Explanatory note

On an opinion proposing harmonised classification and labelling

at EU level of

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

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This note has been prepared by ECHA, based on the opinion of the Committee for Risk Assessment (RAC) as adopted on May 30 2022

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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 Member 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.

The dossier proposing classification of glyphosate was a Combined Draft Renewal Assessment Report and Proposal for Harmonised Classification and Labelling. It was submitted by the Assessment Group for Glyphosate (AGG)[5] and was the subject of a concurrent consultation by ECHA and EFSA from 23 September to 22 November 2021. 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.

A further ad hoc consultation was conducted from 29 March to 14 April 2022, on documents considered potentially relevant to classification of the substance for the following hazard classes: Respiratory Sensitisation (opened for comments during the ad hoc consultation), Specific Target Organ Toxicity - Single Exposure (respiratory irritation), Germ Cell Mutagenicity, Carcinogenicity, Reproductive Toxicity and Hazardous to the Aquatic Environment.

The draft opinion prepared by the Rapporteurs appointed by RAC was provided to the Committee on 30 March 2022 and a revised section on aquatic environment again on 13 May 2022.

The CLH dossier was considered by RAC at its:

- RAC-60 plenary, 16 March 2022 – key issues and stakeholder statements;
- RAC-61 CLH Working Group, 21 and 22 April 2022 – all hazard classes;
- RAC-61 plenary, 30 May 2022 – all hazard classes, including the CLH working group's recommendations; the opinion was adopted.

[1] Regulation (EC) 1272/2008 on the Classification, Labelling and Packaging of substances and mixtures .
[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 5.0, 2017, 646p. 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.
[5] Comprising France, Hungary, The Netherlands and Sweden – for more information: https://ec.europa.eu/food/plants/pesticides/approval-active-substances/renewal-approval/glyphosate/assessment-group_en

RAC meetings are attended by regular[6] and occasional stakeholder organisations as observers representing civil society including trade unions, as well as industry. As noted above, in preparation for the Committee's discussions on Glyphosate, ECHA invited interested parties to present their views to RAC at its 60th meeting in March 2022. This included presentations from the Glyphosate Renewal Group, Bayer, The European Food Safety Authority (EFSA), the Health and Environment Alliance (HEAL), European Environment Bureau (EEB), Client Earth and the Dossier Submitter (AGG)[7].

For reference, the previous RAC opinion on the harmonised classification and labelling (CLH) of glyphosate (ISO); *N*-(phosphonomethyl)glycine (hereafter referred to as glyphosate) was adopted by RAC in 2017 (referred to in this opinion as RAC, 2017), and was based on a CLH dossier submitted by Germany in 2016 (referred to in this opinion as CLH, 2016).

RAC's task was to evaluate whether the potential hazards of the active substance **glyphosate** 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 the 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 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 are 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 according to internationally standardised Guidelines and under the system of OECD Good Laboratory Practice[8]. The assessments of the studies have been conducted according to the relevant EFSA guidance documents on the assessment of active substances under the Plant Protection Products (PPP) Regulation, OECD test guidelines and guidance documents and the CLP guidance.

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.[9] 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

[6] 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)

[7] 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/hot-topics/glyphosate

[8] 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.

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

independent sources may lead to the conclusion that a substance has or has not a particular dangerous property[10]. The role of epidemiology data is specifically considered[11].

Summary recommendations on the specific hazard classes evaluated by RAC

Physical hazards

Glyphosate was considered by the dossier submitter as well as by RAC not to meet the criteria for classification for any of the physical hazards listed in the CLP Regulation which are relevant for a solid substance. Therefore, it did not meet the criteria for classification as an explosive, a flammable solid, a self-reactive substance, a pyrophoric solid, a self-heating substance, a substance which in contact with water emits flammable gases, an oxidising solid, an organic peroxide or a substance which is corrosive to metals.

Acute Toxicity

Acute toxicity addresses the lethality of a substance, after short-term oral, dermal or inhalation exposure. Numerous studies addressed acute oral, dermal or inhalation toxicity of glyphosate. All of these studies were included in the RAC evaluation in 2017 and no additional studies were received for the current evaluation. 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.

No new studies were included compared to the previous evaluation by RAC in 2017. 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 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 clear 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

[10] REACH Annex XI, Section 1.2
[11] CLP Annex I: 1.1.1.4

Skin Corrosion and irritation mean respectively the production of irreversible or reversible damage to the skin. No additional studies were included compared to the RAC evaluation in 2017. Eighteen guideline-compliant studies with rabbits were summarised by the DS. Fifteen of these 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. No data from humans on skin effects after exposure to non-formulated glyphosate alone were reported. 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). RAC noted that no new additional studies were included compared to the RAC evaluation in 2017. Eighteen studies addressing this hazard, were presented in the CLH report and were considered by RAC. Six 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. Eight studies fulfilled the criteria for category 2. For the rest of the studies, no Category could be assigned due to limited reporting of the data.

No human cases of eye effects after exposure to non-formulated glyphosate alone were reported, and no human data relevant for classification are available.

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

Respiratory sensitisation

A respiratory sensitiser is a substance that will lead to hypersensitivity of the airways following its inhalation. No data on respiratory sensitisation was presented in the CLH report and therefore this hazard class was not assessed by the AGG. However, RAC noted that during the consultation of the CLH report, one Academic institution raised the issue of respiratory sensitisation with the presumption of a weak link between glyphosate and respiratory health. After considering the available information, RAC concluded that a limited number of epidemiological studies showed only a weak increased risk of wheeze (allergic or non-allergic) and asthma following exposure to glyphosate-based herbicides. Therefore RAC concluded that no classification for respiratory sensitisation is warranted due to insufficient data.

Skin sensitisation

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 sixteen acceptable 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, including one additional study which was included compared to the RAC evaluation in 2017 (an *in vitro* transcriptomic and proteomic based approach which predicted that glyphosate is not a skin sensitiser), as well as two Buehler tests which gave equivocal results, no classification is warranted 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. 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.

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 (including some studies additional to those used in the RAC assessment in 2017) from an *in vitro* (transcriptome and metabolome profile) study, published neurotoxicity studies, as well as from the short-term, long-term, reproductive and rabbit developmental studies, RAC concluded that STOT RE classification is not warranted 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.

Glyphosate has been tested in a wide range of genotoxicity and mutagenicity assays. All relevant genotoxicity and mutagenicity studies included by the DS have been considered and both guideline- and non-guideline studies form the basis of the current RAC mutagenicity assessment. There were a large number of acceptable and supportive studies assessing germ cell mutagenicity following exposure to glyphosate. In addition to the acceptable and supportive studies included the CLH dossier, RAC notes that the DS also included studies which were not acceptable or of low reliability for *in vitro* and *in vivo* genotoxicity and mutagenicity following exposure to glyphosate. These studies were not included in the overall weight of evidence assessment for germ cell mutagenicity due to factors such as sufficiently high dose levels not having been tested, the purity of the test substance, appropriate controls not included, reporting deficiencies and because cytotoxicity was not assessed.

RAC's mandate was 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 number of oral and intra-peritoneal bone marrow micronucleus tests and two chromosomal aberration test in rodents were reported. All oral tests and some of the intraperitoneal tests were conducted according to the relevant OECD test guidelines. The majority of these bone marrow test were negative. 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. *In vitro* Comet assays (from the open literature, six out of nine of which had not been considered in the previous RAC Opinion on glyphosate from 2017) as well as two *in vivo* comet assays considered in the RAC opinion from 2017 suggested that glyphosate may induce DNA strand breaks in cultured cells. However, no reliable *in vivo* Comet assays were included in the CLH dossier in relevant target organs and 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. There is also some evidence that glyphosate may induce oxidative stress in certain cells and tissues with the potential to induce oxidative DNA-lesions that may lead to mutations if not repaired. It is unclear whether oxidative stress is of biological importance as a mode-of-action for glyphosate, as the data are equivocal.

Taking all the above 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 considerable number of comments were provided to ECHA during the 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 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 herbicide and non-Hodgkin's Lymphoma was found in the Agricultural Health Study cohort, which is the only prospective cohort study available. Weak positive associations have been observed in some case-control studies, and in meta-analyses of glyphosate-based herbicide exposure and non-Hodgkin's Lymphoma. However, one of the studies considered (Kabat et al., 2021) concluded that results of meta-analyses of glyphosate-based herbicide exposure and non-Hodgkin's Lymphoma risk depend on assumptions made about both exposure level and latency period. RAC notes that the increased risk of non-Hodgkin's Lymphoma observed in some case-control studies was not consistently observed in all case-control studies nor in the only cohort study available. For cancers other than non-Hodgkin's Lymphoma, there are less studies available and no consistent indication of an increased risk. In the AHS cohort an association between acute myeloid leukaemia and exposure to glyphosate was reported for the highest quartile of exposure when a 20-year lag period was taken into account, however, a low number of cases was found in this exposure group. RAC notes that this tumour type should be followed in future updates of the AHS. A causal relationship could not be established by RAC because chance, bias, and confounding factors could not be ruled out, and the evidence from epidemiological studies was considered insufficient to demonstrate

carcinogenicity in humans. There were many other factors[12] 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.

There is insufficient evidence to support a classification for carcinogenicity based on the evaluation of seven rat studies. A significant increase in benign pancreatic tumours, was observed in males in the low dose groups of two studies, but no apparent dose-response relationships were seen. No similar increase in tumour incidences was reported for female rats in these two studies and no similar indication of pancreatic tumours were observed in any of the five other long-term studies for either males or females. The same holds true for liver adenomas that were increased in two of seven rat studies and thyroid C-cell adenomas that were increased only in one study. The incidences of liver adenomas were within, whereas the incidences of thyroid tumours were slightly above, the range of the historical control data. The conclusion is supported by the benign nature of the tumours with no suggestions of progression towards malignancy, a low strength of the evidence and a lack of consistency between sexes and across the many studies performed.

An increased trend of skin basal tumours was reported in one study but not in the five other carcinogenicity studies in rats, nor in female rats and it is considered to be of equivocal relevance. Further, no clear effects on the skin were reported following systemic exposure to glyphosate in the repeated dose toxicity studies in animals.

The increased incidences of skin keratoacanthomas in male rats were either non-significant, borderline, or significant depending on the statistical method used. Skin keratoacanthomas were reported in male rats but not in female rats. The incidences exceeded the available HCD; however, it is noted that the HCD are very limited for the induction of skin keratoacanthomas in male rats. Furthermore, the increased incidences in skin keratoacanthomas were only observed at very high dose levels, which slightly exceeded the maximum recommend dose rate according to the OECD TG. It was also noted that skin keratoacanthoma is a benign tumour which is shown to be rather common in aged male rats. Further, it was noted that no malignant squamous cell carcinomas were reported.

In one study, the incidence of pituitary adenomas was increased in both males and females. This is a common tumour in rats and no similar increase was reported in the other rat bioassays.

In the mouse, four tumour types were considered in detail. These were renal tubular tumours, haemangiosarcomas, haemangiomas 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 in haemangiosarcoma were reported in male CD-1 mice at the top dose in two studies, and an increased incidence of haemangioma was reported in female mice in two out of five studies. Further, an increased incidence of malignant lymphoma was reported in three carcinogenicity studies in CD-1 mice and one study in Swiss albino mice. The increases in tumour incidences were all non-significant in pairwise comparisons with control groups by the Fisher's exact test. However, several of the findings were significant when tested by the Cochran-Armitage trend test. RAC considered that the findings in the individual mouse studies were not by themselves strong enough to warrant classification. This is based mainly on an evaluation of statistical significance, biological relevance and consistency of the findings, including comparison

[12] 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.

with historical control data and differences in findings between the sexes. Increased tumour incidences observed at doses above 4000 mg/kg bw/d were given less weight by RAC because the doses used were excessive and exceeded the maximum tolerated dose. Looking at the overall pattern of tumour incidences, RAC notes a tendency for increased incidences of malignant lymphomas in male mice in the high dose groups in four of the five studies available. However, the tumour incidences were highly variable, mostly within the available historical control data incidences, and elevated tumour incidences were not supported by parallel increases in non-neoplastic lymph node lesions. Furthermore, the findings were not consistent between sexes and were not supported by findings in the rat studies.

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 and with RAC's previous evaluation (RAC, 2017).

Reproductive toxicity

Reproductive toxicity is differentiated into effects on fertility and sexual function effects on development as well as effects on or via lactation. 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. No additional standard toxicity studies (generational studies) were identified or assessed by the DS compared to the assessment by RAC in 2017. 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 (including two recent studies provided during consultation) 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. A number of published studies were also available which looked at effects relevant to reproductive systems of males and females. RAC concluded that the studies did not provide any evidence of adverse effects of glyphosate on fertility or male and female reproductive organs.

Overall, RAC is of the opinion that in a weight of evidence assessment and the review of the available information, including published literature which was not included in the previous evaluation by RAC in 2017, does not provide sufficient evidence to conclude that there is some or clear adverse effects of glyphosate on sexual function and fertility.

Developmental toxicity

The Dossier Submitter included five 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. The developmental toxicity reported included statistically significant increases in late embryo-foetal death, post-implantation loss as well as skeletal and visceral malformations, although at low incidences, which for some of the effects was without a clear dose-response relationship and not consistently reported in all rabbit developmental toxicity studies.

Post-implantation loss and late/early embryo-foetal death were reported in only two (acceptable) rabbit studies. Based on the weight of evidence assessment, RAC concludes that following in utero exposure to glyphosate in rabbits no clear relationship between exposure and effects on foetal viability could be determined. Effects on foetal viability were not reported consistently in the four acceptable developmental toxicity studies in rabbits. Only one study reported effects on foetal viability, however, without a clear dose-response relationship and within the historical control range for late and total embryonic deaths. Limited evidence of cardiovascular malformations, skeletal malformations, post-implantation loss and embryo-foetal death were reported following in utero exposure to glyphosate since no clear picture of these effects were reported across the four acceptable rabbit developmental toxicity studies. These effects were reported at low incidences, and in some of the studies without a clear dose-response relationship. Further, it should be noted that the cardiovascular malformations were to some extent clustered together in the same foetuses. Skeletal malformations evident as craniofacial malformations were reported in one study, however, it is noted that no similar malformations were recorded in the other seven acceptable studies at dose levels up to and including 500 mg/kg bw/d. The effects were reported in the presence of severe maternal toxicity including death of the female rabbits and GI tract intolerance to glyphosate exposure. However, it should be kept in mind that some of the deaths were related to mis-gavage and therefore not substance related. Furthermore, in some of the studies serious deficiencies in the reporting of the results were evident.

Epidemiological studies show no convincing evidence of developmental effects following in utero exposure to glyphosate.

RAC concluded that the overall evidence was insufficient for classification for developmental toxicity 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.

Lactation

There are no specific studies submitted for effects on or via lactation, and adverse effects on or via lactation were not assessed in the 2017 RAC opinion. There are no human evidence indicating a hazard to babies during the lactation period and the available one or two generation reproductive toxicity studies in animals does not provide clear evidence of adverse effect in the

offspring due to transfer in the milk or adverse effect on the quality of the milk. There are also no data available from absorption, metabolism, distribution and excretion studies that indicate that the substance is present in potentially toxic levels in breast milk. Therefore, RAC concluded that no classification for adverse effects on or via lactation is warranted.

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. A considerably larger dataset was provided for evaluation by the DS than that assessed by RAC in its previous evaluation in 2017. Based on data in the CLH report, the substance continues to be considered as not rapidly degradable and does not fulfil the criteria for bioaccumulation. Based on the available and reliable information in the CLH dossier on acute aquatic toxicity, studies for the three trophic levels fish, invertebrates and algae/aquatic plants, the L(E)C50 values are all above the threshold of 1 mg/L of the CLP criteria. Therefore, RAC agrees with the DS that no classification as Aquatic Acute is warranted for glyphosate.

The NOEC value of 1 mg/L for fish assessed in the previous RAC opinion (2017) is still considered relevant. RAC also considers relevant and reliable a study on *Myriophyllum sibiricum* with the NOEC value of 0.332 mg/L also warranting an Aquatic Chronic 2 classification. This conclusion is supported by the results from other (published) fish studies as well a study on *Myriophyllum aquaticum* based on a formulation (MON 52276). Consequently, RAC agrees with the DS conclusion that the existing classification as Aquatic Chronic 2 should be retained.

Overall 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. Concerning toxicity to reproduction, RAC recommended no classification for either fertility or development. 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.