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Glyphosate Evaluation: A Severely Skewed Report!

The evaluation report for the renewal of the authorization of glyphosate (RAR) **organizes the invisibility of public studies but at the same time considers as acceptable studies of the industry yet clearly unacceptable** because not meeting the requirements of the guidelines of OECD!

générations FUTURES

Table of content

Research carried out by Générations Futures in collaboration with R.I.S.K. Consultancy, Brussels.

Abstract

Summary of the report on the selection procedures of public studies in the RAR of glyphosate and on the evaluation of studies provided by industry in the same RAR.

We have **highlighted**, with concrete examples, **many flaws in the selection process of public studies** in the RAR of glyphosate :

→ Just by reading **the title and the abstract, many relevant studies are excluded from the outset** (studies judged on their reliability and not their relevance, studies described at conferences which are nevertheless internationally recognized, mechanistic studies relating the effects of glyphosate at molecular and cellular levels, studies carried out outside the EU under conditions which are considered without any explanation not transferable to Europe).

→ A **new cut is made when assessing relevance based on the entire text.** There, all toxicology studies carried out with **formulations different** from the reference product whose authorization is requested in Europe are **excluded**. This involves hundreds of studies! No justification and no means of verifying this assertion is made, the composition of the products being confidential.

Hundreds of studies are thus sidelined and will never be evaluated ...

We have also shown that the assessment of the reliability of public studies is done in a completely non-transparent and unfair way between university studies and those of industry.

The consequences of this selection method are that 92% of public studies are deemed irrelevant! In the end, out of the 7000 or so studies found, only 30 studies, equivalent to 0.4% of the studies found, are deemed relevant and reliable without restriction!

None of these 30 studies weighed in the evaluation of the exclusion criteria of regulation 1107/2009 (CMR and PE properties) and none was considered as a key study that could lead to the definition of a safe dose. exposure. It can therefore be factually concluded that the published scientific literature on the toxicity / ecotoxicity of glyphosate did not influence the opinion of the reviewers in the RAR of glyphosate in a different sense from that of the unpublished studies in scientific journals provided by industry itself.

At the same time, we have shown that the quality of industry studies, in particular genotoxicity studies, show significant methodological flaws calling into question their relevance and reliability.

Conclusion

In the RAR for glyphosate, everything has been done to ensure that:

1 / the minimum number of studies in the literature is considered
2 / the studies in the literature are considered less reliable than those provided by industry
3 / the flaws in the studies of the industry are concealed.

Thus, industry and authorities can ultimately easily argue that in light of the overwhelming number of negative industry studies considered acceptable, positive literature studies have no weight.

Context and method

The request for re-authorization of glyphosate is currently being examined at European level.

In this context, **Générations Futures has already shown** on September 21 in a report (1) **that the industrialists of the GRG (2) set aside almost 60% of the university studies on the toxicity of glyphosate published** during the 10 years preceding the request. of re-authorization.

The assessment report for the renewal of the authorization (RAR) of glyphosate has now been published by the rapporteur member states (AGG) (3) and the public consultation is opened since September 24 to close on November 22. This report will be used directly for the European evaluation of glyphosate and its possible re-authorization.

Générations Futures wanted to assess more precisely this RAR, and in particular **how the various studies carried out by academics or by / for the phytosanitary firms themselves were treated in this file.** The question is whether they are selected and judged s transparently and identically.

The first part of this report focuses on **university studies.** First, it is a quantitative analysis showing how many academic studies are screened out for their supposed lack of relevance or reliability and how many are actually taken into account for the classification and risk assessment. We also critically sought to know the reasons for this exclusion.

After studying the very strict selection process for public studies, Générations Futures investigated **in Part II** of the report whether **industry studies** are selected in the same way. For example, we analyzed the studies provided by the industry on the genotoxicity of glyphosate, considered acceptable by the RAR, by comparing them with the requirements of the OECD guidelines in force in order to know ... if they were actually acceptable, or not.

[1] See: https://www.generations-futures.fr/wp-content/uploads/2021/09/rapport-glypho-etudes-2022-vf.pdf
[2] GRG: glyphosate Renewal Group: the group of manufacturers carrying the request for the reauthorization of glyphosate at European level.
[3] AGG: "Assessment Group on Glyphosate". The rapporteur member states for the ongoing European assessment of glyphosate are France, Hungary, the Netherlands and Sweden.

1 Consideration of academic literature

Article 8.5 of Regulation 1107/2009 is an improvement over the previous legislation on pesticides as it provides for the inclusion of academic studies in the assessment process ... in principle. **Indeed, all the scientific literature published in scientific journals on the toxicity / ecotoxicity of glyphosate during the period in question is not fully taken into account, far from it.**

European regulation 1107/2009 on the marketing of pesticides provides in its article 8.5 that

"The author of the request attaches to the dossier the accessible scientific documentation, as determined by the Authority, validated by the scientific community and published during the last ten years preceding the date of submission of the dossier, concerning the side effects on health, environment and non-target species of the active substance and its relevant metabolites. "

1-1 Study selection method

To explain this small number of public scientific articles found and cited in the RAR, it is necessary to understand the methodology used to carry out this literature search. We will thus see that **this methodology is, among other things, responsible for the non-selection of a very large number of studies.**

The method to be used by industry and authorities (Member States and EFSA) to conduct their research for public studies is described in the **2011 EFSA guideline.** This method is intended to be ***"rigorous, transparent and reproducible".***

The method consists of several steps

1 Define the research strategy for university studies

Define the search strategy by choosing the databases and the keywords used to search in these databases.

2 Selection of relevant studies

Among all the results found, **only the so-called “relevant” studies are selected. Non-relevant studies will not be included in the dossier and therefore not evaluated.** A first selection, called "rapid assessment" is made by looking only at the title and abstract of the study in order to exclude clearly irrelevant studies just by reading the abstract. A second selection is then made from the remaining studies, this time based on the full study reading ("detailed assessment").

3 Classification of relevant studies into 3 categories

Following this detailed review, the studies deemed relevant are **classified into 3 categories:**
* Category A: relevant studies, useful for risk assessment and eco-toxicological classification;
* Category B: studies that are relevant but considered by the industry to provide only "supplementary information", not modifying the existing risk assessment or the classification;
* Category C: studies whose relevance could not be clearly determined

4 Assessment of the reliability of relevant and "useful" studies

Only relevant studies classified in Category A will be judged for their reliability and summarized in the RAR. **Only studies deemed reliable or reliable with restrictions will be taken into account** in the “weight of evidence” for the toxicological and ecotoxicological classification of the substance and to define the reference doses.

The table below summarizes the results of this study selection process at each stage, from start to finish.

Fate and consideration of toxicity results published in scientific journals in the RAR of glyphosate 2021.

		Non relevant studies			Relevant studies		Reliable studies, usefull for evaluation. Cat A			
Type of studies	Result of bibliographic search	Tittle and summary	Entire text	total	'Complementary studies' Category B	Studies usefull for evaluation (Category A	Non reliable	Reliable with restrictions	Reliables	Used as 'Key study'
Toxicity	1550	881	311	1192	286	79	5	63	11	0
Ecotoxicity	1614	1039	412	1451	151	109	38	60	11	0
ED	4024	3654	347	4001	0	23	3	12	8	0
Total	**7188**	**6644 (92%)**			**437 (6%)**	**211 (3%)**	**46**	**135 (1.9%)**	**30 (0.4%)**	**0%**

Note: ED = studies on a possible endocrine disrupting effect of glyphosate.

In other words, of the 7,188 studies found in the literature search, only 211 would be relevant and useful for the evaluation, or only 3%! **Only 0.4% of the studies are considered both relevant, useful for the dossier and reliable!** Would the research work of academics therefore be irrelevant and unreliable 99.6% of the time? Is academic science so far removed from regulatory science?

1-2 Flaws in the method of selecting studies

To try to understand these figures, we sought to know **the reasons for the non-selection of toxicology studies** at each step of the process described by the EFSA guideline. What were the criteria used to exclude all the scientific literature in this way?

We have identified flaws in the selection method at several levels:

1 / at the level of the guideline itself
2 / at the level of the rapid assessment of titles and summaries
3 / at the whole study assessment level
4 / at the level of the examination of the reliability of the study.

0,4 % Only of university studies are considered both relevant, useful for the dossier and reliable!

Flaws in the method of selecting studies

1 Flaws in the EFSA guideline

Each toxicity result should be considered relevant by its very nature. Even if the study has weaknesses for one reason or another, as long as it investigates whether the substance causes adverse health effects, it should be considered relevant.

The EFSA guideline itself indicates this (p.13 / 49): :
" *To avoid missing relevant studies,* ***the relevance criteria should not be too restrictive. Only clearly irrelevant studies should be excluded from a dossier.*** *Evaluating the relevance of a study does not involve considerations of the reliability of the study* "

However, **reliability criteria are clearly used to judge the relevance of a study.** For example, the statistical power of the study, the species and the route of administration used are reliability criteria used to judge the relevance of a study. The very definition of these criteria therefore leads to confusion between relevance and reliability. As a result, a massive initial rejection of university studies can take place at the first stage of the process, relying solely on reading study summaries.

In addition, several relevance criteria set out by EFSA are questionable. In particular, the fact of selecting only studies carried out "on a species relevant to the toxicology of mammals" amounts to excluding all studies carried out on other organisms, such as fish for example. This is what happened in the RAR for glyphosate in which a very large number of studies performed with aquatic species were excluded from the summary. However, more and more studies show that tests carried out on fish may actually be relevant and exploitable for a risk assessment for humans (4). These studies could serve to reduce the toxicity tests done on mammals, which we are trying to avoid as much as possible. This would be the case in particular for genotoxicity tests carried out on fish.

ANSES itself acknowledges this in a report (5):
*"**The use of animal data outside the rodent model should be discussed in particular for mutagenicity.** It would have a potential huge impact on animal testing and would allow taking onboard environmental data (example: mutagenicity observed on fish), aligning CLP with the One Health concept ".*

In addition, the example of the glyphosate dossier detailed below shows that many other criteria of irrelevance are used, some of which are very questionable!

[4] Caballero et al. J Unexplored Med Data 2018; 3: 4 / Alzualde et al. Neurotoxicology and Teratology 70 (2018) 40–50
[5] Inception impact assessment related to the revision of CLP Regulation - ANSES comments

2 Loopholes in the rapid review of titles and abstracts

Out of 1550 toxicology studies found, 881 (57%) were deemed irrelevant after reading the titles and abstracts. Initially not available, the list of these 881 studies with the reasons for their rejection is, after request by the authorities, now available on the AGG website.

After analyzing this list, the authorities "picked up" and asked to have the entire text for only 3 studies. According to the authorities, therefore, this first selection made by the industry was well done since only 3 studies out of 881 appeared to them to be wrongly rejected.

Many of the studies found are indeed irrelevant. For example studies not dealing with glyphosate or looking at a mixture of pesticides whose effects cannot be attributed to glyphosate alone; studies unrelated to toxicity or ecotoxicity (efficacy or analytical method).
However, after a non-exhaustive review (the list being 515 pages), several points alerted us and it seems that far more than 3 studies would in fact be relevant among these 881.

Here is a non-exhaustive list of the reasons for excluding a number of studies in more detail.

Studies whose relevance was judged with reliability criteria.
As described above, inversion of criteria is responsible for the exclusion of some studies upon reading the title or abstract.

Example of excluded study: Zhao WenHong et al; 2013. Tea polyphenol protects mouse sertoli cells against oxidative damage and apoptosis induced by glyphosate. (study rejected because the application rate is considered too high)

Very many (> 80) studies described at conferences were excluded for lack of detail (reliability criterion) and because they were "probably" not peer-reviewed.

However, many of these studies do not have summary available, so it is not possible to know whether the details are missing or not. In addition, these conference abstracts are well published in peer-reviewed journals and the EFSA guideline strongly recommends including them in the research:

" Examples of sources of scientific peer-reviewed open literature are represented by: Bibliographic databases which record documents such as journals, reports, conference proceedings and books" / "Sources other than bibliographic databases, such as reference lists of full-text journal articles (eg reviews); journals 'tables of contents; or websites of conferences or organizations. "

Examples of excluded studies: Muzinic, V et al., 2019. Effect of glyphosate at low concentrations on chromosome missegregation and aneuploidy induction in human peripheral blood lymphocytes in vitro
Mrzyk, Inga, 2017. An extended one-generation reproductive toxicity study of plant protection product containing glyphosate on rats - Androgen- and estrogen-dependent endpoints

Mechanistic studies examining the effects of glyphosate at the cellular and molecular level were excluded because they "cannot be linked to the risk assessment".

However, the explanation of these mechanisms of action, in particular mechanisms linked to the oxidative stress, are essential for understanding the toxicity of the substance. Understanding these mechanisms of action is an integral part of the CLP classification process ... and also of the EFSA guideline:
"Studies that may be useful for the interpretation of other studies present in the dossier, but which do not fall under a particular toxicological endpoint, would be relevant. Examples of such studies are [...] studies clarifying the mode of action of the active substance ".
This type of mechanistic study should therefore be taken into account in the assessment.

Excluded study example: Ugarte, Ricardo, 2014. Interaction between glyphosate and mitochondrial succinate dehydrogenase Fernando Rafael, 2017. Oxidative stress in the hybrid fish jundiara (Leiarius marmoratus × Pseudoplatystoma reticulatum) exposed to Roundup Original (®).

Studies carried out in Asia or South America are excluded upon reading the summary because the conditions would not be comparable to Europe. This mean that aspects relevant to exposure are taken into account the hazard assessment, which is contrary to all principles of hazard and risk assessment.

Excluded study example: Dawson et al., 2010. Acute human lethal toxicity of Agricultural pesticides: a prospective cohort study. The reasons for rejecting this study are that the summary does not identify an effect due to glyphosate and the data from Sri Lanka may not be transferable to Europe. However, in the entire text (available free of charge), glyphosate is clearly mentioned and effects have been found.

Several studies were rejected from the first step on the grounds that they were conducted on a mixture of substances and not with glyphosate alone. However, after checking some abstracts, it turns out that it is, in some cases, false, the study was indeed conducted on glyphosate alone (the 3 studies picked up by the authorities fall into this category).

3 Flaws in the detailed examination of studies

Of the 669 studies remaining after the rapid review of titles and abstracts, 311 were judged irrelevant, 282 were judged to be relevant but just "supportive" (classified as category B), 6 were judged to be of uncertain relevance (category C) . Only 67 studies were classified as Category A (relevant and can be used for risk assessment and classification). Only these 67 studies were therefore really taken into account in the dossier.

What are the reasons for judging 311 studies as irrelevant?

As a justification for irrelevance, we find the reasons already given for the rapid assessment of studies. Once again, many studies seeking to understand the mechanisms at the cellular level leading to oxidative stress are rejected, which is contrary to the recommendations of the CLP and the EFSA.

But at this stage of the selection, the main criterion used by the industry to rule out studies is: "any publication dealing with a formulation of Roundup that is not the representative formulation of the renewal dossier". In question the supposed role of the co-formulants, in particular of the surfactants contained in the formulations.

A major problem then arises: the detailed composition of the formulations is confidential. So we have no way to compare the formulations. Without composition, it is impossible to study these surfactants more closely, their contribution to the overall toxicity of products. It is therefore impossible to be able to dispute or not this assertion which keeps coming up in the file, namely "this formulation is not representative for use in Europe". It is also not known whether the authorities have done the job of evaluating the compositions of these different formulations. In view of the number of studies concerned (almost a hundred just for the toxicology part), this question of the role of co-formulants must absolutely be treated in a transparent manner!

4 Flaws in the reliability analysis

The biggest flaw at this level is the **lack of transparency in the RAR.**

What criteria were used?
What is the weight of each of the criteria in judging the quality of a study?
What are the criteria that must absolutely be met to judge a study as reliable without restriction?
Are there criteria which, if not met, automatically lead to the study beingdeemed unreliable or just supportive?

So many questions that remain unanswered.

The EFSA guideline isn't much more transparent on the subject: out of **50 guideline pages, just half a page is devoted to the assessment of the reliability of a study.** No clear method is proposed. However, remember, this guideline is intended to be "rigorous, transparent and reproducible". It is just said that "general principles should be considered when assessing the reliability of a study." These principles are absolutely not detailed or even cited. The guideline refers to general guides and a publication (6), one of the conclusions of which is that **"there is an urgent need to have harmonized criteria".** The guideline also refers to a tool, ToxRtool, available on the website of the European Commission. This tool seems interesting because it provides precise criteria and recommendations for evaluating the reliability of toxicological studies, thus making the decision-making process for assigning reliability categories more transparent and harmonized. Unfortunately, however, this tool was not used in the RAR of glyphosate. It is not known which method, publication, tool served as the benchmark for the reliability assessment.

Worse, it appears that literature studies have been evaluated for their reliability much more severely than industry studies. In fact, after each study summary of the literature, we find a table listing reliability criteria (see appendix 1) with a “yes or no” box if this criterion is met (once again, we do not know the weight of each of these criteria). However, this kind of table and assessment is absolutely not made for industry studies! Instead, the reliability assessment boils down to saying that the studies were conducted under Good Laboratory Practice (GLP), according to OECD guidelines without further details. In addition, where deviations from these guidelines exist, they are often not reported or detailed. **There are therefore double standards in the evaluation of studies!**

[6] Kaltenhauser et al., Regulatory Toxicology and Pharmacology 88 (2017) 227-237

1-3 Consequences

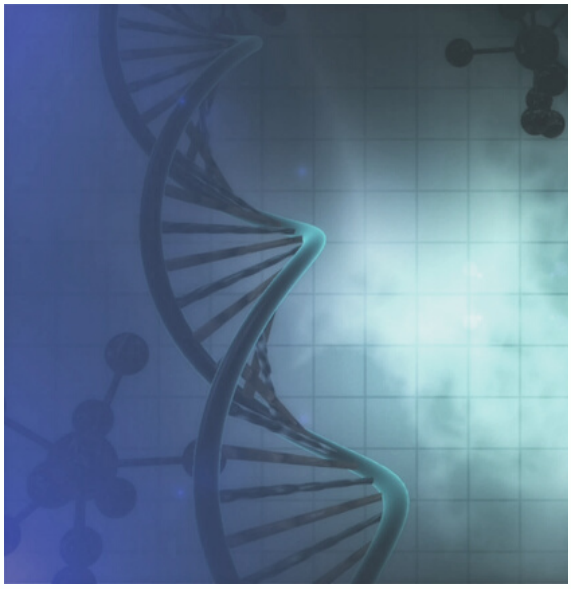
In summary, only 30 studies published in academic journals were deemed to be both relevant and reliable without restriction at the end of the process (out of more than 7000 collected at the start ...)

None of these 30 studies played a role in the evaluation of the CMR or PE properties of glyphosate, properties that could lead to the banning of the substance under the exclusion criteria according to regulation 1107/2009. Although the existence of "reliable" or "reliable with restrictions" studies showing positive results is recognized, these are systematically dismissed under the argument that "in the face of the very large number of studies available respecting the guidelines of the 'OECD' », the weight of evidence still weighs for a non-classification of the glyphosate.

In addition, the regulation provides for the definition of safe exposure doses, for which no harmful effects are expected. These doses are defined for humans, acutely or chronically exposed to glyphosate, but also for non-target organisms such as aquatic or terrestrial organisms.

How many published studies led to lowering the "safe exposure doses" in the RAR? The answer is zero!

2 Analysis of the quality of studies provided by the industry. Example of genotoxicity



We have seen that studies from the literature are hardly, if at all, taken into account in the evaluation. **This raises the question of the quality of the studies provided by industry as well as their evaluation by the authorities.**

To answer this question precisely and in order to illustrate it with examples, we have chosen to focus our analysis on a point that seems particularly critical, which is genotoxicity. **A study made by two Austrian toxicologists (7) has already found that only 2 studies out of 53 industry genotoxicity studies could be considered unrestricted reliable and 34 were unacceptable.** We wanted to assess in more detail why these studies are not acceptable **in order to highlight the inconsistencies in the assessment made by industry and authorities, compared to their own guidelines.**

In particular, we looked at all the tests provided by manufacturers called "micronucleus studies" carried out in vivo (described in the OECD guideline No. 474 of 2016).

This test assesses the clastogenic potential of glyphosate, that is, its potential to cause DNA breaks and cause chromosomal aberrations. **We made this choice because, based on the results of open literature studies performed in vitro, glyphosate appears to be clastogenic.**

However, these literature studies are considered to be either unreliable or just supportive and their (positive) result should be considered "with caution". In the end, these studies have no weight because *"considered in parallel with the constantly negative conclusions of the mutagenicity / genotoxicity studies carried out according to the OECD guides, it is concluded that DNA damage is rather secondary to other toxic events than to be the consequence of the genotoxic potential of glyphosate. In addition, as demonstrated by the constant negative results found in vivo, the secondary DNA damage induced by glyphosate does not occur in vivo ".*

Is this argument hammered out as soon as a study of the literature is found positive correct?

[7] Armen Nersesyan and Siegfried Knasmueller, Evaluation of the scientific quality of studies concerning genotoxic properties of glyphosate - 2021

14 in vivo micronucleus studies were submitted, one of which was classified as confidential, not accessible. These 14 tests are negative. Of the 14 micronucleus tests, 4 studies were rightly judged not to be acceptable and were not taken into account in the dossier. Of the remaining 10, 4 are considered acceptable and 6 are considered acceptable with “restrictions”. In practice, little distinction is made between "acceptable" studies and "acceptable with restriction"studies. We therefore sought to confirm that these **10 studies are indeed "acceptable", that is to say that they meet all the acceptability criteria set out in the OECD 474 guideline of 2016, currently in force.**

3 major flaws have been revealed

1 Insufficient number of cells analyzed in all studies

As the studies are relatively old (dating from 1991 to 2015), none have been carried out following the current guideline in which changes in methodology have been made compared to the previous version of 1997. **As a result, none study analyzes the sufficient number of cells compared to current recommendations:** Instead of 4000 erythrocytes (type of blood cells produced in the bone marrow studied in the test) to analyze, only 2000 erythrocytes, and even 1000 for a study, have been studied. However, the number of cells to be analyzed is part of the criteria requested to say whether a study is acceptable or not according to the guideline: “The following criteria determine the acceptability of the test: [...] c) The appropriate number of doses and cells is analyzed. "

2 In none of the available studies, exposure of the target cells has been proven

However, to be able to say that a substance is clearly negative in the test, it is necessary to show that the assessed substance has indeed reached the bone marrow (where the erythrocyte cells are that will be analyzed):

"Provided that all the acceptability criteria are met, a test chemical is considered to be clearly negative if, under all of the experimental conditions studied: [...] d) there has been exposure of the bone marrow to the test chemical (s). "

For any study it is therefore not possible to say that the test is clearly negative, as yet stipulated by the authorities. **Since no evidence of bone marrow exposure is provided in any of the 9 available studies, the question of whether glyphosate actually reached the bone marrow arises.** It goes without saying that if the target is not reached, no toxic effects can take place. In addition, no toxicokinetic studies, which could show bone marrow exposure, were performed in mice, the species used in 9/10 tests. Only one study showed bone marrow exposure. No luck, this study is confidential and therefore inaccessible! The micronucleus test, however repeated 14 times (counting unacceptable studies) is therefore perhaps not a relevant test to assess the genotoxic effects of glyphosate! One of the EFSA guides on genotoxicity (8) states this very clearly:

"A negative result from an in vivo study has limits or even no relevance if there is no indication in the study that the test substance has reached the target tissue and if there is no other data, eg. toxicokinetic data, on which such a hypothesis could be based."

[8] EFSA Journal 2011;9(9):2379 - Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment

3 Where have the laboratory historical data gone?

Historical laboratory data was not provided at all for 6/10 studies and partially for 3/10. However, these data are part of the study's acceptability criteria according to OECD guideline 474.

In the end, **no industry study should be qualified as acceptable**, or even acceptable with restrictions, **and therefore their weight against public literature studies should be much lower!**

Conclusion & requests

We have highlighted, with concrete examples, **many flaws in the selection process for university studies in the RAR of glyphosate.**

Just by reading the title and the abstract, studies that are nevertheless relevant are excluded from the outset (studies judged on their reliability and not their relevance, studies described at conferences which are nevertheless internationally recognized, mechanistic studies relating the effects of glyphosate at the molecular and cellular levels, studies carried out outside the EU under conditions which are considered without any explanation not transferable to Europe).

A new cut is made when assessing relevance based on studying the entire text. There, all toxicology studies carried out with formulations different from those of the reference product whose authorization is requested in Europe are excluded. This involves hundreds of studies! No justification and no means of verifying this assertion is provided, the composition of the products being confidential.

We have also shown that the assessment of reliability is done in a completely non-transparent and unfair manner between academic studies and those of industry. The consequences of this selection method are that 92% of university studies are deemed irrelevant! In the end, out of the 7000 or so studies found, only 30 studies, equivalent to 0.4% of the studies found, are deemed relevant and reliable without restriction!

None of these 30 studies weighed in the evaluation of the exclusion criteria of regulation 1107/2009 (CMR and PE properties) and none was considered as a key study that could lead to the definition of a safe dose. exposure. It can therefore be factually concluded that the published scientific literature on the toxicity / ecotoxicity of glyphosate did not influence the opinion of the reviewers in the RAR of glyphosate in a different sense from that of the unpublished studies in scientific journals provided by the industry itself.
At the same time, we have shown that the quality of industry studies, in particular genotoxicity studies, show significant methodological flaws calling into question their relevance and reliability

Weight of evidence

The glyphosate dossier has this particularity that very many toxicity studies are available, with a mixture of negative and positive studies. In this case, no single study can serve as a basis for the toxicological and ecotoxicological classification of glyphosate.
All studies and results found must be taken into consideration, according to "expert judgment". This is what we know as"the weight of evidence". **Each study has more or less weight depending on its relevance and reliability.** This assessment is therefore **very dependent on the assessor.** Hence the importance of having a transparent and fair assessment of the relevance and reliability of all studies.

In short :
In the RAR of glyphosate, every effort has been made to ensure that
1 / the minimum number of public studies is considered
2 / studies in the literature are considered less reliable than those provided by industry
3 / the flaws in industry studies are obscured.

Requests

With the elements found in this report, **Générations Futures asks (10) therefore to the authorities to review their approach by genuinely considering all the relevant studies in the literature and by having a transparent and fair evaluation of the reliability of the studies. No decision on glyphosate should be made until this overhaul.**

It is important to remember that, on the contrary, the IARC only examined the studies published in scientific journals and retained more than 260 of them to base its opinion in its 2015 monograph classifying glyphosate as a probable carcinogen for 'man'.

Finally, we are entitled to wonder if the flaws found in the glyphosate dossier are not found in all the pesticide evaluation report ?
Générations Futures therefore calls for an in-depth reform of pesticide evaluation methods so that the scientific literature is really taken into account and industry studies are evaluated in the same way.

[9] Monograph 112, downloadable at: https://publications.iarc.fr/549
[10] See here https://shaketonpolitique.org/interpellations/glyphosate-stop-authorization /

Annex

List of reliability criteria used to assess academic genotoxicity studies

Reliability criteria for *in vitro* toxicology studies made by the applicant

Publication: De Almeida et al., 2018.	Criteria met? Y/N/?	Comments
Guideline-specific		
Study in accordance to valid internationally accepted testing guidelines	N	
Study performed according to GLP	N	
Study completely described and conducted following scientifically acceptable standards	?	
Test substance		
Test material (Glyphosate) is sufficiently documented and reported (i.e. purity, source, content, storage conditions)	Y	Purity of 99.5 %. Source: Supelco Analytical USA.
Only glyphosate acid or one of its salts is the tested substance	N	Also glyphosate-based formulations were tested.
AMPA is the tested substance	N	
Study		
Test system clearly and completely described	Y	Whole blood from volunteers, breast cancer cells (MCF7 and MDA-MB-231) and endometrial cancer cells (HEC1A).
Test conditions clearly and completely described	Y	
Metabolic activation system clearly and completely described	N	
Test concentrations in physiologically acceptable range (< 1 mM)	N	For cytotoxicity testing glyphosate concentrations from 0.1 to 500 µg/mL were used. For comet testing only glyphosate concentrations of 500 and 1000 µg/mL were used (> 1 mM).
Cytotoxicity tests reported	Y	
Positive and negative controls	Y	
Complete reporting of effects observed	Y	
Statistical methods described	Y	
Historical negative and positive control data reported	N	
Dose-effect relationship reported	Y	Was studied but not established.
Overall assessment		
Reliable without restrictions		
Reliable with restrictions	Y	
Not reliable		
This publication is considered relevant for the risk assessment of glyphosate but reliable with restrictions because the Comet assay was only conducted at concentrations that are physiologically not feasible in *in vivo* toxicology studies (> 1mM).		

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