El glifosato: un incumplimiento sistemático de las normas por parte de las autoridades

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Carcinogenicity of glyphosate: A failure in regulatory assessment

How industry strategized (and regulators colluded) in an attempt to save the world's most widely used herbicide from a ban

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El glifosato: un incumplimiento sistemático de las normas por parte de las autoridades

Son tres las instituciones que han certificado que el glifosato no es carcinógeno: en primer lugar, el Instituto Federal Alemán para la Evaluación de Riesgos (BfR), responsable de la evaluación del glifosato en la UE; a continuación, la Autoridad Europea de Seguridad Alimentaria (EFSA); y, finalmente, la Agencia Europea de Sustancias y Mezclas Químicas (ECHA). El BfR elaboró un informe de evaluación para la EFSA y, posteriormente, para la ECHA.

Por el contrario, el Centro Internacional de Investigaciones sobre el Cáncer (CIIC) de la Organización Mundial de la Salud (OMS) clasificó el glifosato como «probablemente carcinógeno para los seres humanos». Este grado de clasificación, el segundo de los posibles, fue elegido teniendo en cuenta los siguientes resultados que se habían obtenido:

- Evidencia suficiente del efecto carcinógeno en animales de laboratorio («sufficient evidence»);
- Evidencia sólida de que existen dos mecanismos por los cuales el glifosato puede provocar cáncer («strong evidence»);
- Evidencia epidemiológica limitada en seres humanos («limited evidence»).

El Dr. Peter Clausing, toxicólogo que también intervino como observador en las reuniones de la ECHA, analizó la evaluación de los estudios con animales realizada por las autoridades de la UE. En su análisis, indica que estas:

- ignoran y pasan por alto pruebas claras del efecto carcinógeno en animales, y
- en gran medida, no se ajustan a las recomendaciones y los documentos de orientación de la OCDE ni de la propia ECHA, por los que debería guiarse su trabajo.

Según el Reglamento (CE) nº 1272/2008, las conclusiones de los estudios realizados con ratas y ratones son de central importancia.

Así, basta con que haya dos estudios independientes uno del otro en los que se constate que una sustancia incrementa la incidencia de tumores para clasificarla como carcinógena.

En el caso del glifosato, de los doce estudios a largo plazo llevados a cabo, en al menos siete se observó un incremento de la incidencia de tumores.

Las autoridades solamente pudieron llegar a la conclusión de que el glifosato no es carcinógeno a pesar de los hallazgos comentados violando el Reglamento (CE) nº 1272/2008, su propio documento de orientación de 2015 y la guía de la OCDE de 2012, además de omitiendo y tergiversando los hechos. A continuación, pasamos a describir las cinco faltas más graves.

1. Negligencias y tergiversaciones en el análisis estadístico

Existen dos tipos de métodos estadísticos (las denominadas «pruebas de tendencia» y las «comparaciones por pares») que se emplean para comprobar si los tumores observados en animales de laboratorio se deben al principio activo objeto de un experimento. Independientemente del método con el que se trabaje, siempre que se obtenga un resultado significativo desde el punto de vista estadístico, este ha de reconocerse en ambos casos. Eso es lo que dicen tanto la guía nº 116 de la OCDE, de 2012, como el documento de orientación de la ECHA del año 2015.

Al principio, por no recurrir a una «prueba de tendencia», el BfR ni siquiera reconoció una serie de efectos tumorales significativos. Había confiado en los resultados de las «comparaciones por pares» de los informes de estudios realizados por parte del sector industrial, el cual solamente había señalado un efecto carcinógeno del glifosato en un único estudio y para un solo tipo de tumor.

Tras la publicación en julio de 2015 de la monografía sobre el glifosato del CIIC, el BfR revisó su propia evaluación. De ahí resultaró las citadas incidencias significativas en siete de doce estudios.

No obstante, el BfR, al igual que las autoridades de la UE, que se basaron en el trabajo previo de este instituto, pasaron por alto otros ocho efectos tumorales significativos. Estos otros diagnósticos han sido identificados recientemente por el catedrático Christopher Portier, exdirector del Centro Nacional de Salud Ambiental de EE. UU. (NCEH), tras analizar los datos de los estudios del sector industrial que, de otra manera, habrían sido mantenidos en secreto.

Las autoridades restaron importancia a la incidencia que ya conocían de los dos estudios con ratas y cinco estudios con ratones poniendo como requisito que los resultados de una «comparación por pares» fueran significativos para conceder relevancia suficiente a la incidencia en cuestión. Por el contrario, mencionaban las pruebas de tendencia, pero considerándolas insuficientes. Esto implica un incumplimiento grave de la guía vigente de la OCDE, pues se trata de algo que no es necesario:

> Si los resultados de *cualquiera [!]* de los métodos de prueba son significativos, ello basta para rebatir la hipótesis de que se deban al azar. (Guía n.º 116 de la OCDE, pág. 116: «*Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.*»)

2. Supuestos «efectos por dosis elevadas»

A fin de atenuar la sigficancia de los ahora claros efectos carcinógenos del herbicida, el BfR y la EFSA afirmaron que

- a los animales de laboratorio podía administrárseles una dosis máxima diaria de 1000 mg/kg de peso corporal y
- que los efectos carcinógenos observados solamente se daban en casos de «toxicidad excesiva».

El primer punto es absolutamente ficticio. Si comprobamos las guías pertinentes, veremos que, para los estudios sobre el cáncer, no se establece ningún máximo diario o dosis límite de 1000 mg/kg. Esta definición se tomó sin más de otro tipo de estudio.

En cuanto al segundo punto, resulta insostenible tras un análisis desde la perspectiva científica. El único supuesto de «toxicidad excesiva» reside en que, en unos cuantos experimentos, el peso corporal de los animales del grupo al que se le administraron dosis altas era menor. No obstante, el consumo de alimentos de dichos animales fue, de forma análoga a su peso, también menor, lo que seguramente se deba a que, al añadirles el glifosato, cambiaban de sabor, sin que ello tuviera nada que ver con una «toxicidad excesiva». Esto no influyó en el período de vida de los animales y, a excepción de los propios tumores, no hubo ningún otro diagnóstico patológico en los órganos afectados por estos.

Conclusión: El argumento de los «efectos por dosis elevadas» pretende rela-tivizar la incidencia constatada de cáncer.

3. Supuesta falta de relación dosis-efecto

Cuando un efecto aumenta al incrementar la dosis de un principio activo, los toxicólogos hablan de una «relación dosis-respuesta». Siempre que hay una relación tal, se le da especial importancia al efecto en cuestión. No obstante, esto no implica que un efecto sea irrelevante porque solo se observe en el grupo con la dosis más alta.

En el detallado informe se prueba que, solo en el marco de los estudios llevados a cabo con ratones, se pudieron demostrar cuatro casos de clara relación dosis-respuesta. Además, al contrario que las comparaciones por pares, las pruebas de tendencia sí que son aptas para detectar relaciones dosis-respuesta. A este respecto, en la guía de la OCDE se explica que:

> «Una prueba de tendencia [...] se emplea para observar si aumentan los resultados en todos los grupos expuestos a medida que se incrementa la dosis.»
>
> – (Guía n.º 116 de la OCDE, pág. 116: «A trend test … asks whether the results in all dose groups together increase as the dose increases.»)

En los estudios sobre el glifosato los efectos significativos quedaron mayoritariamente demostrados a través de las pruebas de tendencia.

Con relación a los efectos tumorales observados, el BfR, la EFSA y la ECHA evitaron hacer referencia a las relaciones dosis-respuesta. Al mismo tiempo, con respecto a la incidencia de otros tumores, resaltaron que no había ninguna relación de ese tipo. Está claro, pues, que las autoridades trataron de ocultar los indicios que apuntaban a un efecto carcinógeno del glifosato.

4. Empleo indebido y distorsionado de «controles históricos»

Los «controles históricos» son los datos resumidos de los animales de control de estudios previos a los que no se les había administrado el herbicida. Este tipo de datos solamente pueden ayudar a interpretar mejor los resultados de estudios si se dan ciertas condiciones. En los estudios sobre el cáncer, de lo que se trata es de clasificar los tumores que aparecen «de forma espontánea».

Al igual que en el ser humano, la frecuencia de aparición espontánea de tumores puede estar condicionada por numerosos factores, tales como el estrés, la alimentación y la predisposición genética. Es por este motivo que las guías en cuestión afirman que, a la hora de evaluar los resultados, lo más importante es siempre comparar los animales a los que se les ha administrado el herbicida con el grupo de control del experimento en sí. Solamente debería recurrirse a «controles históricos» en caso de dudas fundadas acerca de los resultados de los experimentos, y siempre aplicando una serie de normas muy estrictas: la comparación debe realizarse entre animales del mismo filo taxonómico en el mismo laboratorio y con una antigüedad máxima de cinco años.

En el caso del glifosato, las autoridades no solamente se saltaron de forma flagrante todas estas restricciones, sino que tergiversaron una serie de hechos hasta el punto de que ya no podían reconocerse. Así, de las excepciones detectadas en los controles históricos, hicieron la norma. Con relación a esto, el ejemplo más absurdo lo constituye un estudio llevado a cabo con ratones en el año 1997 en el que los datos de controles históricos de ocho de nueve estudios corroboraban la incidencia significativa de tumores. No obstante, las autoridades recurrieron a los datos del noveno estudio, con una tasa de tumores extremadamente elevada, para cuestionar la relevancia de estas incidencias de tumores.

Las autoridades descartaron aquellos estudios para los que había disponibles controles históricos adecuados y que confirmaban el efecto tumoral observado. En otros estudios, decidieron emplear datos de controles históricos que claramente no debían ser utilizados, con la finalidad de negar efectos carcinógenos significativos, lo cual representa un patente incumplimiento de las normas.

Conclusión: La argumentación referente a los controles históricos presentada por las autoridades es un castillo de naipes que se derrumba por su propio peso en cuanto se atiende a criterios científicos o a las especificaciones de la OCDE y de la propia ECHA.

5. Selección arbitraria de los estudios

En los estudios con ratones, un efecto especialmente claro del glifosato fueron los tumores del sistema linfático (linfomas malignos). En tres de los estudios se registró un incremento significativo desde el punto de vista estadístico de estos tumores. En dos de ellos, había una clara relación dosis-respuesta. En el tercero (del año 1997), el efecto solo se observaba en el caso de la dosis más alta. Asimismo, también hay estudios epidemiológicos que indican que, en el ser humano, el contacto con el glifosato potencia el riesgo de aparición de cáncer en el sistema linfático (linfoma no Hodgkin).

En otros dos estudios llevados a cabo con ratones, según la evaluación de las autoridades, no se registró un aumento de los linfomas malignos por la administración de glifosato. Uno de ellos, tras ser sometido a un análisis crítico y dadas las graves carencias que presentaba, resultó ser totalmente inservible. El otro contenía una serie de vaguedades terminológicas, por lo que su valor era cuestionable. A pesar de ello, las autoridades consideraron estos estudios plenamente válidos como evidencia de la inocuidad del glifosato.

La suerte que corrieron los tres estudios que probaban un aumento significativo de los linfomas malignos derivado de la administración del herbicida pone de manifiesto la forma de trabajar de las autoridades.

El estudio de 1997 quedó excluido de la evaluación recurriendo a una absurda tergiversación de los datos de controles históricos (ver punto 4). La EFSA clasificó uno de los dos estudios con efectos dependientes de la dosis como inservible alegando para ello una supuesta infección vírica. En el informe elaborado por el BfR para la ECHA, el primer organismo reconoció que esta no había sido probada en absoluto. La única «prueba» de la supuesta infección vírica fue un comentario de un funcionario de Estados Unidos durante una conferencia telefónica. A pesar de ello, el estudio solo se tuvo en cuenta con reservas. Una serie de correos electrónicos internos de Monsanto, hechos públicos recientemente ante un tribunal, subrayan lo cuestionable de esta forma de proceder. En ellos se describe al funcionario estadounidense en cuestión como diligente aliado de la empresa.

Así, por tanto, la conclusión a la que llegaron las autoridades de que el glifosato no produce linfomas malignos se fundamenta en tres estudios, dos de los cuales, empleados como evidencia negativa, tras ser analizados en detalle, resultan inservibles o de valor cuestionable. Al tercer estudio, en el que se exponía un incremento significativo de los linfomas malignos en función de la dosis, las autoridades le «restaron importancia» artificialmente al no tener en cuenta el análisis estadístico correcto y utilizar controles históricos cuando no debían haberlo hecho.

Conclusión final:

Las autoridades de la UE disponían de un total de doce estudios llevados a cabo con ratas y ratones de los cuales al menos siete indicaban un aumento significativo de los tumores bajo los efectos del glifosato. No obstante, dichas autoridades emplearon argumentos extremadamente dudosos para obviarlos, contradiciendo claramente la normativa vigente.

Los responsables políticos no deberían entrar en este juego tan cuestionable desde el punto de vista científico y, al parecer, motivado por intereses. Deberían, más bien, aplicar el principio de precaución y encargarse de que las pruebas científicas de las que disponemos se analicen correctamente. ¡Está en juego la salud de 500 millones de ciudadanos de la UE!

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Introduction

On 15 March 2017, the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA) published its verdict that the scientific evidence did not meet the criteria specified in the Classification, Labelling and Packaging (CLP) Regulation to classify glyphosate as a carcinogen.

ECHA's opinion is regarded by the EU Commission and some Member States as the central argument to remove doubts on the re-approval of glyphosate. However, this report shows that ECHA failed to perform its assessment in accordance with EU legal requirements and relevant guidelines from the OECD (the Organization for Economic Cooperation and Development, which sets standards for chemicals testing and assessment). ECHA's opinion also violates the principles of objective science. Therefore it is legally and scientifically unsound. As a consequence of this flawed opinion, the health of an unknown number of Europeans could be jeopardized.

Specifically, ECHA failed to properly apply the CLP criteria, which govern the classification of chemicals, in its opinion. Instead of correcting the wrong conclusions of the Harmonized Classification and Labelling (CLH) Report drafted by the German Federal Institute for Risk Assessment (BfR), ECHA supported those conclusions. In order to reach its verdict, ECHA dismissed compelling evidence for the carcinogenic potential of glyphosate, just as EFSA did in 2015.

In order to better understand the extent of this failure, this report first looks at the scientific and regulatory framework for assessing carcinogenicity. Then it applies this framework to the available data to make an assessment consistent with the legislation. Finally it presents a critique of the assessment by the authorities and their arguments used to dismiss that glyphosate is a carcinogen.

It is important to take note of a recent re-analysis of the original data which revealed eight further tumours in regulatory rat and mouse carcinogenicity studies that were not described in the original study reports by industry or noticed by the German Federal Institute for Risk Assessment (BfR), the European Food Safety Authority (EFSA), or the European Chemicals Agency (ECHA) (Portier 2017). As Professor Christopher J. Portier, former director of the US National Center for Environmental Health at the Centers for Disease Control and Prevention in Atlanta, requested in his letter (Portier 2017) to Jean-Claude Juncker, the President of the European Commission, the authorities should be instructed to review the evidence submitted in this letter and not make any decision on glyphosate until these positive findings are included in the assessment of the substance's carcinogenicity.

Chapter 1

Carcinogenicity assessment: How to get it right

The European Regulation (EC) 1107/2009 prohibits the approval of pesticides (active ingredients) classified as carcinogens in category 1A or 1B (see Box 1). These categories are respectively for substances known to have carcinogenic potential for humans, based primarily on human evidence (1A) and substances presumed to have carcinogenic potential for humans, based primarily on animal evidence (1B). The reason for precaution is because for the majority of these chemicals – those with genotoxic properties – no safe dose can be defined concerning carcinogenicity.

Regulation 1107/2009 acknowledges this and in principle prohibits them from being marketed in the EU. This way of looking at the problem is called the "hazard approach".

> 3.6.3. An active substance, safener or synergist shall only be approved, if, on the basis of assessment of carcinogenicity testing carried out in accordance with the data requirements for the active substances, safener or synergist and other available data and information, including a review of the scientific literature, reviewed by the Authority, it is not or has not to be classified, in accordance with the provisions of Regulation (EC) No 1272/2008, as carcinogen category 1A or 1B, unless the exposure of humans to that active substance, safener or synergist in a plant protection product, under realistic proposed conditions of use, is negligible, that is, the product is used in closed systems or in other conditions excluding contact with humans and where residues of the active substance, safener or synergist concerned on food and feed do not exceed the default value set in accordance with Article 18(1)(b) of Regulation (EC) No 396/2005.

Box 1

The classification of chemicals, including pesticides, with regard to carcinogenicity and other toxic properties is governed by another EU legislation, Regulation (EC) 1272/2008. According to this regulation, a chemical is classified as a category 1B carcinogenic hazard (probable human carcinogen, based on animal studies) if there is "sufficient evidence of carcinogenicity" in experimental animals. This regulation, also called the CLP Regulation, defines "sufficient evidence" as follows:

"A causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms" in at least two independently conducted valid animal studies (Article 3.6.2.2.3.b).

Normally, for market approval, the carcinogenicity assessment of a pesticide is based on the results of at least two carcinogenicity studies, one performed in rats and the other in mice. If both studies are positive, i.e. if a significant increase in the number of tumours is observed in treated animals in both studies, the pesticide qualifies as a category 1B carcinogen. However, according to the CLP Regulation, significant carcinogenic effects observed in two independently conducted studies performed in one species only are also considered sufficient for a category 1B classification. For glyphosate, seven rat and five mouse carcinogenicity studies are available. Such an accumulation of studies can happen when a pesticide is on the market for a long time, because several producers may have applied independently for market authorization.

Carcinogenicity studies last at least 24 months for rats and 18–24 months for mice. This means that the studies cover around two-thirds of the lifespan of the test animals. The design of these studies is described in guidelines agreed upon by the Organisation for Economic Co-operation and Development (OECD) to ensure that they are comparable and of adequate quality.

In such studies, tumour incidences in the low, mid, and high-dose groups are compared with the incidences in a control group within the same experiment (called the concurrent control group). In a typical study, 50 animals per sex per group are used. The tumour incidences are analysed separately for males and females, because of a potential difference between the sexes in the

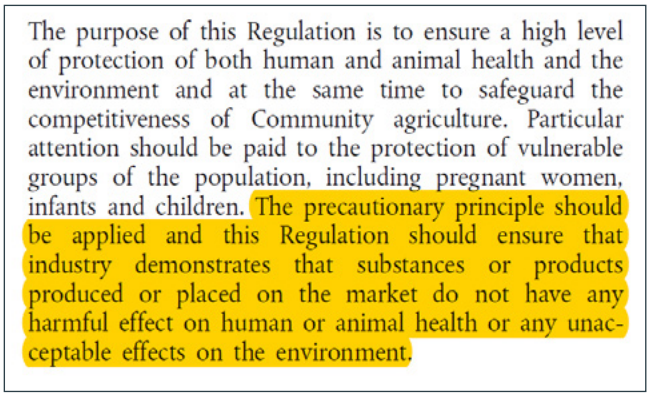
tumour rates. If no sex differences are seen, the incidences are also subject to a combined analysis.

Normally the test compound is given to the animals by putting it in their feed. Tumours are detected and evaluated by histopathological examination, in which tissues are examined under the microscope. The tissues of all animals – those found to be dying or dead during the study and those that survive until the end of the study – are examined in this way. Samples of more than 40 different tissues are processed and examined microscopically. While this effort seems immense – with between 8,000 and 16,000 histological slides per study being examined microscopically – it appears minuscule considering that the potential carcinogenic hazard for more than 500 million EU citizens is assessed in just two studies of approximately 400 animals each.

To cover this gap, at least partially, OECD guidelines (OECD 2009a, 2009b) require that the high-dose group is treated with a sufficiently high amount of test compound to increase the likelihood of detecting a carcinogenic effect. Such sufficiently high doses are called "maximum tolerated doses" (MTDs). They are intended to maximise possible effects without jeopardising the study itself, e.g. by causing the premature deaths of the animals.

Variability of response is a typical feature of biological systems. Such variability is seen in animals' reaction to chemicals, including the development of tumours in long-term studies. It is good scientific practice to use appropriate methods to ensure that observed effects in a particular experiment are true effects and not due to random chance, because of this biological variability. Nevertheless a certain "error probability" will remain which can go in two opposite directions: the first is when a true effect is masked because of biological variability; and the second is when an effect that is due to chance (because of biological variability) is mistaken for a "true" effect.

Science has methods of reducing this error probability – these are described in more detail in the next chapter. However, Regulation (EC) 1107/2009 makes clear that some degree of scientific uncertainty is not a valid reason to allow potentially hazardous active substances to enter or remain on the market. Item (8) of the preamble states that "The precautionary principle should be applied and this Regulation should ensure that industry demonstrates that substances or products produced or placed on the market do not have any harmful effect on human or animal health or any unacceptable effects on the environment" (see Box 2).


The purpose of this Regulation is to ensure a high level of protection of both human and animal health and the environment and at the same time to safeguard the competitiveness of Community agriculture. Particular attention should be paid to the protection of vulnerable groups of the population, including pregnant women, infants and children. The precautionary principle should be applied and this Regulation should ensure that industry demonstrates that substances or products produced or placed on the market do not have any harmful effect on human or animal health or any unacceptable effects on the environment.

Box 2

In addition, Article 1 of the main text of Regulation (EC) 1107/2009 states that scientific uncertainty shall not prevent Member States from applying the precautionary principle "to ensure that active substances or products placed on the market do not adversely affect human or animal health or the environment".

On the other hand, "strength of evidence" also has to be taken into account when making a judgment about the carcinogenicity of a pesticide. According to the Regulation, "Strength of evidence involves the enumeration of tumours in human and animal studies and determination of their level of statistical significance" (Regulation (EC) 1272/2008, item 3.6.2.2.3). This will be discussed in more detail in the next chapter.

To summarize, given enough strength of evidence, a significant increase in the number of tumours in two valid, separate long-term studies in rats and/or mice are considered "sufficient evidence of carcinogenicity" for a category 1B classification, as stated by the CLP Regulation.

Chapter 2

Scientific methods to reduce uncertainties

Science offers a number of tools to minimize the uncertainties arising from biological variability. Two important guidance documents describe these tools and how to use them – OECD Guidance 116 (OECD 2012) and the CLP Guidance published by ECHA (ECHA 2015). While the principal tool is the statistical analysis, other important tools include:

- The appropriateness of the doses used in the study
- Dose-response-relationships*
- Historical control data
- The reproducibility of effects in case comparable studies are available, and
- Whether the effect was seen in one sex only or in both sexes.

While statistical analysis is a cornerstone in the assessment of carcinogenicity, biological relevance also has to be considered. This is accounted for in OECD Guidance 116: "Denoting something as statistically significant does not mean it is biologically important. … Similarly, declaring a result non-significant (…) should not be interpreted as meaning the effect is not biologically important or that the null hypothesis is correct" (OECD 2012, p. 118). It is important to keep in mind the second sentence – we will return to this later.

In general, dose-response-relationships, the reproducibility of effects in comparable studies, and knowledge of a mechanism of action are important components to assess the biological relevance in addition to statistical significance. But first we will look at those tools that are discussed in guidance documents and guidelines: statistical analyses, historical control data and the appropriateness of the high dose used.

Statistical analysis

Regarding which type of statistical analysis should be carried out in carcinogenicity studies in animals, OECD Guidance 116 states: "Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumour incidence. A trend test such as the Cochran-Armitage test (Snedecor & Cochran, 1967) asks whether the results in all dose groups together increase as the dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over the control group" (OECD 2012, p.116).

In the same paragraph, this guidance emphasizes:

"Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result. A statistically significant response may or may not be biologically significant **and vice versa**." (OECD 2012, p. 116, emphasis added).

The ECHA Guidance points out that "**any** statistically significant increase in tumour incidence, especially where there is a dose-response relationship, is generally taken as positive evidence of carcinogenic activity" (ECHA 2015, p. 375, emphasis added).

Taken together, the considerations offered in these guidance documents clearly lead to the conclusion that it is wrong to play off the two different approaches (trend test vs. pairwise comparisons) against each other.

One- or two-tailed statistical tests

An additional key question about the statistical analysis is whether one-tailed or two-tailed test should be used.

Two-tailed tests analyze the statistical significance of a change due to treatment in both directions. For instance, in response to exposure to a certain substance, blood glucose levels could increase or decrease. In contrast,

* This means that the effect increases with the dose, strengthening the argument that the effect is caused by the chemical being tested.

one-tailed tests analyze the statistical significance of a change only in one direction, thereby doubling the statistical power. Because of this difference, it is important to mention in the reports whether one-tailed or two-tailed tests were used. In the case of carcinogenicity testing for hazard assessment, common sense tells us that only an **increase** of tumour incidences is relevant. While for blood parameters (glucose or protein concentrations), both increases and decreases may be biologically relevant, it is obvious that carcinogenicity is measured as an **increase** in tumours, as compared to control animals.

In spite of the considerations in the preceding paragraph, OECD Guidance 116 is not entirely clear about preferences for one-tailed or two-tailed test: "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" (OECD 2012, p. 133).

In any event, these considerations contribute to the view that lack of statistical significance in a two-tailed pairwise comparison has to be put into proportion with other statistical approaches.

Appropriateness of the high dose used

The ECHA Guidance cautions that tumours "occurring **only** at excessive doses associated with **severe** toxicity generally have a more doubtful potential for carcinogenicity in humans" (ECHA 2015, p.379, emphasis added). At the same time, ECHA and OECD guidance documents state that minimal toxicity (e.g. characterized by an approximately 10% reduction in body weight gain) needs to be induced in the high-dose group. Such a dose is expected not to alter the lifespan of the animals "from effects other than carcinogenicity" (ECHA 2015, p. 379). This dose inducing "minimal toxicity" is also called the "maximum tolerated dose" (MTD).

Both guidance documents point out that excessive toxicity should be avoided, because it may compromise the usefulness of the study. Two concerns relate to excessive toxicity. In the extreme, a too-high dose could reduce the lifespan of the animals and thereby reduce the time to develop tumours, or it could reduce statistical power because too many animals were lost. The other concern refers to toxic effects that could become secondary causes of cancers that are not directly induced by the test compound, such as tissue necrosis with associated regenerative hyperplasia. In sum, the top dose should be low enough to avoid such side-effects but high enough to increase the ability to detect carcinogenicity (Rhomberg et al. 2007).

In addition, a "limit dose" is defined in OECD Guidance 116. It recommends a maximum of 50,000 mg test compound per kg of diet for "nutritional and possibly other physiological reasons" (OECD 2012, p. 54). This would translate into a dose of approximately 5,000 mg per kg of body weight for mice and 2,500 mg per kg of body weight for rats.

The significance of the level of the top dose will become clear later in this report.

Dose-response relationship

According to ECHA's Guidance, "Any statistically significant increase in tumour incidence, **especially where there is a dose-response relationship**, is generally taken as positive evidence of carcinogenic activity." (ECHA 2015, p. 375, emphasis added). No further explanation is given, but it is self-explanatory that an increase in the effect with increasing dose adds to the strength of evidence.

Historical control data

For carcinogenicity studies, historical control data is a compilation of tumour incidences in control animals of earlier studies. ECHA encourages the use of historical control data in particular for tumour types that occur "with variable and potentially high incidence", in order to ensure that the effects seen in the study are valid and do not occur by chance (ECHA 2015, p.375). Nevertheless, according to OECD

Guidance 116, "it should be stressed that the concurrent control group is **always** the most important consideration" (OECD 2012, p. 135, emphasis added).

Because spontaneous tumour incidences can be considerably influenced inter alia by housing conditions and genetic background, both guidance documents strongly recommend that historical control data should match the concurrent control group as closely as possible. To ensure this, historical control data should be from the same strain, ideally from the same laboratory, and collected within the last 5 years prior to the study (OECD 2012, p. 135, ECHA 2015, p.376). In addition, it is recommended to refrain from using certain statistical parameters (arithmetic means and standard deviations) to describe the historical control data, because they can be affected by "rogue" outliers (OECD 2012, p. 135). The simple range is not even mentioned in the OECD Guidance, because it is much worse than the standard deviation, with the potential of making "rogue" outliers the norm. Therefore the simple range should be avoided to ensure scientific integrity. Guidance 116 encourages the use of the median instead of the arithmetic mean and the interquartile range (midspread) instead of the simple range.

Following these recommendations can be a useful tool to strengthen the assessment of the study outcome. Neglecting these recommendations, on the other hand, can result in seriously misleading conclusions.

Reproducibility of effects in comparable studies

It is obvious that it adds to the strength of evidence when the same effect is seen in different studies. However, it should be kept in mind that environmental conditions, genetic background of the animals, and other variable factors can have a massive influence on substance-related effects. Therefore, in order to avoid wrong conclusions, it is vital to ensure that any studies that are compared are truly comparable – that is, that they are similar in the important respects.

When comparing results from different studies, it is less problematic to make qualitative comparisons: in other words, whether or not an effect is seen at all. But for quantitative comparisons, which look at whether a similar effect (same type of tumour with a similar incidence) is seen at approximately the same dose, the same restrictions should apply as for historical control data: only studies conducted in the same strain, within the same period of time, and with the same housing and other environmental conditions can be compared. In practice, different studies are rarely quantitatively comparable, since factors such as study conditions and genetic backgrounds of the animals often vary. Therefore, when dealing with studies not comparable in these aspects, only qualitative comparisons should be made.

Chapter 3

Reality check: Is glyphosate carcinogenic?

Equipped with the knowledge summarized above, we will now look at the data to come to a science-based conclusion as to whether or not glyphosate is carcinogenic. The basis of our considerations will be the tumour incidences seen in the various animal studies. Table 1 serves as a point of reference. It contains a condensed presentation of the data derived from the report sent by the German authorities to ECHA (BAuA 2016), including duration of study, animal strain, doses, and tumour incidences.

Table 1: Basic study information and summary of tumour incidences in males (unless otherwise indicated) in the studies taken into consideration by the EU authorities. A p-value of 0.05 (a 5% chance) or less is considered statistically significant; p-values for pairwise comparisons are for high-dose vs. control group. Two-sided tests were used. Animal numbers per group were between 43 and 60 in the different studies.

Study (Year) Duration (months)	**Species/Strain**	**Tumour type**	**Doses (mg/kg body wt.) ---------- Tumour incidences**	**p-values for trend test/ pairwise comparison (significant values bold and underlined)**
Lankas (1981) (26 mo.)	Rat/ SD	Pancreatic carci- noma	0 – 3 – 10.3 – 31.5 ---------- 0 – 0 – 0 – 1	**0.0496** / 1.000 (Fisher's)
Stout & Ruecker (1990) (24 mo.)	Rat/ SD	Pancreatic islet cell adenoma	0 – 89 – 362 – 940 ---------- 1 – 8 – 5 – 7	0.1687 / 0.062 (Fisher's)
		Liver cell adenoma	0 – 89 – 362 – 940 ---------- 2 – 2 – 3 – 7	**0.0171** / 0.162 (Fisher's)
		Liver cell adenoma and carcinoma	0 – 89 – 362 – 940 ---------- 5 – 4 – 4 – 9	0.0752 / 0.392 (Fisher's)
		Thyroid C-cell adenoma in females	0 – 89 – 362 – 940 ---------- 2 – 2 – 6 – 6	**0.0435** / 0.168*** (Fisher's)
Knezevich and Hogan (1983) (24 mo.)	Mouse/ Crl:CD-1, Charles River Wilmington	Lymphoreticular neoplasms *	0 – 157 – 814 –4841 ---------- 2 – 5 – 4 – 2	No significant difference; no details given in CLH-Report
		Renal carcinoma	0 – 157 – 814 –4841 ---------- 0 – 0 – 1 – 2	**0.0370** / 0.495 (Fisher's)

		Renal adenoma and carcinoma	0 – 157 – 814 –4841 ---------- 1 – 0 – 1 – 3	**0.0339** / 0.617 (Fisher's)
Atkinson et al. (1993) (24 mo.)	Mouse/ Crl:CD-1, Charles River Portage	Malignant lymphoma**	0 – 100 – 300 – 1000 ---------- 4 – 2 – 1 – 6	No statistics possible due to incomplete histopathology
		Haemangiosarcoma	0 – 100 – 300 – 1000 ---------- 0 – 0 – 0 – 4	**0.0004** / 0.059 (Fisher's)
Sugimoto (1997) (18 mo.)	Mouse/ Crj:CD-1	Malignant lymphoma	0 – 165 – 838 – 4348 ---------- 2 – 2 – 0 – 6	**0.0085** / 0.269 (Fisher's)
		Haemangiosarcoma	0 – 165 – 838 – 4348 ---------- 0 – 0 – 0 – 2	**0.0078** / 0.495 (Fisher's)
		Renal tubular adenoma	0 – 165 – 838 – 4348 ---------- 0 – 0 – 0 – 2	**0.0078** / 0.495 (Fisher's)
Kumar (2001) (18 mo.)	Mouse/ Swiss Albino	Malignant lymphoma	0 – 15 – 151 – 1460 ---------- 10 – 15 – 16 – 19	0.0655 / 0.077 (Fisher's)
		Malignant lymphoma in females	0 – 15 – 151 – 1460 ---------- 18 – 20 – 19 – 25	0.068 / 0.225 (Fisher's)
		Renal tubular adenoma	0 – 15 – 151 – 1460 ---------- 0 – 0 – 1 – 2	**0.0390** / 0.495 (Fisher's)
Wood et al. (2009) (18 mo.)	Mouse/ Crl:CD-1	Malignant lymphoma	0 – 71 – 234 – 810 ---------- 0 – 1 – 2 – 5	**0.0037** / 0.067 (Chi-square)

*no specification of malignant lymphoma

**the incidences shown are only from lymph nodes with macroscopic changes (BAuA 2016)

***own calculation, not given in BAuA (2016)

In compliance with guidance recommendations that significance in either kind of test – pairwise comparisons or trend test – is sufficient to reject that differences are due to chance, there was a total of 11 statistically significant increases in tumour incidences observed in two rat and five mouse studies. Four more tumour incidences become statistically significant if one-tailed statistical tests are employed (see OECD 2012, p. 133).

Bearing in mind that "**any** statistically significant increase in tumour incidence… is generally taken as positive evidence of carcinogenic activity" (see "Statistical analysis" above for full quote) and that two studies with an increased number of tumours are required by Regulation (EC) 1272/2008, this is more than sufficient evidence to place glyphosate into CLP category 1B – for substances presumed to have carcinogenic

potential for humans, based on animal evidence. This is re-emphasized in the ECHA Guidance: "In general, if a substance involves a treatment related increase in tumours then it will meet the criteria for classification as a carcinogen. If the substance has been shown to cause malignant tumours this will usually constitute sufficient evidence of carcinogenicity supporting Category 1B" (ECHA 2015, p. 377).

Recently, based on a re-analysis of the original data from the study reports, a total of eight further significantly increased tumour incidences (using a one-tailed statistical test) were identified in seven different studies (Portier 2017, Portier and Clausing 2017). If these are taken into consideration, the number of studies with significant tumour effects increases to six rat and five mouse studies, with a total of 18 significantly increased tumour incidences.

Weight of evidence

In the previous chapter of this report ("Scientific methods to reduce uncertainties"), a number of tools were described that can help to minimize uncertainties arising from biological variability. Commonly, applying these tools in an assessment is called a "weight of evidence" approach. As it will be shown below, the weight of evidence approach, if properly applied to the available studies on glyphosate, further strengthens the conclusion that the chemical qualifies as a category 1B carcinogen. To keep it simple, we will concentrate on mouse studies, bearing in mind that a significant increase in the number of tumours in two valid, separate studies in rats and/or mice is considered "sufficient evidence of carcinogenicity" according to Regulation (EC) 1272/2008 (Article 3.6.2.2.3.b).

Reproducibility of the effect between studies

Three different types of tumours exhibited a statistically significant increase in the five mouse studies: Renal (kidney) adenoma/carcinoma, haemangiosarcoma (cancer of blood vessel linings) and malignant lymphoma (cancer of the white blood cells and their precursors). It should be stressed that for kidney tumours and malignant lymphoma, an increase was seen in three separate studies, and for haemangiosarcoma an increase was seen in two different studies – demonstrating a qualitative repeatability of the effect.

A quantitative comparison would be inappropriate, because the studies were carried out in different laboratories, in different mouse strains, and in some cases, at considerably different times. If it were nonetheless believed necessary to make quantitative comparisons, then good scientific practice would demand that similar requirements were applied as for historical control data (see section above, "Historical control data").

For example, different strains of mouse have been shown to respond differently to known carcinogens, as summarized by Festing (1995). So studies in which different strains of mouse are used should not be grouped together and used to make conclusions on the quantitative reproducibility of an effect between studies.

Dose-response relationship

While haemangiosarcomas were only seen at the top doses of the studies in question, two out of three studies with an increased incidence in malignant lymphoma exhibited a dose-response relationship. Likewise, two out of three studies showed incidences increased with dose for renal (tubular) adenoma and carcinoma. The data are shown in Table 1.

Appropriateness of the doses used in the studies

For all studies, the doses used were below the upper limit recommended by OECD Guidance 116, i.e. a maximum of 50,000 mg of test compound per kg of diet (OECD 2012, p. 54). Too-low doses would be a concern if no carcinogenic effects were seen – but this was not the problem in case of glyphosate. On the other hand, no evidence for excessive toxicity was provided in the RAR (RMS Germany 2015a) where the study reports were summarized, leading to the conclusion that excessive toxicity did not exist in any of these studies. Survival was not affected. No significant increases in pathological changes at the sites of

tumour development were reported.

While the guidance documents recommend a benchmark of an approximately 10% decrease in body weight gain to determine that the maximum tolerated dose (MTD) was reached (OECD 2012, ECHA 2015) it should be taken into account that in the Knezevich and Hogan (1983) study the test compound was administered at a concentration of 30g glyphosate per kg of diet (30,000 ppm) and in the Sugimoto (1997) study at 40g glyphosate per kg of diet (40,000 ppm). In the Sugimoto (1997) study, the body weight of males in this dose group was 7% lower than control animals at the end of the study, but food consumption was similarly decreased (6% lower than controls). No data were available for the Knezevich and Hogan (1983) study. No differences in body weight compared with the concurrent controls were seen in the Wood et al. (2009) or Kumar (2001) studies. For Atkinson et al. (1993), again, no data were presented in the RAR, but the top dose was 1,000 mg/kg body weight, and therefore within the range of the Wood et al. (2009) and the Kumar (2001) studies.

Historical control data

The use of historical control data is most relevant for malignant lymphoma, because this is a tumour type that occurs "with variable and potentially high incidence" (ECHA 2015, p. 135). Acceptable historical control data for malignant lymphoma are available in the authorities' reports (RMS Germany 2015a, BAuA 2016) for the Kumar (2001) and the Sugimoto (1997) study, whereas for the Wood et al. (2009) study, the historical control data were useless. They were only available as combined data for both sexes, but due to the pronounced sex-difference for malignant lymphoma (females have a consistently higher incidence), it is crucial to have them separated by sex.

For the Kumar (2001) study, the high-dose tumour incidence (38%) was even above the simple historical control data range (30%). Using appropriate statistical measures (median, inter-quartile range), the difference between these benchmarks and the incidence in the high-dose group would be even bigger, meaning that the study would provide even stronger evidence of glyphosate's carcinogenicity.

For the Sugimoto (1997) study, the incidence of malignant lymphoma in the high-dose group was 12%, as compared to eight of the nine studies comprising the historical control data, which had an incidence of 6% or lower, according to the German authorities' Renewal Assessment Report or RAR (RMS Germany 2015a, Volume 3 B.6, p. 528). In other words, except for the control animals of one previous study (which is to be considered a "rogue" outlier, according to OECD) the animals of the high-dose group had a two-fold or higher incidence of malignant lymphoma, compared with historical controls. This supports the conclusion that the statistically increased incidence in malignant lymphoma in the high-dose group is biologically relevant.

Further weight of evidence considerations

Four more elements mentioned in ECHA Guidance (2015) and Regulation (EC) 1272/2008 need to be taken into account when assessing the weight of the evidence of glyphosate's carcinogenicity.

First, multi-site responses are considered to add to the weight of evidence. This was shown for five of the seven studies listed in Table 1.

Second, responses were seen in rats as well as in mice (see Table 1, above, and Portier 2017). This also adds to the weight of evidence.

Third, the progression of lesions to malignancy adds to the weight of evidence. This was seen for kidney tumours in the Knezevich and Hogan (1983) study. It should be noted that this was a 24-month study in mice. Two other studies – the Sugimoto (1997) study and the Kumar (2001) study – showed no renal carcinoma, but only renal tubular adenoma. However, these were 18-month studies. A progression to malignancy could be expected if the studies had lasted 24 months. For haemangiosarcoma and malignant lymphoma, progression to malignancy cannot be assessed because of the type of tumour.

Fourth and last, two possible mechanisms for the carcinogenicity of glyphosate were described by IARC (2015), based on numerous publications in the scientific literature: genotoxicity (ability to damage DNA) and oxidative stress.

Summary of the weight of evidence

A total of 11 statistically significant increases in tumour incidences were observed in two rat and five mouse studies. Important factors to judge the weight of evidence are presented in Regulation (EC) 1272/2008 (see Box 3) and discussed in ECHA Guidance (ECHA 2015).

Applying the factors listed in Box 3 to the data available for the assessment of glyphosate, the conformance with these factors is as follows:

Annex I: 3.6.2.2.6. Some important factors which may be taken into consideration, when assessing the overall level of concern are:

(a) tumour type and background incidence;

(b) multi-site responses;

(c) progression of lesions to malignancy;

(d) reduced tumour latency;

(e) whether responses are in single or both sexes;

(f) whether responses are in a single species or several species;

(g) structural similarity to a substance(s) for which there is good evidence of carcinogenicity;

(h) routes of exposure;

(i) comparison of absorption, distribution, metabolism and excretion between test animals and humans;

(j) the possibility of a confounding effect of excessive toxicity at test doses;

(k) mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity." (Reg (EC) No 1272/2008, Annex 1, ASB2015-8591)

Box 3 Important factors which may be taken into consideration when assessing the overall level of concern for carcinogenicity according to Regulation (EC) 1272/2008, item 3.6.2.2.6.

(a) Supported by historical control data

(b) Supported, as demonstrated by experimental data

(c) Supported for kidney tumours; not applicable for malignant lymphoma and hemangiosarcomav

(d) Not supported because not demonstrated

(e) Not supported because effects in males dominate, but some effects were also seen in females

(f) Supported: effects were seen in rats and mice

(g) Not supported: no known carcinogens with structural similarities are known

(h) Supported: the oral exposure route is highly relevant for humans

(i) Not possible, as there is no human data available for absorption, distribution, metabolism and excretion

(j) Supported: effects were seen without excessive toxicity

(k) Supported: genotoxicity and oxidative stress have been identified as possible mechanisms.

Taken together, 10 of the 11 criteria were applicable, and seven of these 10 criteria support the conclusion that statistical increases in tumour incidences seen in the glyphosate carcinogenicity studies were true effects.

Chapter 4

How the authorities got their glyphosate assessments wrong

There appears to be a strategy of denial by the EU authorities – BfR, EFSA, and ECHA – of the existing scientific evidence. First and foremost this relates to the core issue of glyphosate's carcinogenicity, as revealed by the results of the statistical analysis. Originally BfR, in its report prepared for EFSA (RMS Germany 2015a, Volume 3 B.6), reported only one significantly increased tumour incidence (both in males and females) in one mouse study and one other in the low dose group of a rat study. Later, due to the publication of the International Agency's for Research on Cancer (IARC's) monograph on glyphosate (IARC 2015), which classified glyphosate as a probable human carcinogen, the authorities were pressured into admitting the existence of the statistically significant findings listed in Table 1 (RMS Germany 2015b, BAuA 2016).

Recently it was revealed that there are eight additional incidences of significantly increased tumours seen in two mouse and five rat studies (Portier 2017, Portier and Clausing 2017), which were neither reported by industry nor noticed by the EU authorities.

In order to maintain the claim of non-carcinogenicity, EFSA and ECHA resorted to constructing "supporting evidence". In order to do this, they violated recommendations given in guidance documents (OECD 2012, ECHA 2015), as well as the rules of good scientific practice.

While the ECHA Guidance points out that "in most cases, expert judgment is necessary to be able to determine the most appropriate category for classification for carcinogenicity" (ECHA 2015, p. 370), it is crucial to acknowledge that this expert judgment needs to sail within the limits of these guidance documents in order to avoid shifting the assessment away from science-based decisions to the advantage of certain interest groups. This chapter provides evidence that such a shift has taken place in case of the assessment of the carcinogenic hazard of glyphosate, and that the experts have exceeded the limits set by these guidance documents.

Use of statistical methods by the authorities

Originally the authorities made the claim that there were no statistically significant increases in tumour incidences due to treatment with glyphosate. In the final draft of the Renewal Assessment Report (RAR) dated 31 March 2015, BfR had identified just a single mouse study with one significantly increased tumour type (malignant lymphoma), out of a total of five mouse studies. BfR stated that "there was limited evidence of a carcinogenic potential of glyphosate in this mouse strain", leading to the overall conclusion that glyphosate is not carcinogenic.

However, as it turned out, these data were generated by a flawed use of statistical methods. The publication of IARC's monograph on glyphosate (IARC 2015) forced BfR to re-assess its own evaluation. It published its re-evaluation in the Addendum to the RAR, completed on 31 August 2015. In this Addendum BfR admitted that "initially" it had "relied on the statistical evaluation provided with the study reports" (RMS Germany 2015b, p. 36), rather than checking industry's evaluation or performing its own.

BfR's re-assessment of its own statistics in the Addendum to the RAR yielded statistically significant increases for a total of 11 tumour incidences, seen in two rat and five mouse studies. This was the result of applying trend tests to the study results, as recommended in applicable guidance documents.

The finding by Portier (2017) that another eight significantly increased tumour incidences (in six rat studies and two mouse studies) existed that had not even been mentioned by the

industry or identified by the EU authorities is extraordinarily damning. That these were not detected calls into question BfR's claim of having made a "detailed, quality-assured examination of all… original studies and the studies published in the scientific literature", and that "for all chapters [of the RAR] the BfR made its own assessment".* It also casts serious doubts on the thoroughness of the rapporteurs' assessment of ECHA's RAC.

After presenting the results of these re-calculations using the trend test, the authorities continued to use pairwise comparisons as their (unjustified) "gold standard", thereby violating OECD's recommendation that significance in either kind of test should be considered as sufficient to reject the hypotheses that chance was responsible for the increased incidence. EFSA insisted: "No evidence was confirmed by the large majority of experts (with the exception of one minority view) in either rats or mice due to lack of statistical significance in pairwise comparison tests" (EFSA 2015, p.11). Likewise, ECHA concluded: "The increases in tumour incidences were all non-significant in pairwise comparisons with control groups by the Fisher's exact test." (ECHA 2017, p. 52). As explained above, this way of doing the statistical evaluation breached the OECD recommendations.

But it was not the only flaw in the authorities' statistical assessment.

There are good reasons for using one-tailed statistical tests (see "One- or two-tailed statistical tests", above). In particular his applies to the increase in malignant lymphoma in the Kumar (2001) study, which is statistically significant if two arguments described in the guidance documents are taken together. ECHA contends that the Z-test used in the study report is inappropriate, and that "when the more usual Fisher's exact test had been used, p-values of 0.077 or even 0.225 would have been obtained and the significance lost in both sexes", and that "the trend test also provided a p-value above the significance level of 0.05" (BAuA 2016, p. 69) – meaning that it was not statistically significant. However, for males, the p-values were just slightly above 0.05 for both pairwise comparisons and trend tests (see Table 1), meaning that the results were statistically significant when using the one-sided test. The fact that statistically significant increases in malignant lymphoma were seen in two other mouse studies should justify considering this study as relevant. As the OECD states, "declaring a result non-significant… should not be interpreted as meaning the effect is not biologically important" (OECD 2012, p. 118).

In fact, when using a one-sided statistical test (OECD 2012, p.133), significantly increased tumour incidences indicated by p-values below 0.05 (p-values in Table 1 need to be divided by 2) become apparent for trend tests in seven studies, and in addition for pairwise comparisons in four studies. One-sided statistical tests may be considered more appropriate, because for the assessment of the carcinogenic hazard of a pesticide, only an increase in tumours should be considered relevant.

These facts, plus the complete omission of eight significant increases in tumours described above (Portier 2017, Portier and Clausing 2017), cast serious doubts on the scientific validity of the statistical assessments performed by EFSA and ECHA. Only by neglecting OECD's recommendations concerning statistical analyses was EFSA able to conclude that "no evidence of carcinogenicity was observed in rats or mice" (EFSA 2015, p.10).

ECHA's Risk Assessment Committee (RAC) also adopted this approach and came to the same conclusion, supported by a presumed lack of statistical significance in pairwise comparisons. In doing so, ECHA violated its own guidance, which states that "**any** statistical significant increase in tumour incidence, especially where there is a dose-response relationship is generally taken as positive evidence of carcinogenic activity" (ECHA 2015, p. 375, emphasis added).

Weight of evidence

Once statistical significance in tumour increases became difficult to deny for EFSA and ECHA, since it was confirmed by their own evaluations when using trend tests, these agencies turned to a "weight of evidence approach" to defend their conclusion that glyphosate was not carcinogenic. The term "weight of evidence approach" implies that the authorities made a

* According to a letter from the German Ministry of Agriculture, dated 29 June 2015 and signed by Peter Bleser, answering a written inquiry by Harald Ebner, member of the German parliament.

thorough and objective evaluation. However, a closer look at how they applied this approach shows that their methodology was heavily flawed. In fact, if used properly, this approach would support the correct statistical analysis, leading to the clear conclusion that glyphosate is a category 1B carcinogen (see also Clausing 2017).

Reproducibility of the effect between studies

For the mouse studies, a statistically significant increase was seen for renal tumours in three out of five studies, for haemangiosarcoma in two out of five studies, and for malignant lymphoma in three out of three studies (as explained below, for malignant lymphoma, two studies were not valid and should not be taken into consideration). This **qualitative** reproducibility (the fact that an effect was seen) was even acknowledged in ECHA's opinion (ECHA 2017, p. 38), while EFSA, in contrast, flatly claimed "lack of consistency in multiple animal studies" (EFSA 2015, p.11).

Regarding **quantitative** comparisons, these are only legitimate if the studies under consideration are truly comparable, as explained above. This is not the case when they were performed in different laboratories at considerably different times and in animals of different origin or strain. Comparability was not demonstrated by EFSA or ECHA for the five mouse studies under consideration. Thus quantitative comparisons, as made by BfR in its reports for EFSA and ECHA to claim quantitative inconsistency between study results, are scientifically unfounded.

For a similar reason, no toxicologist would base the dose selection for a long-term study on the results of a study performed in a different laboratory, conducted years ago on animals purchased from a different breeding facility or even from a different strain. This illustrates the flaws in the authorities' quantitative comparison of different study results.

Dose-response relationship

Increased tumour incidences were visible at the low and mid doses, as well as the high doses, in a dose-dependent manner (Table 2). This fact, which strongly argues for glyphosate's carcinogenicity, was not taken into consideration by EFSA or ECHA. Moreover, these effects were statistically significant in trend tests. This last fact needs to be seen in the context that a "trend test… asks whether the results in all dose groups together increase as the dose increases" (OECD 2012, p. 116).

In some of the studies in which tumours were observed only at the top dose, dose-dependence might have become apparent with a study duration of 24 months. This applies to haemangiosarcoma in the 18-month study by Atkinson et al. (1993) and to haemangiosarcoma and renal tubular adenoma in the 18-months study by Sugimoto (1997) – see Table 1 for details.

Study	Tumour type	Dose Group			
		Control	Low	Mid	High
Knezevich & Hogan (1983)	Renal carcinoma	0	0	1	2
Kumar (2001)	Malignant lymphoma	10	15	16	19
Kumar (2001)	Renal tubular adenoma	0	0	1	2
Wood et al.	Malignant lymphoma	0	1	2	5

Table 2: Tumour incidences in male mice with dose-dependent increases (for further details, see Table 1)

Appropriateness of the doses used in the studies

EFSA dismissed significant carcinogenic effects in glyphosate-treated animals with the justification that these were so-called high-dose effects that occurred only above the alleged limit dose of 1,000 mg per kg of body weight (see above). But this argument is not correct and is not supported by the applicable OECD guidelines (OECD 2009a, 2009b), or by the data provided with the study reports.

First, the presumed 1,000 mg/kg limit dose does not exist for carcinogenicity studies. The "limit dose" of 1,000 mg per kg of body weight mentioned In OECD Guideline 453 (for combined carcinogenicity and chronic toxicity testing) refers to "the chronic toxicity phase of the study" (OECD 2009b, p. 6). Neither this guideline nor OECD Guidance 116 refers to carcinogenicity testing when mentioning this limit dose. In addition, OECD Guideline 451 (guideline for carcinogenicity testing) does not mention a "limit dose" of 1,000 mg per kg of body weight at all.

In fact, in chronic toxicity tests, OECD Guidance 116 recommends a maximum of 50,000 mg of test compound per kg of diet for "nutritional and possibly other physiological reasons" (OECD 2012, p. 54), which would translate into a dose of approximately 5,000 mg/kg body weight for mice and 2,500 mg/kg body weight for rats. Both doses are significantly higher than EFSA's alleged limit dose. Thus EFSA appears to have manufactured an argument to dismiss the carcinogenic effects of glyphosate.

Second, a statistically significant increase for malignant lymphoma was seen in the Wood et al. (2009) study with a top dose of 810 mg per kg of body weight. Besides, this increase was dose-dependent.

Likewise, an increased incidence in malignant lymphoma was seen in the Kumar (2001) study with a top dose of 1,460 mg/kg, again with dose-dependence. This effect was statistically significant using the one-tailed test for both pairwise comparison and trend test.

Finally, EFSA and ECHA claimed that "excessive toxicity" was observed in dose groups above 1,000 mg glyphosate per kg of body weight. But this is not true. As confirmed in the ECHA opinion: "no treatment-related reductions in survival were observed" in the 5 mouse studies (ECHA 2017, p.41). Furthermore, no histopathological changes typical for excessive toxicity were reported (RMS Germany 2015a).

The only presumed excessive toxicity supported by data was an over 15% decrease in body weight gain in high-dose groups in the Knezevich and Hogan (1983) and Sugimoto (1997) studies (RMS Germany 2015b, p. 2; ECHA 2017, p. 41). However, for the Sugimoto (1997) study, for which food consumption data are available in the RAR, it becomes obvious that the reduced body weight gain was associated with a similar decrease in food consumption (RMS Germany 2015a, p. 522). This is not surprising when 1 kilogram of food contains 30 or 40g of glyphosate, probably affecting palatability, but it has nothing to do with excessive toxicity.

For the other two studies, no food consumption data are available in the RAR. But the unaffected lifespan of the high-dose groups, the lack of excessive histopathological changes, and the association between a reduced body weight gain and reduced food consumption, are clear evidence that the contention of excessive toxicity is wrong.

In sum, the EU authorities' statement that carcinogenic effects were only seen at excessive doses and the application of the 1,000 mg/kg "limit dose" by EFSA are further examples of a false "weight of evidence" approach.

Historical control data

The EU authorities used historical control data as one of their main arguments to dismiss the significant tumour findings described in the Addendum to the RAR (RMS Germany 2015) and the CLH Report (BAuA 2016).

On the one hand, the strong recommendations given by OECD (2012) and ECHA (2015) – that the comparison with the concurrent control group should always be given the highest priority and that historical control data should be used with caution, applying strict rules – were ignored. Thus the EU authorities

violated these general rules, as described below.

Furthermore, the valid historical control data actually supported the conclusion that glyphosate was carcinogenic. This fact was either ignored or insufficiently taken into consideration by the authorities.

The available historical control data for the Kumar (2001) and the Sugimoto (1997) studies actually support the study findings that glyphosate is carcinogenic. Study-specific historical control data for the Wood et al. (2009) study were useless. To use the German authorities' own words, "the quality and regulatory value of the historical control data is very much compromised by the fact that the sexes were not considered separately. Moreover, the data were apparently not all obtained from the same laboratory but, instead, also from other testing facilities of the Harlan group in Europe" (RMS Germany 2015a, Volume 3.B.6, p. 517).

While the Kumar (2001) study was dismissed using other arguments (see "An inconvenient study", below), the authorities claimed that the historical control data for the Sugimoto (1997) study supported the conclusion of non-carcinogenicity, because the observed incidence in the high-dose group (12%) was below the upper limit of the historical control data range (19%).

But this is not true. According to the authorities' own report, eight out of the nine studies forming the historical control data had an incidence of malignant lymphoma of 6% or lower (RMS Germany 2015a, Volume 3.B.6, p. 528). In contrast, the high-dose group of the Sugimoto (1997) study had an incidence of 12%. In other words, this high-dose group had an incidence at least twice as high as eight out of nine historical control data groups. This actually supports the conclusion that the significant increase in malignant lymphoma in this high-dose group is a true effect from glyphosate. But the BfR and EFSA resorted to using a single "rogue" outlier* of 19% in this database to make their argument.

While neglecting study-specific historical control data or using them contrary to the evidence, EFSA and ECHA frequently referred to data compiled by Giknis and Clifford (2000, 2005) to "prove" that the carcinogenic effects caused by glyphosate were within the simple range of historical controls. These compilations were the tumour incidences in Crl:CD1 mice from control groups used in 51 studies performed in 7 different laboratories and initiated between January 1987 and December 1996 (Giknis and Clifford 2000), or used in 59 studies performed in 11 different laboratories and initiated between 1987 and 2000 (Giknis and Clifford 2005).

This is an extreme violation of the recommendations given by OECD and EFSA (OECD 2012, ECHA 2015). The EU authorities should have used interquartile ranges of study-specific historical control data from the same laboratory within the last five years from the same strain and origin of animals. But instead they used simple ranges of data collected from seven or 11 different laboratories over 10 or even 15 years to support their dismissal of statistically significant increases of tumour incidences over concurrent control groups – the control groups which, according to OECD Guidance 116, should always be the most important consideration. In addition, in case of the Sugimoto (1997) study, they compared the results obtained from Crj-mice with historical control data from Crl-mice.

In conclusion, ECHA and EFSA need to re-evaluate their assessment, respecting the proper use of historical control data.

Carcinogenic effects seen only in one sex

ECHA claims that tumour effects were seen only in one sex: males. Restriction of an effect to one sex is part of the weight of evidence considerations, according to Regulation (EC) 1272/2008. This is the only argument used by the EU authorities that has some degree of credibility. But even this aspect has to be put into perspective.

In fact, significant increases in tumour incidences were also seen in females. This applies to malignant lymphoma in mice in the Kumar

* See paragraph on historical control data in section "Scientific methods to reduce uncertainties".

(2001) study (RMS Germany 2015a, Volume 3 B.6), to thyroid C-cell adenoma in rats in the Stout and Ruecker (1990) study, and – as uncovered by Portier (2017) – to haemangiosarcoma in mice in the Sugimoto (1997) study. In other words, carcinogenic effects were mostly seen in male animals, but not exclusively.

Most importantly: "Effects seen only in one sex in a test species may be less convincing than effects seen in both sexes… However, there is no requirement for a mechanistic understanding of tumour induction in order to use these findings to support classification" (ECHA 2015, p. 377–378). In other words, if a carcinogenic effect is seen only in one sex, a mechanistic understanding of this sex difference is desirable, but it is not a requirement. Besides, the "one-sex-only" issue is just one of many considerations in the weight of evidence approach (ECHA 2015), while other aspects of the weight of evidence approach that were wrongly used by the authorities (consistency across studies, dose-dependence and comparison with the available valid historical control data) actually support the conclusion that glyphosate is carcinogenic, if the criteria are applied properly. Adding to the weight of evidence is the observation of an increased risk for non-Hodgkin lymphoma in epidemiological studies and the identification of plausible mechanisms for carcinogenicity (oxidative stress and genotoxicity), as described by IARC (2015).

Study selection

Study selection – the decision to keep or dismiss certain studies – is an important way either to strengthen the validity or to manipulate the overall outcome of an assessment.

A total of seven rat and five mouse studies were available for the overall assessment as to whether glyphosate is carcinogenic or not.

While statistically significant increases of tumour incidences were demonstrated for an array of different tumour types in a total of two rat and five mouse studies, the evidence for malignant lymphoma was most compelling. However, even for malignant lymphoma, EFSA and ECHA concluded that there is no evidence for carcinogenicity. The EU authorities base their arguments on "lack of dose-response relationship", restriction of the tumour effects to a "high-dose phenomenon" and lack of "consistency across studies".

In order to give those arguments some degree of credibility, the authorities had to exclude one particular study from consideration and to keep another study in the game, although the latter study was severely compromised with regard to malignant lymphoma.

In this section we question the credibility of study selection by EFSA and ECHA, which ultimately leads us to question the overall conclusion drawn by EFSA and ECHA.

Three arguments played an important role in declaring the observed statistically significant tumour findings as irrelevant:

- The claim of "lack of consistency" between studies
- The claim that glyphosate's carcinogenic effects were a "high-dose phenomenon"
- The claim that all tumour findings were within historical control ranges.

An inconvenient study

Regarding all three arguments listed above, the finding of an increased incidence of malignant lymphoma in the Kumar (2001) mouse carcinogenicity study was an obstacle. Most importantly, the Kumar (2001) study and the Wood (2009) study comprised two separate studies showing a clearly dose-dependent, statistically significant increase in the same tumour type, at doses that could not be accused of being a "high-dose phenomenon". Moreover, the Kumar (2001) study was one of two studies with valid historical control data that clearly supported the conclusion that the observed increase in malignant lymphoma was real. In contrast, the EU authorities used invalid historical control data for the other studies to claim that increased tumour incidences were within historical range and thus could be dismissed.

Clearly the Kumar (2001) study proved a challenge to the authorities' case that glyphosate was non-carcinogenic. This explains why the

exclusion of this particular study from further consideration was so important.

Let's consider first how EFSA dealt with this inconvenient study. In November 2015 EFSA wrote that "no evidence of carcinogenicity was observed in rats or mice" (EFSA 2015). Although in its Addendum to the Renewal Assessment Report (RAR), BfR had demonstrated statistically significant increases in one or several tumour types in seven rodent carcinogenicity studies, EFSA insisted that there was only one mouse study – Kumar (2001) – with statistical significance. However, EFSA declared the study "not acceptable due to viral infections that could influence survival as well as tumour incidence – especially lymphomas" (EFSA 2015, p. 10).

The alleged "viral infections" were the key argument. But while this argument was used over and over again, the way in which it was used was contradictory. The RAR refers to a reported earlier or even in the studies described in this RAR".

However, in EFSA's conclusion, which is based on the RAR (finalized on 31 March 2015) and a teleconference of EFSA's experts on 29 September 2015, the "possible association" turned into evidence. EFSA assessed the Kumar (2001) study "as not acceptable due to viral infections that could influence survival as well as tumour incidence – especially lymphomas" (EFSA 2015, p. 10).

Then, in the draft CLH Report, the "viral infections" claimed by EFSA disappeared:

"During a teleconference (TC 117) on carcinogenicity of glyphosate hold by EFSA (EFSA, 2015, ASB2015-12200), it was mentioned by an US EPA observer that the Kumar (2001, ASB2012-11491) study had been excluded from US EPA evaluation due to the occurrence of viral infection that could influence survival as well as

which the animals used in the glyphosate studies were obtained. During a teleconference (TC 117) on carcinogenicity of glyphosate hold by EFSA (EFSA, 2015, ASB2015-12200), it was mentioned by an U.S. EPA observer that the Kumar (2001, ASB2012-11491) study had been excluded from U.S. EPA evaluation due to the occurrence of viral infection that could influence survival as well as tumour incidences, especially those of lymphomas. However, in the study report itself, there was no evidence of health deterioration due to suspected viral infection and, thus, the actual basis of EPA's decision is not known.

On request of the DS, reliable historical control data was provided by the Japanese laboratory in which the study by Sugimoto (1997, ASB2012-11493) had been run. In male Crj:CD-1 (ICR) mice, incidence of malignant lymphoma in this laboratory varied very much. It ranged from 3.85% to 19.23% in the control groups from 12 studies that had been performed between 1992 and 1998 (Kitazawa, 2013, ASB2014-9146). Thus, the 12% incidence at the top dose level in the study with glyphosate was well covered by the range even though it was above the mean value of 6.33%. (In

Box 4 (BAuA 2016, p. 72)

possible association between malignant lymphoma and an infection of the animals with oncogenic (cancer-causing) viruses, based on a quote from the scientific literature: "The authors ascribed these tumours mainly to 'infectious expression of murine leukemia viruses'" (RMS Germany 2015a, Volume 3 B.6, p. 511). Yet in the next sentence, BfR makes clear that no evidence exists for such an infection in any of the carcinogenicity studies performed with glyphosate, including in the Kumar (2001) study: "It is not known to which extent such a latent infection might have contributed to lymphoma incidences tumour incidences, especially those of lymphomas. **But in the study report itself, there was no evidence of health deterioration due to suspected viral infection and, thus, the actual basis of EPA's decision is not known**" (BAuA 2016, p. 72, emphasis added).

US EPA observer identified

On 15 May 2017 Jose Tarazona, head of EFSA's Pesticide Unit, confirmed the name of the US EPA observer at the EFSA teleconference in September 2015. It was Jess Rowland, who left the US EPA in 2016. At the time of the EFSA

teleconference, Rowland was the chair of the EPA's Cancer Assessment Review Committee (CARC), which was assessing the carcinogenicity of glyphosate. This is of particular significance, because documents recently released (http://bit.ly/2tjvmIb) by the US district court in San Francisco show that Rowland was in close contact with Monsanto behind the scenes. According to Monsanto employee Daniel Jenkins, Rowland, referring to another agency's planned investigation into the health risks of glyphosate, told him on the phone, "If I can kill this I should get a medal". Rowland told Jenkins, "I am the chair of the CARC and my folks are running this process for glyphosate in reg[ulatory] review".

The fact that in EFSA's and ECHA's documents no further evidence of the claimed viral infections is available is a strong indication that the dismissal of the Kumar (2001) study was based solely on Rowland's unsubstantiated testimony during the September 2015 teleconference.

Therefore it appears that EFSA's conclusions may have been unduly influenced by Monsanto.

ECHA's RAC warned of a virus infection in spite of an admitted lack of evidence and no information as to where this claim actually came from. In its opinion, referring to the CLH report, EFSA's RAC insisted upon "a possible role of oncogenic [cancer-causing] viruses" (ECHA 2017 p. 30) – which it apparently deemed sufficient argument to exclude this important study from the overall assessment. This becomes obvious on page 41 of ECHA's opinion, where the conclusion about the "biological and human relevance of the findings" completely ignores the Kumar (2001) study.

Historical control data indicates cancer-causing virus not a problem

Another indication that the Kumar (2001) study was not affected by oncogenic viruses comes from the historical control data. The incidence of malignant lymphoma in the control group of the Kumar (2001) study – 20% – was almost identical to the 18.4% of the historical control database (5 studies between 1996 and 1999, BAuA 2016, p. 67).

If oncogenic viruses were the cause of malignant lymphoma in the Kumar (2001) study, one would expect a clearly higher incidence as compared to the historical control data.

The author of this report asked ECHA whether the 18.4% incidence in the historical control database should be considered as indication that oncogenic viruses did not play a role in the Kumar (2001) study. The question remained unanswered.

Invalid study kept in the EU assessment

A second study, the mouse carcinogenicity study by Atkinson (1993), now comes into play. With regard to malignant lymphoma, this study is useless, because only lymph nodes with macroscopic changes were assessed histopathologically (RMS Germany 2015a, BAuA 2016). It is impossible to make a judgment about the real incidence of malignant lymphoma in groups of 50 animals, when only those animals that had macroscopic changes (changes visible to the naked eye) in the lymph nodes were examined.

Moreover, the way in which the incidences are presented in the RAR and CLH Report is simply wrong. It is incorrect to calculate the incidence of malignant lymphoma as a percentage of the total number of animals per group, if only those animals with macroscopic changes were assessed. These obvious deficiencies were explicitly criticized in Pesticide Action Network Germany's public comment on the CLH Report (Pesticide Action Network Germany 2016). ECHA mentioned these deficiencies briefly on page 40 of its opinion, but then ignored them in its overall assessment (ECHA 2017, p.41), nourishing the suspicion that this was done on purpose.

Keeping the Atkinson (1993) study as valid helped to rescue the chain of arguments that the observed increase in malignant lymphoma was coincidental and not related to glyphosate treatment. The use of this invalid study, combined with the use of the wrong statistical analyses (see above), supported the EU authorities' claim of inconsistent results across studies.

Malignant lymphoma was reported in a total of four mouse carcinogenicity studies (in a fifth

study it was "assumed" that "lymphoreticular neoplasms" correspond to malignant lymphoma).

As was shown above, if the methods of assessment, including the statistical analysis, had been applied correctly, there would be three mouse studies remaining with regard to malignant lymphoma: Sugimoto (1997), Kumar (2001), and Wood (2009).

- In all three studies, the finding of malignant lymphoma was statistically significant when the Cochran Armitage trend test was used (in one case, significance was achieved only with the one-tailed statistical test).

- In two of the studies, the term "high dose phenomenon" was not applicable, and in the third study, no excessive toxicity was seen.

- These two studies also showed a clear dose-response relationship between glyphosate treatment and malignant lymphoma.

As seen above, one of these studies – Kumar (2001) – was excluded by the authorities, using highly questionable arguments. And another study – Atkinson (1993) – that was severely deficient in the histopathological assessment of malignant lymphoma was kept as part of the assessment and served to strengthen the claims of lack of statistical significance (in pairwise comparison) and lack of dose-dependence. In this way it became possible for BfR, EFSA and ECHA's RAC to contend that there were "inconsistent results across studies".

Conclusion

This report shows that the ECHA opinion on glyphosate was not developed in accordance with relevant European regulations or with ECHA and OECD guidance. As such it is legally and scientifically flawed.

Moreover, the "contra-factual" conclusion that glyphosate is not carcinogenic was transmitted from the European Food Safety Authority (EFSA) to the European Chemicals Agency (ECHA).

While IARC reviewed a smaller number of studies, its rigorous and systematic evaluation led it to conclude that glyphosate is "probably carcinogenic to humans" (IARC 2015). Serious concerns about the integrity of EFSA's and ECHA's assessments of glyphosate arise from their failure to comply with Regulation (EC) 1272/2008 and the applicable OECD and ECHA guidance documents and guidelines. Specifically the authorities are guilty of the following:

- Strongly violating the recommendations in OECD (2012) and ECHA (2015 guidance for the statistical analysis of tumour incidences
- Failing to detect eight additional significant increases of tumour incidences not mentioned in the study reports by industry
- Failing to acknowledge existing dose-response relationships for kidney tumours and malignant lymphoma in at least three different studies. These studies support the conclusion that the observed increases in tumour incidences are a true effect, visible at least from the mid-dose group
- Failing to consider multi-site responses seen in five different studies as supporting the strength of evidence. Regulation (EC) 1272/2008 defines multi-site responses as an important factor to strengthen the evidence for carcinogenicity
- Making false statements that carcinogenic effects by glyphosate were only seen at excessive toxicity levels, not taking into consideration existing dose-response relationships, manufacturing an alleged "limit dose" of 1,000 mg/kg, and misinterpreting reduced body weight gain.
- Using historical control data in flawed and false ways as an argument to dismiss the observed increased tumour rates in glyphosate-treated animals.

Additional concerns arise from unresolved questions about the selection of studies taken into consideration. One study supporting the conclusion that glyphosate could induce malignant lymphoma was excluded from consideration, possibly due to influence from a former US EPA employee who is suspected of having colluded with Monsanto. Another study that the EU authorities used to show that glyphosate does not induce malignant lymphoma was severely flawed and therefore useless with regard to the assessment of this type of cancer.

The conclusions and proposals currently offered by the authorities jeopardize the health of an unknown percentage of more than 500 million EU citizens. To restore the public trust into EFSA and ECHA that has been continuously lost during the course of the last two years, a thorough, independent, and honest re-assessment of the regulatory documents on glyphosate must be performed.

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