas in rats, malignant lymphoma and kidney tumours in mice).

Even more aberrant is that the HCD supporting the evidence (Table 1, malignant lymphoma, study M3, 1997) has been used by the AGG to weaken the finding. This was done by including an "outlier" [24] and widening substantially the HCD range in order to claim that the observed incidence was within this new range (RAR, p. 292) [25]. **This is not considered good scientific practice.**

3.5 Comparing apples with pears: pseudo-quantitative comparisons between studies

In the dRAR/CLH, the AGG relies on semi-quantitative comparisons across animal studies to dismiss the evidence of tumour incidences. **It compares the magnitude of responses from one study to the next (e.g. for statistical significance in different tests across studies, dose-response effects and responses in control animals), although the studies are not directly comparable.**

As noted in OECD Guidance 116 (p. 135); *"It is widely recognised that large differences can result from disparities in factors such as pathology nomenclature, strain, husbandry, pathologists."* Thus, it is clear that studies performed in different laboratories many years apart, with different substrains of rats and mice, and of different durations, are not directly comparable without taking into account the differences in the study designs. Nevertheless, the AGG provides 14 tables [26] containing such unacceptable comparisons in the dRAR/CLH.

The AGG selectively uses incomparable data in order to claim that the observed tumours are not reproduced across the studies in a dose-response manner, and as a result excludes them from the assessment.

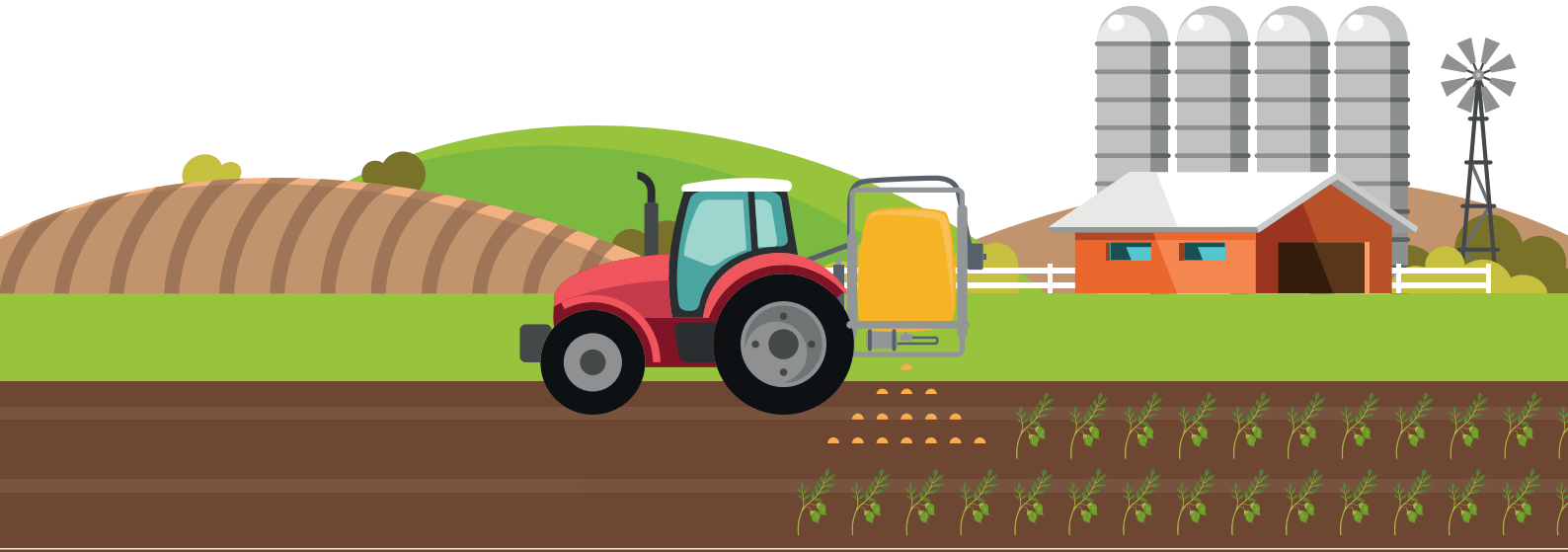
The AGG could have carried out certain adjustments to the calculations to allow comparison (e.g. by applying the methods used in epidemiological 'pooling' to the animal studies, as explained by Portier, 2020 [27]), however, it has not fulfilled any of these requirements.

On the contrary, the AGG appears to selectively turn a blind eye to the overall reproducibility of certain tumours: in the majority of rat studies (four out of six), animals developed skin keratoacanthoma (a tumour subject to an ongoing scientific debate regarding whether it is malignant or not) and in the majority of mouse studies animals developed malignant lymphoma (four out of five) or kidney tumours (three out of five; Table 1).

3.6 A 'non-integrated' weight of evidence approach

The weight of evidence (WoE) approach is defined by EFSA as *"a process in which evidence is integrated to determine the relative support for possible answers to a scientific question."* In the dRAR/CLH, instead of using the 'weight of evidence approach' to bring all the evidence together, the AGG employs it with the apparent intention of reinforcing the flawed findings explained in the previous sections and completely dismissing any carcinogenicity proofs from the assessment.

The following section details certain important factors that should have been considered "when assessing the overall level of concern" in line with the provisions of the CLP Regulation, but have been overlooked by the AGG. **According to Dr. Clausing and Prof. Portier, considering these factors would have further strengthened the tumour findings during the WoE approach.**



Dose-response relationship

Typically, carcinogenicity studies have at least three different dose groups of increasing exposures to the substance being tested. According to CLP, any statistically significant increase in tumour incidence should be taken as positive evidence of carcinogenic activity, "especially where there is a dose-response relationship". In other words, when the number of tumour incidences rises along with increasing exposure, it is an indication that these tumours are carcinogenic. As indicated in Table 1 and Figure 1, within the glyphosate cancer studies included in the dRAR/CLH, an increased incidence of tumours along with increasing exposure groups was observed for skin keratoacanthoma in one rat study (R6), for malignant lymphoma in two mouse studies (M1, M2) and for kidney tumours in two mouse studies (M2, M5).

The dose-response increasing number of tumours observed in these four studies should be considered as positive evidence of carcinogenic activity. The AGG, however, makes no reference to these observations. On the contrary, the only times it uses the dose-response relationship argument is to dismiss the tumour evidence in all the other animal studies, when a dose-response relationship is not observed.

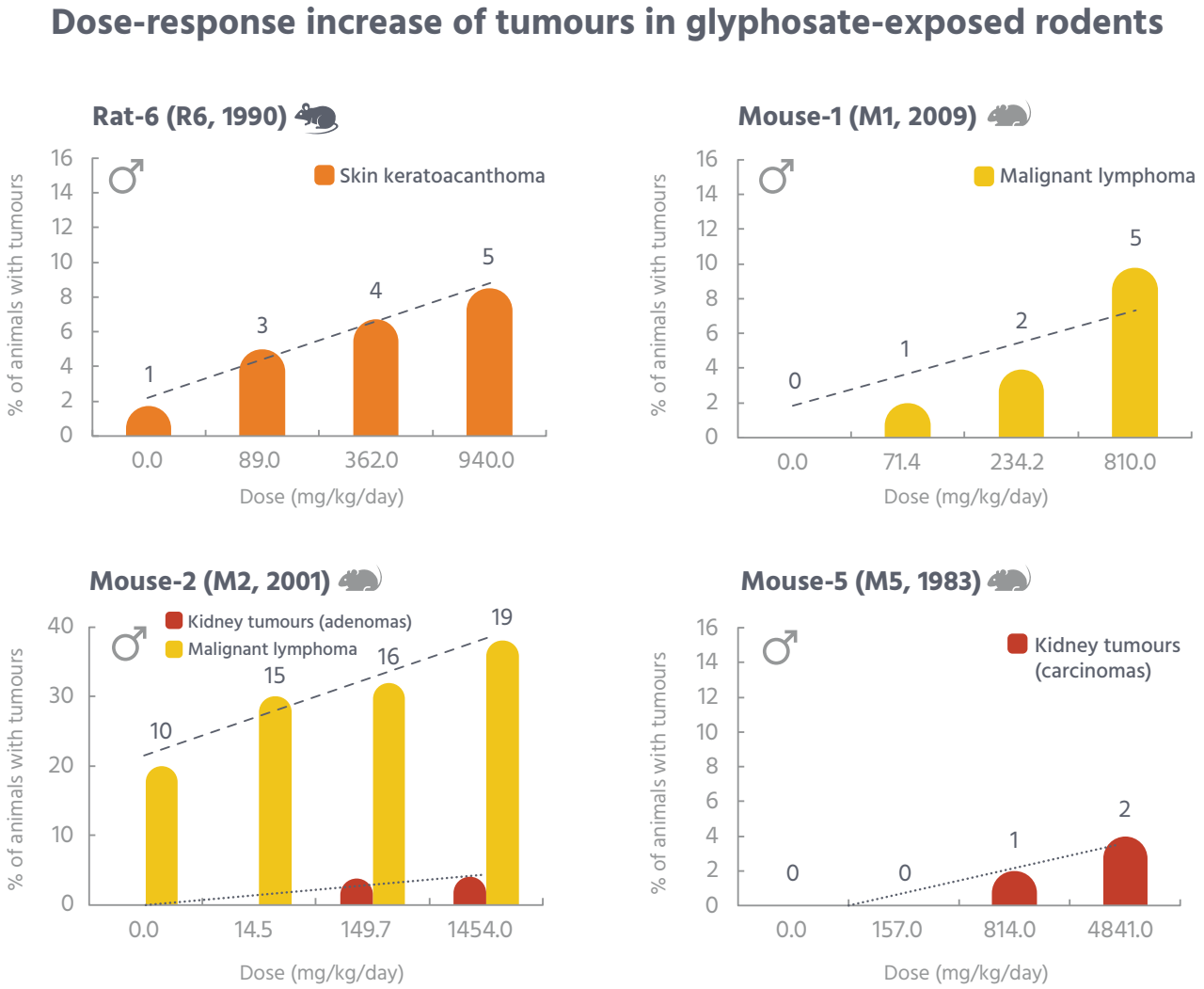


Figure 1. Dose-response: Increase of the percentage (%) of animals with different tumours in male rats (R6 study) and male mice (M1, M2 and M5 studies), with increasing exposure (dose) to glyphosate. The doted line indicates an upward dose-response trend, which is statistically significant from the control group ($p<0.05$). The numbers on the top of the bars show the number of tumours per glyphosate exposure group

Multi-site responses

As shown in Table 1, two rat (R3, R6) and three mouse studies (M2, M3, M4) exhibit multiple within-study tumour responses, **as more than one type of tumour has been observed in the animals exposed to glyphosate.** This observation is not mentioned by the AGG.

Responses in both sexes

According to CLP, another factor to take into consideration is whether the responses are observed in single or both sexes. In the assessment of glyphosate, **although the strong evidence on tumour incidences comes from males, there is also some evidence in females.**

In mice, females exposed to glyphosate (M2, 2001) also developed malignant lymphomas, which were statistically significant at high dose (Table 1). The dRAR/CHL includes another study from 1999, which although the full study report was not available to the AGG, has been taken into consideration as 'supportive' information. This study reports a statistical significant increase in malignant lymphoma in females from the high-dose exposure group (Table 1, M6).

In rats, two types of tumours were observed in female rats in R5 (1990) study (thyroid C-cell adenoma and adrenal cortical carcinoma). This evidence should not be disregarded from the cancer assessment of glyphosate.

Progression to malignancy

Progression to malignancy, i.e. the conversion of a benign tumour into an aggressive form, adds to the 'weight of evidence'. The malignant kidney tumours observed in the 24-month study (M5), indicate that the renal tubular adenomas (benign) observed in the 18-month studies (M2, M3) have the potential to progress to malignancy, and therefore should not be overlooked. Once again, this was not considered by the AGG.

Oxidative stress as glyphosate's mode of action

Oxidative stress is a recognised mechanism of DNA damage that can cause carcinogenicity according to IARC (Smith et al. 2016 [28]). It is also a known adverse effect caused by exposure to glyphosate in animals [3].

This knowledge that glyphosate can cause oxidative stress, together with the observed increases of tumour incidences in the long-term rodent studies, provides an insight into its possible mode of action. Therefore, it should be considered as an important factor in the assessment of glyphosate for the carcinogenicity classification.

The AGG did not discuss this mechanism of DNA damage in the carcinogenicity section of the dRAR/CHL. **During recent years,** a more studies have been published, including three mouse studies, demonstrating that glyphosate causes oxidative stress [29]. Gao et al. (2019) in particular, showed that glyphosate caused the development of kidney tumours in mice and provided evidence that oxidative stress was the underlying mechanism.

Moreover, a recent independent scientific analysis of the genotoxicity assessment section of glyphosate has revealed that the potential of glyphosate to cause DNA damage has not been adequately investigated by the companies (Box 2) [30]. In fact, the regulation on pesticide data requirements to assess genotoxicity includes two OECD test guideline genotoxicity studies that have not been submitted by the industry consortium [31]. These two studies are key, as they have the potential to show whether glyphosate is genotoxic to the liver of mice and other organs. It is concerning that this data gap has not been addressed by the AGG and the conclusion that glyphosate is not genotoxic has been reached without taking into account these crucial studies.

BOX 2

EU glyphosate genotoxicity assessment based on "inadequate studies"

In 2021, Dr. Armen Nersesyan and Prof. Siegfried Knasmueller of the Institute of Cancer Research of the University of Vienna reviewed the full reports of the studies provided by the companies for the genotoxicity assessment of glyphosate (its potential to cause DNA damage), which were part of the 2017 glyphosate renewal assessment report (RAR). Their aim was to examine whether these studies were performed according to the international agreed test guidelines and protocols. **The analysis, published in July 2021, reveals that the EU's 2017 conclusion that the active substance glyphosate is not genotoxic cannot be justified on the basis of manufacturers' studies** [32]. About 64% of the studies were found to be 'unreliable' from a methodological point of view, whatever the result, and only two studies were found to be completely 'reliable'.

Additionally, almost half of these studies were based on the "Ames assay", a testing method that uses bacteria. However, glyphosate which is patented both as a herbicide [33] and as an antibiotic agent [34] can be toxic to a wide range of bacteria. Therefore there are doubts whether the use of a bacterial assay such as the Ames test to examine the potential of glyphosate to cause mutagenicity will bring correct results. Yet, the only two studies that were found reliable from a methodological point of view were actually "Ames" tests.

According to Prof. Knasmueller, **"better tests for the detection of genotoxic carcinogens" have not been submitted by the companies** [35].

A screening of the current dRAR/CLH shows that almost all of the genotoxicity studies on "pure" glyphosate submitted in the previous assessment have been again submitted by the pesticides companies. The consortium did not submit any new genotoxicity studies on the active substance glyphosate.

Concerns had been already raised regarding the the potential of glyphosate to cause DNA damage during the 2017 hazard assessment of glyphosate [36]. Despite the numerous studies submitted by the industry consortium, neither of the two tests that form part of the regulatory data requirements for genotoxicity assessment (Comet assay, OECD TG 489 and Transgenic rodent assay TG 488, as required under Regulation 283/2013) have been provided by industry [37]. However, without requesting these two guideline studies, the AGG concluded that glyphosate is not genotoxic.

Several peer-reviewed scientific studies show that glyphosate causes genotoxicity in a wide range of animal species, including humans [38]. However, the AGG continues to base its assessment on selective analysis of the industry studies and concludes that glyphosate is not genotoxic.

[Details provided in HEAL's submission to the consultation [39]]

Epidemiological evidence

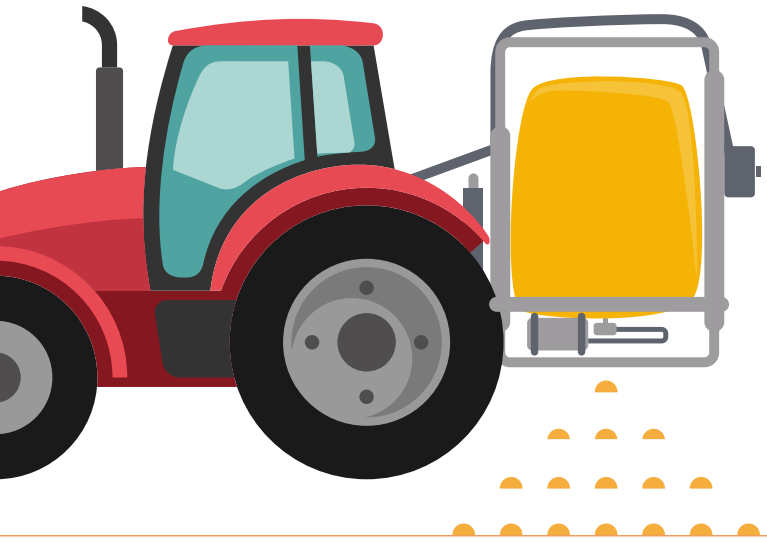
The AGG concedes that *"a weak association can be seen for persons with a relatively high exposure and acute myeloid leukaemia and Non-Hodgkin Lymphoma after a 20-year lag time"* (i.e. the time between exposure and tumour development) and *"that some of the case-control studies reported slightly increased odds ratio (ORs) trends for certain tumours classified as not being Hodgkin lymphoma, (p.311-312)".*

In fact, at least four case-control epidemiology studies that were carried out in different countries found that workers exposed to glyphosate had a statistically significant increased risk for non-Hodgkin lymphoma. A recent analysis of the human epidemiological studies, including the recent cohort Agricultural Health Study (AHS) and five case-control studies, found a compelling link between exposures to glyphosate herbicides and increased risk for non-Hodgkin lymphoma [40, 41].

According to the CLP Regulation, *"on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals".* Furthermore, limited evidence of carcinogenicity in humans refers to *"a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding* ***could not be ruled out with reasonable confidence."***

In his 2021 review, which includes three recent publications that were missing from the AGG's preliminary assessment, Prof. Portier emphasises that the definition of *"limited evidence of carcinogenicity in humans"* perfectly fits the existing epidemiological literature [42]. **These epidemiological studies provide evidence for lymphoid cancer, thereby complementing the existing evidence on malignant lymphoma from animal studies.**

However, the AGG rules out all the evidence from epidemiology studies and concludes in the dRAR that *"the results reported in the epidemiological studies do not warrant classification and labelling of glyphosate".*



Weight of evidence analysis according to good scientific principles

Overall, by integrating all of the abovementioned evidence in a weight of evidence approach in line with the directions provided in the CLP Regulation (Annex I, 1.1.1 and 3.6.2.2), we observe the following:

- **Animal studies.** Based on the 11 studies considered relevant for the assessment, the findings show three different tumour types, for which a statistically significant increase in tumour incidences was observed in multiple (three or more) studies:
  - skin keratoacanthomas in four of six rat studies
  - malignant lymphoma in four of five mouse studies
  - kidney tumours in three of five mouse studies
- This total of 10 cases of tumour incidences was supported by HCD in six cases and dose-dependence in five cases. Moreover, multi-site tumour responses were observed in two rat and three mouse studies.
- **Underlying causal mechanism.** The observation of significantly increased tumour incidences in these carcinogenicity studies is supported by a recognised mechanism of how glyphosate can cause carcinogenicity, that is oxidative stress. This was shown in particular for kidneys in male mice, i.e. the same organ, sex and species, where an increased tumour incidence was observed in mouse studies. Furthermore, the genotoxicity potential has not been adequately investigated [Box 2] by the companies.
- **Limited but existing human evidence.** The statistically increased incidences of malignant lymphoma in four of five mouse studies, confirms the limited epidemiological evidence of an association between glyphosate exposure and lymphoid tumours in humans.

By bringing all these lines of evidence together, it becomes clear that glyphosate fulfils the criteria laid out in the CLP Regulation to be classified as a "presumed carcinogen". Therefore the AGG's conclusion that "no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria" (RAR 2021, p. 316) is incorrect and not in line with the implementation of good scientific principles.

4 CONCLUSION

At the core of the Treaty on the Functioning of the European Union is the tenet that all EU policies should ensure 'a high level of human health protection'[43]. This includes CLP and pesticide regulations. Nevertheless, as the case of glyphosate reveals, chemicals for which there is evidence suggesting they may cause harm, may still go through the authorisation process[44]. As a result, they make their way onto the EU market with the presumption of safety, because their potential for harm remains overlooked.

Disagreement in science is not uncommon and can lead to lack of consensus. When such situation arises and there is uncertainty on the safety of a pesticide, the EU law on pesticides provides the possibility for the EU Commission and member states to implement the precautionary principle and remove the substance from the market or severely restrict its use[45]. This option is available in order to ensure that pesticide active substances and products that enter the market do not cause any harm to humans or to the environment.

To date, this has not been the case for glyphosate. In a repeat of 2017, the current EU assessment of glyphosate has so far failed to acknowledge and integrate the scientific evidence that shows that glyphosate may cause cancer. Ten out of 11 studies animals show that animals exposed to glyphosate developed tumours, revealing the carcinogenic potential of glyphosate. Nevertheless, the pesticide companies, the AGG and now ECHA's Risk Assessment Committee concluded that this active substance is not carcinogenic.

Instead of taking this evidence into consideration, along with peer-reviewed scientific literature on the carcinogenicity potential of glyphosate, the AGG chooses to endorse the industry's application conclusions. Following the footsteps of the industry, the AGG dismisses the tumour evidence using scientifically unfounded arguments, concluding that the tumours that the animals developed were by chance and were not linked to glyphosate exposure. In the process, the AGG breaches both internationally established protocols and EU rules, and ultimately the principles of good scientific practice.

Considering that glyphosate is the most used pesticide in Europe, it is critical that the scientific assessment of its safety is impeccable. All the carcinogenicity evidence should be acknowledged, and in case of doubt, the Commission and member states must apply the precautionary principle to ensure its ban in the European Union. EU laws include important provisions that commit to the protection of human health and the environment. It is unacceptable that chemicals, for which we have significant scientific evidence for cancer-causing potential, such as glyphosate, can remain on the market, and, ultimately, endanger people's health. The protection of human health must come first.

5 APPENDIX

All statistically significant tumour incidences in glyphosate-exposed rats

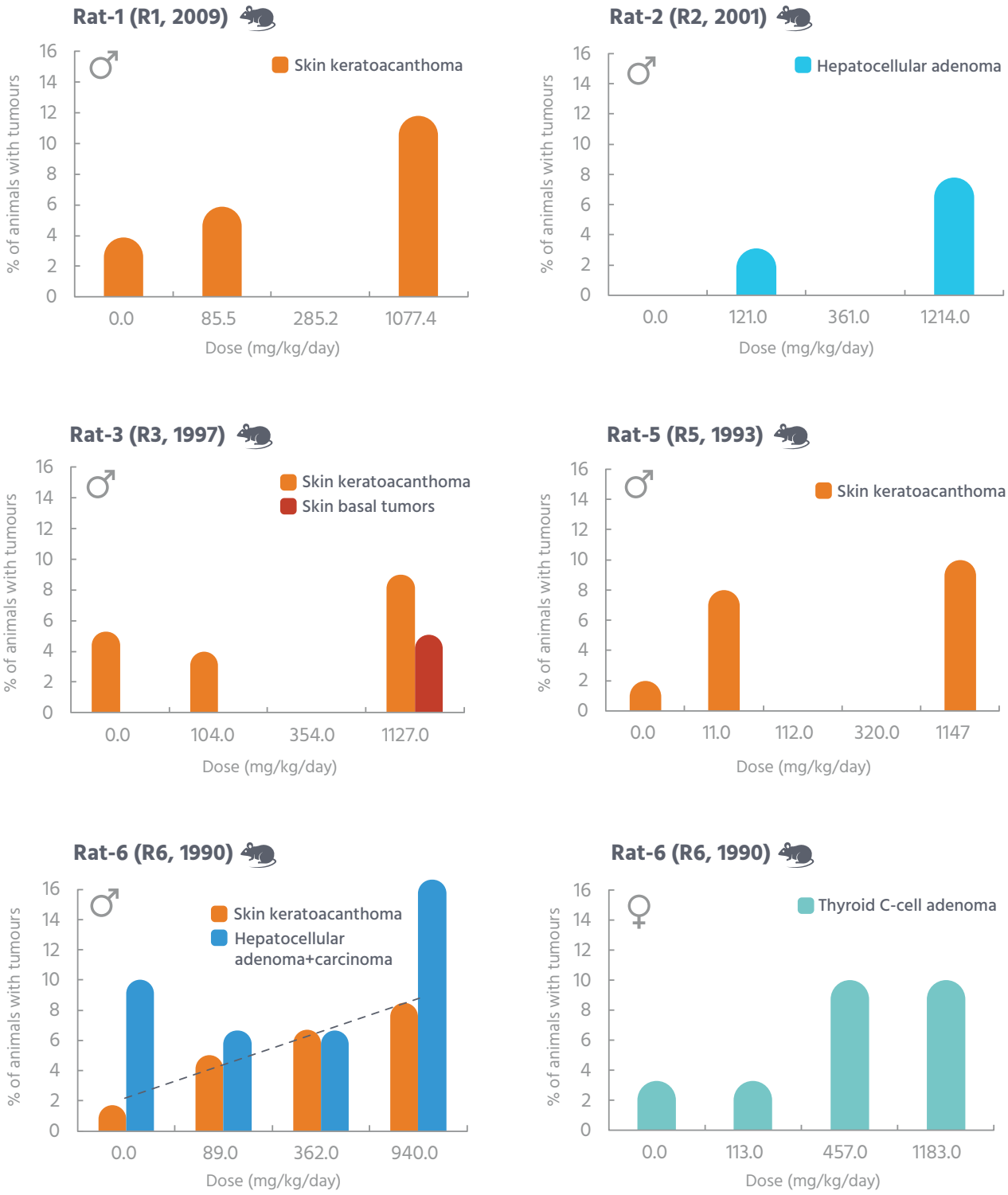


Figure A1. Percentage (%) of rats with statistically significant tumours in the different glyphosate-exposure groups ($p<0.05$, 1 or 2-sided, see Table 1).

All statistically significant tumour incidences in glyphosate-exposed mice

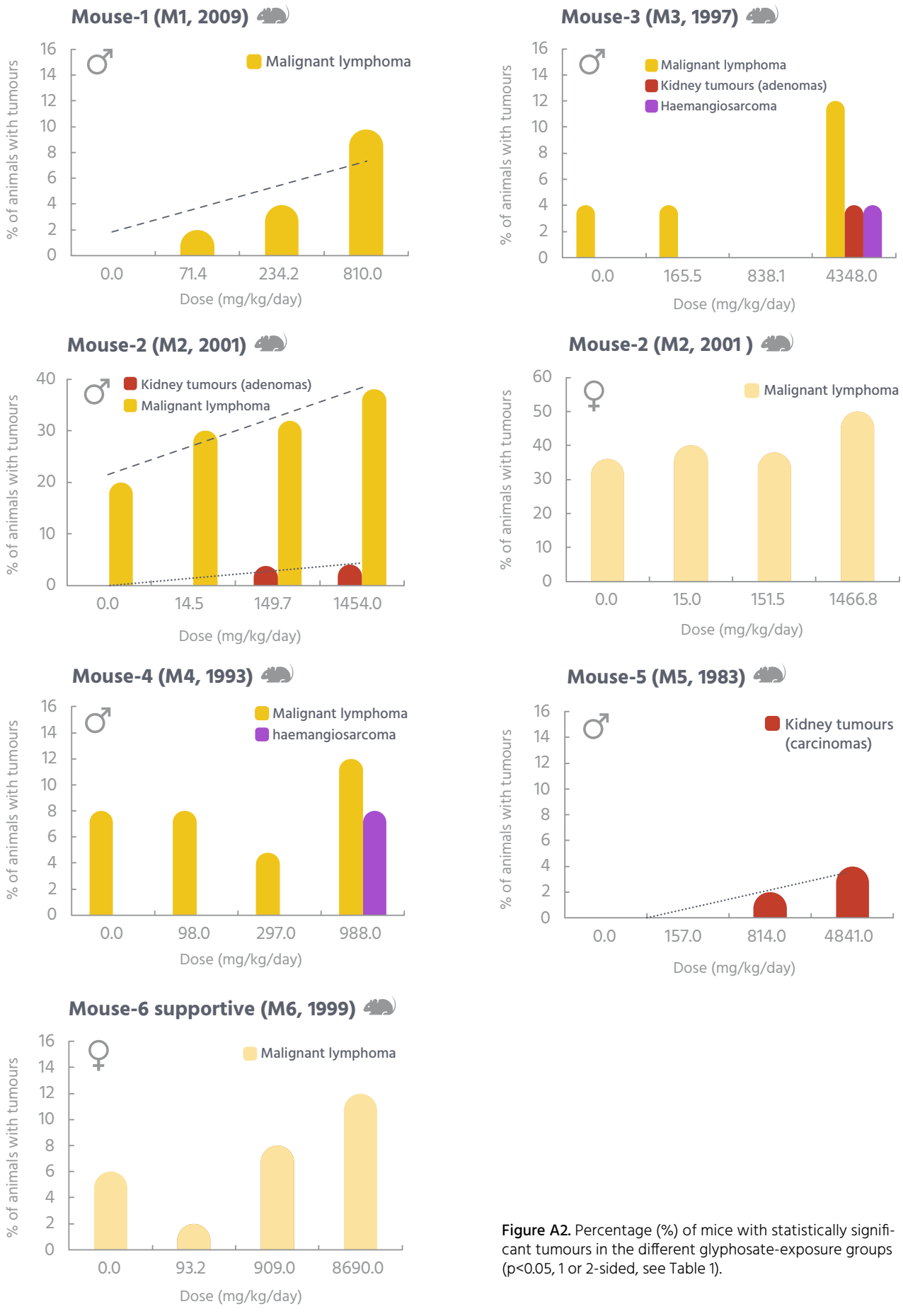


Figure A2. Percentage (%) of mice with statistically significant tumours in the different glyphosate-exposure groups ($p<0.05$, 1 or 2-sided, see Table 1).

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12. Prof. Christopher J. Portier is an expert in the design, analysis, and interpretation of environmental health data with a focus on carcinogenicity. He has served on numerous advisory committees at the U.S. EPA, National Council on Science and Technology, World Health Organization, European Commission and others. Dr. Portier served as the Director of the US National Center for Environmental Health at the Centers for Disease Control and Prevention, and Director of the Agency for Toxic Substances and Disease Registry. Prior to this, Dr. Portier was at the U.S. National Institute of Environmental Health Sciences (NIEHS) and served as the Director of the Environmental Toxicology Program and the Associate Director of the National Toxicology Program; Dr. Peter Clausing is a toxicologist, certified by the German Society for Pharmacology and Toxicology, with 3-years of post-doctoral research at the U.S.FDA's National Center for Toxicological Research and with extended experienced in regulatory toxicology (Head of the Department of Toxicology of Scantox, a CRO in Denmark, and – until retirement – Senior Toxicologist of Boehringer-Ingelheim pharmaceutical company in Germany).
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On 30th May 2022, ECHA's Committee for Risk Assessment (RAC) concluded that glyphosate does not meet the criteria to be labeled as a carcinogenic or genotoxic agent: **https://echa.europa.eu/nl/-/glyphosate-no-change-proposed-to-hazard-classification**

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22. OECD Guidance 116, Appendix 1 "Moreover, the lower the body weight, the less sensitive the animal may be to agent-induced toxicity, including cancer. A significant decrease in body-weight gain therefore could reduce the animal's ability to respond to compound-induced toxicities".

23. Historical controls are control, unexposed, animals from experiments that have taken place in the past, other than the one under evaluation (called the concurrent control).

24. Outlier is a data value that differs significantly from other observations. When this value is not reproduced in other studies it is considered an error and should be removed from the data set.

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