# Explanatory note

On an opinion proposing harmonised classification and labelling
at EU level of

**glyphosate (ISO); N-(phosphonomethyl)glycine**

**EC Number: 213-997-4**
**CAS Number: 1071-83-6**

**This note has been prepared by ECHA, based on the opinion of the Committee for Risk Assessment (RAC) as adopted on March 15, 2017**

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# Background

The Classification Labelling and Packaging Regulation (CLP)[1] contains detailed criteria for assigning a classification under many different hazard classes. Extensive technical Guidance[2] in support of classification decisions is available.

The ECHA Committee for Risk Assessment (RAC) was set up under Article 76 of REACH[3] as part of the European Chemicals Agency and its role and responsibilities are set out in Article 77(3). One important part of its duties is the evaluation of proposals submitted by Members States to harmonise the classification and labelling of substances under CLP in the EU. The members of RAC are nominated for a three-year term by their EU/EEA Member States but are appointed in their personal capacity as scientists by the Management Board[4] of ECHA. RAC appoints one or two rapporteurs to each CLP dossier with the responsibility of drafting the opinion and ensuring that the views of the Committee are appropriately reflected in the final draft for adoption. Given the exceptionally large volume of studies to be examined in the case of glyphosate, a rapporteur and co-rapporteur were appointed in addition to an *ad hoc* working group comprised of six regular members, in order to support the Rapporteurs in their work.

The dossier proposing classification of glyphosate was submitted by Germany on 17 March 2016. Once declared in accordance, the dossier was the subjected of a public consultation from 2 June to 18 July 2016. The results of this consultation are contained in a Response to Comments document which provides both the Dossier Submitter's and the RAC Rapporteurs' responses to the submitted comments.

RAC's task was to evaluate whether the potential hazards of the active substance **glyphosate ISO** should be classified under CLP. Data related to glyphosate-based herbicidal products was not therefore considered, except in the case of human epidemiology. As with all RAC opinions under CLP, the Committee's work is restricted to an evaluation of the hazards, i.e. arising from the intrinsic properties of the specific chemical. The risks to humans or the environment arising from the use of glyphosate containing products are not addressed in this evaluation.

CLP specifically requires an evaluation on the basis of available information. The Dossier Submitter plays a key role in selecting the most scientifically robust studies in their proposal. To consolidate the database, RAC evaluates and adds to the relevant material from the Dossier Submitter, the Public Consultation and the recent literature.

As it is obligatory for the Chemical Industry in the EU/EEA to demonstrate the safety of their substances, most studies are therefore commissioned by Industry. However, data available in the public domain is also used. Where animal studies are concerned, RAC in following both the CLP and REACH Regulations prioritises from among the animal studies, those carried out

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[1] Regulation (EC) 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures, etc.

[2] Guidance on the Application of the CLP Criteria - Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures, Version 4.1, 2015, 644p. https://echa.europa.eu/documents/10162/23036412/clp_en.pdf/58b5dc6d-ac2a-4910-9702-e9e1f5051cc5

[3] Regulation (EC) 1907/2006 on Registration, Evaluation Authorisation and Restriction of Chemicals (REACH)

[4] The ECHA Management Board is composed of 28 representatives from EU Member States, appointed by the Council, three Commission representatives and two independent members appointed by the European Parliament.

according to internationally standardised Guidelines and under the system of OECD Good Laboratory Practice[5]. Human epidemiology studies are assessed on a case-by-case basis.

The CLP Regulation requires that a weight of evidence approach is applied to the process of evaluating a dossier. Guideline and non-Guideline studies are included and considered when all the evidence is weighed together to reach a conclusion. With multiple studies, where the CLP classification criteria cannot be applied directly, e.g. to a single key study, then all the available information bearing on the determination of hazard is considered together.[6] The quality and consistency of the data is given appropriate weight. Both positive and negative results are assembled together in a single weight of evidence determination. Where the information from each single source alone is regarded as insufficient, the weight of evidence from several independent sources may lead to the conclusion that a substance has or has not a particular dangerous property[7]. The role of epidemiology data is specifically considered[8].

RAC meetings are attended by regular[9] and occasional stakeholder organisations as observers representing civil society including trade unions, as well as industry. In preparation for the Committee's discussions on Glyphosate, ECHA invited interested parties to present their views to RAC at its 39th meeting in December 2016. This included presentations from the International Agency for Cancer Research (IARC), The FAO/WHO Joint Monitoring Programme on Residues (JMPR), The Glyphosate Task Force, The European Food Safety Authority (EFSA), the Health and Environment Alliance (HEAL), and the German Dossier Submitter (BAuA)[10].

# Summary recommendations on the specific hazard classes evaluated by RAC

### *Acute Toxicity*

Acute toxicity addresses the lethality of a substance, after short-term oral, dermal or inhalation exposure. More than 20 studies addressed oral or dermal acute toxicity and a further 13 studies examined inhalation toxicity of glyphosate. The doses at which deaths were observed after single oral or dermal exposures or via inhalation led RAC to conclude, in line with the Dossier Submitter's proposal that no classification for acute toxicity is justified for glyphosate.

### *STOT SE (Specific Target Organ Toxicity – Single Exposure)*

STOT SE categories 1 and 2 refer to effects on target organs in the body after single exposure. Classification for STOT SE category 3 addresses specifically narcotic effects and irritation of the respiratory tract.

In a number of acute toxicity studies in rats and mice, the effects were confined to very high doses and were non-specific. Furthermore, no evidence of neurotoxicity was observed in an acute neurotoxicity study in rats even at doses greater than the upper threshold for classification for acute toxicity, or in any of the other toxicity studies. RAC therefore agreed with the Dossier

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[5] Good Laboratory Practice is an OECD developed quality system and is mandatory in the EU/EEA, the USA and Japan for the testing of chemicals. It is central to the credibility of studies and GLP accredited laboratories undergo regular facility inspection. The archived study files are open to inspection by the National GLP inspectorate.

[6] CLP Art 9(3) + Annex I: 1.1.1

[7] REACH Annex XI, Section 1.2

[8] CLP Annex I: 1.1.1.4

[9] EEB (European Environment Bureau), ETUI (European Trade Union Institute), CONCAWE, EuCheMS (European Association for Chemical and Molecular Sciences), CEFIC (European Chemical Industry Council), ECPA (European Crop Protection Association and Eurometaux (European Non-ferrous Metals Association)

[10] These presentations are the responsibility of their respective authors; they provide valuable background to the current opinion and these contributions are gratefully acknowledged. They are available at https://echa.europa.eu/chemicals-in-our-life/hot-topics/glyphosate

Submitter that no classification for STOT SE categories 1 or 2 was considered appropriate. Furthermore, a classification with STOT SE 3 (narcotic effects), was not considered relevant since no narcotic effects were reported in the toxicity studies.

There was no data from humans to support classification with STOT SE 3 for respiratory tract irritation. Although a variety of relevant clinical signs were observed in animals in a number of acute toxicity studies conducted via the inhalation route, they were not seen consistently in the studies and did not always occur together but in isolated studies. These effects were considered to be transient in nature. RAC therefore concluded in agreement with the Dossier Submitter that there was not sufficient evidence amongst these studies to meet the CLP criteria for classification for STOT SE 3 (respiratory tract irritation).

***Skin corrosion/ irritation***

Skin Corrosion and irritation mean respectively the production of irreversible or reversible damage to the skin. Nine out of 11 studies addressing the effects of glyphosate on skin irritation were negative, and the results from the remaining two studies (very slight erythema in one animal that had, in each study, cleared within 24 hours) clearly indicated that no classification was warranted. There was very limited information on skin irritation in humans and where it was reported, it was unclear whether it was related to glyphosate or co-formulants in glyphosate-based herbicides. Thus, RAC agreed with the Dossier Submitter that no classification for skin irritation is warranted.

***Eye damage/ irritation***

Serious eye damage means the production of damage to the eyes, which is not fully reversible. Glyphosate has an existing classification (from 1999) for eye damage (category 1 - causes serious eye damage). Thirteen studies addressing this hazard, (which were not evaluated in the past by the relevant committee), were presented in the CLH report and were considered by RAC. Two studies clearly fulfilled the CLP criteria for classification in category 1, and a third study also suggested that classification in this category would be appropriate. A fourth study had eye scorings close to the criteria for a category 1 classification. Other studies fulfilled the criteria for category 2 and some of the studies were negative.

Humans experiencing contact with glyphosate-based herbicides have reported at least transient eye irritation to be a frequent symptom. It is however unclear if this is caused by the substance itself or if it can be caused or enhanced by co-formulants in the formulated product.

Taking all the data into account, in particular the clear evidence for eye damage in some studies, RAC agreed with the Dossier Submitter that the existing classification for eye damage (category 1), is justified and should be retained.

***Respiratory and skin sensitisation***

A respiratory sensitiser is a substance that will lead to hypersensitivity of the airways following its inhalation. There was no data provided on respiratory sensitisation and therefore this hazard class was not assessed by RAC.

A skin sensitiser is a substance that will lead to an allergic response following skin contact. There was no evidence of skin sensitisation in the fourteen animal studies (Magnusson & Kligman Maximisation Tests and Local Lymph Node Assays) addressing this hazard class which were summarised in the CLH report. RAC concluded that based on the consistently negative results from all the available studies, no classification is justified for skin sensitisation.

***STOT RE (Specific Target Organ Toxicity – Repeated Exposure)***

To determine specific, target organ toxicity arising from a repeated exposure to a substance or mixture, all significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included. Mortality among pregnant rabbits was used by the Dossier Submitter to justify the proposal for classification of glyphosate for STOT RE 2. According to the CLP regulation, morbidity or death resulting from repeated or long-term exposure can be taken into account for classification as STOT RE.

However, in the opinion of RAC, the mortality in rabbits following exposure to glyphosate was considered to be related to mis-dosing, infections or diarrhoea due to the gastrointestinal irritating properties of glyphosate, and the possible mechanism of caecotrophy (ingesting of faecal material) and thereby recycling of glyphosate, potentially led to a higher exposure than expected from the dose. By contrast, no mortalities were recorded in the repeated dose toxicity studies in rats.

On the basis of the weight of the evidence and with due consideration of all data from the short-term, long-term, reproductive and rabbit developmental studies, RAC concluded, contrary to the Dossier Submitter's proposal, that STOT RE classification is not justified for glyphosate.

***Mutagenicity***

This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. The results from mutagenicity or genotoxicity tests *in vitro* and in mammalian somatic and germ cells *in vivo* are also considered.

The number of studies available for evaluation of germ cell mutagenicity of glyphosate is extensive and includes bacterial and mammalian cell mutagenicity assays as well as mutagenicity assays conducted in animals, in addition to some human data. RAC was requested to consider the active substance glyphosate, therefore mutagenicity data related to its main metabolite and to glyphosate-based herbicides were not considered. However, data from blood samples taken from humans exposed to glyphosate-based herbicides (biomonitoring data) was considered by the Committee. Genotoxicity data from animal studies conducted with non-mammals were not included in the assessment, because the relevance of the findings to humans is less clear than in the very many studies available that were conducted using internationally standard protocols and commonly used mammalian species.

A limited number of studies have examined markers of possible genotoxicity in blood cells from humans exposed occupationally, or from the general population in regions with high use of glyphosate-based herbicides. Some of these studies showed an apparently positive relationship between exposure to glyphosate and levels of some markers indicating genotoxicity. However, all of these studies were compromised by the lack of clear information about exposure to glyphosate itself and/or glyphosate-based herbicides, and the extent to which other substances could have contributed to the findings. In some cases, the low numbers of subjects involved was also a limiting factor. These studies did not provide sufficiently robust evidence of glyphosate genotoxicity to justify classification.

The bacterial mutation assays and mammalian cell gene mutation tests gave consistently negative results. Furthermore, a total of seven oral and seven intra-peritoneal bone marrow micronucleus tests and two chromosomal aberration test in rodents were reported. All oral tests and three of the intraperitoneal tests were conducted according to the relevant OECD test guidelines. The majority of these bone marrow test were negative, one was considered to have deficiencies making the interpretation uncertain and was hence given less weight in the overall assessment. The other presented a statistically significant increase that was within the values usually seen in controls. Thus, the evidence from these two positive studies was overridden by the overall conclusion from the numerous other *in vivo* mutagenicity studies, showing that glyphosate does not induce somatic cell mutations.

Since glyphosate is only metabolised to a very limited degree and is not a DNA reactive substance, the genotoxicity observed in some studies is most likely caused by indirect mechanisms. Glyphosate induced transient DNA strand breaks in the *in vitro* and *in vivo* comet assays. However, as glyphosate does not induce gene mutations and the micronucleus bone marrow mutagenicity tests are considered negative, their biological importance in relation to mutagenicity is uncertain. It is unclear whether oxidative stress is of biological importance as a mode-of-action for glyphosate as the data are equivocal.

Taking all data into account, and based on the overall negative responses in the existing gene mutation and oral mutagenicity tests, RAC concluded that there is not sufficient evidence to warrant classification of glyphosate for germ cell mutagenicity.

***Carcinogenicity***

A carcinogen means a substance that induces cancer or increases its incidence. The number of studies addressing the carcinogenicity of glyphosate is extensive. A large number of comments were provided to ECHA during the public consultation, addressing this hazard class. RAC based their assessment on data from human epidemiological studies and a wide range of experimental carcinogenicity studies (seven conventional rat and five mouse cancer studies). The exposure route was oral in both the rat and the mouse studies and the doses used were sufficiently high in all but one of the evaluated studies. There were no data that suggested significant human-rodent differences and the studies performed and the tumour types evaluated are considered relevant to humans.

No association between exposure to glyphosate-based herbicides and findings of cancer was found in the United States Agricultural Health Study (AHS), which is the only prospective cohort study available. Available epidemiological case-control studies, reviews, re-analyses and meta-analyses showed weak statistically significant associations between exposure to glyphosate containing herbicides and findings of cancer, especially one type of cancer, non-Hodgkin's lymphoma (NHL). This could indicate a potential concern for human health. However, chance, bias and confounding factors could not be ruled out and a causal relationship could thus not be confirmed by RAC. Weak associations were seen in small studies with low statistical power. There were many other factors[11] which reduced the strength of the evidence from these studies.

Therefore, based on the epidemiological data, RAC considered that classification of glyphosate as Carc. 1A (substances known to have carcinogenic potential for humans) is not justified. The findings in the epidemiology studies were weighed together with the findings in animals.

No indication of tumours was observed in five of the long-term studies in either male or female rats. However, a significant increase in benign pancreatic tumours, was observed in male rats in the low dose groups of two studies, but no dose-response relationships were apparent. No similar increase in tumour incidences was reported for female rats in these two studies. The same holds true for liver adenomas and thyroid C-cell adenomas that were increased only in one of the rat studies. The incidences of liver adenomas were within the range of the historical controls, whereas the incidences of thyroid tumours were slightly above. The tumours were benign with no suggestions of progression towards malignancy, strength of the evidence was low and the findings were not consistent between sexes or across the many studies performed. There was insufficient evidence to support a classification for carcinogenicity based on the evaluation of the rat studies.

In the five studies conducted in mice, three tumour types were considered in detail. These were renal tubular tumours, haemangiosarcomas and malignant lymphomas. An increase in renal tumours was reported in males in the high exposure group in three of the five studies. Increased incidences of haemangiosarcoma was reported in males at the top dose in two studies, and an increased incidence of malignant lymphoma was reported in four carcinogenicity studies in two different strains of albino mice. The increases in tumour incidences were not statistically significant in pair-wise comparisons with control groups (by the Fisher exact test), but several of the findings were significant when tested by the (Cochran-Armitage) trend test. The tumour incidences were highly variable, mostly within the available control incidences, and elevated tumour incidences were not supported by parallel increases in non-neoplastic lymph node lesions.

Although RAC noted a tendency for increased tumour incidences in male mice in the high dose groups across the studies available, the Committee considered that the findings in the individual mouse studies were not by themselves strong enough to warrant classification. This conclusion was based mainly on an evaluation of statistical and biological significance of the findings,

[11] These included: a) the extent to which previous exposure could be recalled accurately (both for duration and dose) especially in the case-control studies, b) the lack of biomonitoring data (evidence of glyphosate in the body), c) lack of adjustment for co-exposure to other pesticides; d) risk estimates which often became lower when more comprehensive adjustment for confounders was applied, e) the possible presence of a toxic co-formulant (e.g. POE-tallowamine), and f) the changes in the definitions of NHL/other cancers over the years.

including comparison with historical control data and differences in findings between the sexes and inconsistencies in the findings between studies. The incidences of the findings were generally low, not supported by findings at lower exposure levels, were generally seen without a clear dose-response relationship and there was no evidence of progression to malignancy. Increased tumour incidences observed at doses above 4000 milligrams per kilogram body weight per day (mg/kg bw/d) were given less weight by RAC because the doses used were excessive and exceeded the MTD (as defined in the relevant OECD guideline).

RAC did not find sufficient evidence to support a genotoxic mechanism of action for glyphosate and concluded that based on the epidemiological data as well as on data from long-term studies in rats and mice, taking a weight of evidence approach, no hazard classification for carcinogenicity is justified for glyphosate according to the CLP criteria. This is in line with the proposal of the Dossier Submitter.

***Reproductive toxicity***

Reproductive toxicity is differentiated into effects on fertility and sexual function as well as development. In determining the significance to humans of reproductive toxicity effects, the question of whether they might be direct effects of the substance or secondary effects arising from parental toxicity needs to be considered in addition to the relationship between: a) the effects observed and the dose, b) the historical control data and c) statistical significance.

*Fertility and sexual function*

Effects of glyphosate on sexual function and fertility were investigated in rats in six two-generation studies considered to be of acceptable quality and a further three-generation study with deficiencies in its reporting. Based on the findings, the Dossier Submitter proposed no classification for this hazard class. RAC also examined the same studies. Any effects seen were of equivocal relevance for classification and were confined to high dose levels (greater than 1000 mg/kg bw/d) in the presence of parental toxicity ruling them out as relevant effects for a classification for fertility and sexual function. Several epidemiological studies had investigated a possible impact of exposure to glyphosate-based herbicides and effects on fertility, but there was considered to be a lack of statistically significant positive associations for these findings. RAC concluded that the studies did not provide any evidence of effects of glyphosate on fertility or male and female reproductive organs.

*Developmental toxicity*

The Dossier Submitter included six developmental toxicity studies in rats and seven studies in rabbits in their evaluation of developmental toxicity following exposure to glyphosate. The findings from four of the studies in rats showed effects at very high doses (3500 mg/kg body weight per day) which included malformations as well as post-implantation losses. These effects were considered to be secondary to maternal toxicity in one study, ruling them out as relevant effects for classification for developmental toxicity. In another study, there was a small but non-statistically significant increase in malformations which was not dose-dependent. Overall, taking all the studies in rats together, considering also the studies which showed no evidence of developmental toxicity, they were not considered to provide evidence of developmental toxicity.

The developmental toxicity studies indicate that pregnant rabbits are a more sensitive animal model than pregnant rats to exposure to glyphosate.

In the rabbit developmental toxicity studies, effects on foetal viability were only reported in one out of the seven studies, but that was without a clear dose-response relationship, with high variability of the effects reported and with findings within the historical control range for late- and total embryonic deaths. In five out of seven developmental toxicity studies performed in rabbits, foetal skeletal and visceral malformations were reported, however at low incidences and within the range of the historical control data when available.

The increases in incidences of visceral (soft tissue) malformations (ventricular septal defects seen in two studies and an increase in dilated heart in one study) raised some concern for the potential for induction of heart malformations following *in utero* exposure to glyphosate in rabbits. However,

two studies were reported to have serious deficiencies. A high number of maternal deaths was reported at the high dose in some studies (500 mg/kg bw/d and 350 mg/kg bw/d) leading to an insufficient number of foetuses being available for assessment. Furthermore, the specific cardiovascular malformation seen following treatment with glyphosate was not reported consistently in the seven developmental toxicity studies in rabbits. Where they were reported, the incidences were low, without a clear dose-response relationship and were also reported in the control groups. An increase in skeletal malformations, evident as cranial bone malformations (fissure and or splitting of parietal bones) was reported in a single study, but no similar finding was reported in the other (acceptable) studies. Overall, the foetal skeletal and visceral malformations were seen in the presence of severe maternal toxicity including death and gastro-intestinal tract intolerance. Deaths were reported to be both substance related (doses ranging from 100 to 500 mg/kg bw/d) and due to infections or technical problems with the dosing of the animals.

RAC concluded that the overall evidence was insufficient for classification because the findings seen (at low incidences) were either likely to be due to maternal toxicity and/or the uncertainties described suggested that they could be considered as chance findings.

***Environmental hazards***

Hazard to the aquatic environment is divided into acute and long-term and is based on acute and chronic toxicity to aquatic organisms, bioaccumulation and for organic chemicals, degradation. Glyphosate has an existing classification as Aquatic Chronic 2. Based on data in the CLH report, the substance continues to be considered as not rapidly degradable and to fulfil the criteria for classification as Aquatic Chronic 2 (0.1 mg/L < NOEC ≤ 1.0 mg/L). Consequently, the existing classification should be retained.

Based on the additional information on the aquatic plant *Myriophyllum aquaticum*, and in view of the relatively slow mode of action in plants, RAC notes that the classification is not necessarily based on an appropriate data set. As a result, the classification might need to be reviewed if further relevant aquatic plant data (e.g. for rooted emergent macrophytes, particularly over long test durations) become available.

# Conclusion

RAC did not find sufficient evidence to support a genotoxic mechanism of action for glyphosate. It concluded, based on the epidemiological data as well as on data from long-term studies in rats and mice, taking a weight of evidence approach and in line with the proposal of the Dossier Submitter, that no hazard classification for carcinogenicity is justified for glyphosate according to the CLP criteria. Where toxicity to reproduction is concerned, RAC recommended no classification for both fertility and development. RAC also concluded that there was insufficient evidence to support the proposal of the DS to classify glyphosate for specific target organ toxicity after repeated exposure (category 2). However, RAC agreed with the DS that the existing classifications for eye damage (category 1) and long term hazard for the aquatic environment (category 2) should be retained and that no classification for any of the other hazard classes was warranted.