

# 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

Three authorities have testified that glyphosate is not carcinogenic: first, the German Federal Institute for Risk Assessment (BfR – in charge of the evaluation of glyphosate in the EU); then the European Food Safety Authority (EFSA); and finally, the European Chemicals Agency (ECHA). BfR produced the assessment report for EFSA, followed by another for ECHA.

In contrast, the International Agency for Research on Cancer (IARC) classified glyphosate as “probably carcinogenic to humans”. This second-highest of the possible classifications resulted from consideration of the following findings:

- “Sufficient evidence” of a carcinogenic effect in experimental animals
- “Strong evidence” of two possible mechanisms for the carcinogenicity of glyphosate

- “Limited” epidemiological evidence of a carcinogenic effect in humans.

The following assessment of the animal studies by the EU authorities shows that the authorities

- disregarded and brushed aside clear evidence of a carcinogenic effect in experimental animals, and
- violated the very OECD and ECHA directives and guidelines that are supposed to guide their work.

The results of animal studies on rats and mice are, according to Regulation (EC) 1272/2008, of fundamental importance:

**A substance is to be considered carcinogenic, if two independently conducted animal studies show an increased tumour incidence.**

**In the case of glyphosate, at least seven out of twelve such long-term studies found an increased tumour incidence.**

In spite of these findings, the authorities arrived at the conclusion that glyphosate is not carcinogenic. This conclusion was only made possible by violating Regulation (EC 1272/2008), the ECHA Guidance of 2015, and the 2012 OECD Guidance, as well as through non-disclosure and distortion of the facts. The five most important violations are described below.

## 1. Non-compliance and distortion in the statistical analysis

There are two types of statistical methods to determine whether tumours observed in test animals are caused by the tested substance – “trend tests” and “pairwise comparisons”. Statistically significant results in either kind of test must be taken into account, as stated by the 2012 OECD Guidance 116 and the CLP (classification, labelling and packaging) Guidance (ECHA 2015).

Initially, the German Federal Institute for Risk Assessment (BfR) failed to recognise numerous significant tumour incidences, due to its failure to apply a “trend test”. It had instead relied on the “pairwise comparisons”, as used in the industry study reports. Those had only indicated a carcinogenic effect of glyphosate for a single type of tumour in a single study.

Due to the IARC monograph on glyphosate, which was published in July 2015, the BfR re-assessed its own evaluation. As a result, the above-mentioned significant incidences in seven out of twelve studies were acknowledged.

Nevertheless, the BfR – and the EU authorities, which relied on the BfR’s groundwork – failed to notice a further eight significant tumour effects. These additional incidences were recently identified by Professor Christopher Portier, former director of the US National Center for Environmental Health at the Centers for Disease Control and Prevention in Atlanta, after he analysed the data of the otherwise undisclosed industry studies.

The authorities played down the tumour incidences in the two rat and five mouse studies now known to them, by declaring significance in a “pairwise comparison” a mandatory requirement in order for the incidences to be considered relevant. “Trend tests”, on the other hand, were only mentioned, but flagged as inadequate. This constitutes a violation of the relevant OECD Guidance, as such a requirement does not exist. According to this Guidance, if in either of the two testing methods, **no matter which**, there is significance, the hypothesis that the tumours occurred by chance and not due to the chemical being tested is to be considered

refuted. As is clearly stated by the OECD Guidance 116: “Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result” (p. 116).

## 2. Alleged “high-dose effects”

To weaken the significance of the now obvious tumour incidences, the BfR and EFSA claimed:

- i. There was a maximum limit of 1,000 mg per kg of body weight as the highest dose with which test animals should be treated with per day, and
- ii. The observed tumour incidences only presented due to “excessive toxicity”.

However, item (i) is entirely fictitious. A review of applicable guidelines shows that a maximum of 1,000 mg/kg per day, also called a “limit dose”, does not exist for cancer studies. This definition was implicitly adopted from another type of study.

Moreover, item (ii) cannot stand up to scientific scrutiny. The only presumed “excessive toxicity” supported by the data consists of a lower body weight of animals in the high-dose group in a very few studies. However, these animals’ food consumption was reduced correspondingly with their body weight, which probably resulted from the altered palatability of the food due to the mixed-in glyphosate. Hence it is unlikely to involve any “excessive toxicity”. The lifespan of the test animals was not affected and there were no other pathological findings in the tumour-affected organs apart from the tumours.

In sum, the argument relating to “high-dose effects” has no scientific merit and appears to have been introduced in an attempt to discredit the determined tumour incidences.

## 3. Alleged lack of dose-response relationships

When an effect increases with an increasing dosage of a substance, toxicologists call this a “dose-response relationship”. When there is

such a relationship, the effect is considered to be of particularly high significance. This does not mean, however, that an effect is irrelevant if it is only observed in the highest dose group.

The full report provides evidence that in the mouse studies alone, four cases of clear dose-response relationships could be substantiated. Furthermore, trend tests are – in contrast to pairwise comparisons – capable of capturing dose-response relationships. The OECD Guideline states accordingly:

**// A trend test ... asks whether the results in all dose groups together increase as the dose increases. //**

– (OECD Guideline 116, p. 116).

In the glyphosate studies, significant tumour effects were predominantly verified with trend tests.

BfR, EFSA and ECHA avoided mentioning existing dose-response relationships in the observed tumour effects. At the same time, they emphasised the lack of such a relationship in other tumour incidences. This suggests that the authorities tried to cover up evidence for the carcinogenic effects of glyphosate.

#### **4. Incorrect and distorted use of “historical control data”**

“Historical control data” are the compiled data from untreated control animals in previous studies. Such data can, in certain circumstances, assist in validating study results. Cancer studies are particularly concerned with the occurrence of “spontaneous” tumours.

As in humans, the prevalence of spontaneous occurrence of tumours can be influenced by numerous factors, such as stress, diet and genetic predisposition. These factors vary between different experiments. For this reason, relevant guidance documents state that the most important factor in the assessment of results is always the comparison of treated animals with the concurrent control group. Recourse to “historical control data” should only be taken where there are serious doubts regarding the

test results, and only with the application of strict rules: comparisons can be made only with animals from the same strain, from an experiment conducted in the same laboratory, and within a maximum period of five years of the experiment under question.

In the case of glyphosate, the authorities not only violated all these restrictions on a grand scale, but also distorted the facts beyond recognition. The authorities declared outliers in the historical controls to be the norm. The most absurd example in this regard is a 1997 mouse study, where the historical control data supported the significant tumour incidence in eight out of nine studies. However, the authorities utilised only data from the ninth study, which had an extremely high tumour incidence, to discredit the relevance of these tumour incidences.

Studies for which suitable historical controls were available, and which confirmed the observed tumour effect, were disregarded by the authorities. Other clearly inadmissible historical control data were utilised by the authorities to deny significant tumour effects – a clear violation of guidance documents and guidelines.

In sum, the argument of historical controls, as constructed by the authorities, is a house of cards that collapses as soon as scientific standards and OECD guidelines – or even ECHA’s own guidelines – are applied.

#### **5. Arbitrary selection of studies**

The observed tumours of the lymphatic system (malignant lymphoma) were a particularly clear effect of glyphosate in the mouse studies. Three studies demonstrated a statistically significant increase in these tumours. In two of them, a clear dose-response relationship was evident. In the third study (conducted in 1997), the effect was only observable at the highest dose. Epidemiological studies also indicate an increased risk for the development of cancer in the lymphatic system (non-Hodgkin’s lymphoma) through contact with glyphosate in humans.

According to the assessment of the EU authorities, no increase of malignant lymphoma

after treatment with glyphosate was observed in two other mouse studies. But on closer examination, one of them was completely unfit for consideration due to its serious deficiencies. The other was of questionable value due to its ambiguous use of terminology. Nevertheless, the authorities took both studies into full consideration – as “proof” that glyphosate is harmless.

The three studies that demonstrated a significant increase in malignant lymphoma due to treatment with glyphosate suffered a fate that highlights the authorities’ biased assessment process.

The 1997 study was excluded from the evaluation by using absurdly distorted historical control data (see point 4 above). One of the two studies with dose-dependent effects (Kumar 2001) was classified by EFSA as unusable due to an alleged viral infection. But in its report prepared for ECHA, BfR conceded that there was no evidence for such an infection. The sole “evidence” for the alleged infection was a comment by a US EPA official during a telephone conference. Nevertheless, the study was only considered with reservations.

This process is of a dubious nature, which is emphasized further by Monsanto in-house emails that were recently released by a court in San Francisco. In these emails, the US official is presented as an industrious helper of the corporation who boasted that he should “get a medal” if he succeeded in killing another agency’s investigation into glyphosate’s health effects.

The conclusion of the authorities that glyphosate does not cause malignant lymphoma is therefore based on three studies. Two of these, which serve as negative evidence, were useless or of doubtful value upon closer inspection. For a third study, which demonstrated a significant and dose-dependent increase in malig-

nant lymphoma, the EU authorities apparently fabricated a “devaluation” by disregarding the correct statistical analysis and justifying this with historical control data, which were used in flawed and false ways.

Another study, for which BfR and EFSA originally acknowledged a statistically significant increase in malignant lymphoma, was dismissed by claiming a viral infection for which – according to ECHA’s report – there was no evidence.

## **Conclusion**

Altogether, twelve rat and mouse studies were available to the authorities for assessment. At least seven of those demonstrated significant increases in tumours following exposure to glyphosate. The EU authorities failed to acknowledge this, using highly questionable arguments, and in clear violation of existing guidance documents.

Political decision-makers should not play along with the pesticide industry in this scientifically questionable and, as it seems, interest-driven game. Instead they should be objective in their assessment of glyphosate, ensure that the existing scientific evidence is evaluated correctly, and apply the precautionary principle to guarantee a high level of protection for humans and the environment. The health of 500 million EU citizens is at stake.