Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the Opinion proposing harmonised classification and labelling at EU level of

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

CLH-O-0000001412-86-149/F

Adopted
15 March 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (GLYPHOSATE (ISO); N-(PHOSPHONOMETHYL)GLYCINE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

DOSSIER SUBMITTER'S (DS) INTRODUCTION:

A total of 285 comments was submitted in the chapter "General comments", 6 comments in the chapter "Other hazards and endpoints – hazardous to the aquatic environment" and two comments in the chapter "Other hazards and endpoints – physical hazards".
25 comments were submitted by the Member States Finland, Spain, Norway, Denmark, Belgium, Netherlands and Sweden and France. Mainly, these comments deal with the classification of repeated dose toxicity, genotoxicity, carcinogenicity, reproductive toxicity and acute toxicity.
Approximately 40% of the submitted general comments contained a standardised text which was submitted in French or English language. These comments were answered together in the responses on comment 4 and comment 21. It was noted that comment 26, even its wording, was exactly the same as no. 21, even though one came from Germany but the other from Ireland. The same holds true with regard to many following comments (e.g. # 32, 42, 43, 47 and many more) coming from different countries. Unfourtunately, these comments did not provide any valuable proposals in support of classification and labelling.
Approximately a further 30% of the general comments covered the intended use, the risk assessment of glyphosate or further issues without detailed or new toxicological information on hazard identification or on classification and labelling.
Approximately a further 20% of the general comments contained detailed and scientifically justified arguments. Some of these comments were very extensive.
Approximately 1% of the general comments discussed the activity of glyphosate against bacteria. However, this activity was not considered relevant for classification and labelling.
Furthermore, 6 of the 285 comments (# 87/119/131/134/135/257) discussed questions related to ecotoxicology which were also not relevant for human health classification.

In support of the DS's answers to the comments on the carcinogenicity of glyphosate,an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' is provided by the DS as an **Addendum to the CLH dossier** which is attached at the end of this document.

Substance name: glyphosate (ISO); N-(phosphonomethyl)glycine
EC number: 213-997-4
CAS number: 1071-83-6
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	1
Comment received				
Behördenirrtümer sind nichts Ungewöhnliches. Man denke an DDT, Holzschutzmittel, hormonell wirksame Substanzen oder an Contergan bei den Medikamenten. Ursache war jedes Mal Unkenntnis biologischer Vorgänge. Immer wieder stellt sich heraus, dass in den vorgeschriebenen Tests zur Erkennung von Risiken, der regulatorischen Toxikologie, große Lücken klaffen. So ist es auch beim Glyphosat. Nur ein Teil der Effekte von Glyphosat wird regulatorisch erfasst: Wie wirkt Glyphosat (G)? 1. Über direkte Enzymhemmung ☐ Hemmung der 5-Enol-pyrovyl-shikimate-synthase (EPSP) betroffen: Pflanzen, Bakterien (teilweise) Auswirkung: blockierte Synthese aromatischer Aminosäuren, dadurch Hemmung der Proteinsynthese. Verminderung der Knöllchenbakterien ☐ Blockade der Succinat-Bindungsstelle der Succinat-Dehydrogenase Betroffen: Mitochondrien der Leber- und Hodenzellen (Nachweis bei Ratten) Auswirkung: Reduzierung der Zellatmung Hemmung d. Testosteronsynthese ☐ Entkopplung der oxidativen Phosphorylierung durch Hemmung der Cytochrom P450- Enzyme betroffen: Darmbakterien, Pflanzen, Embryonen von Fröschen, Hühnern, Schweinen und Menschen Auswirkungen: Dysbiose im Darm (→Botulismus), verminderte Synthese aromatischer Aminosäuren, verminderte Entgiftung, zahlreiche Krankheiten, neuronale und andere Missbildungen bei Embryonen ☐ Acetylcholinesterase-Hemmung Betroffen: Neuronen, Nachweis bei Fischen, Säugetieren? Mensch? ☐ Hemmung der Serin-Hydroxymethyltransferase Betroffen: rasch proliferierende Zellen u. Neuronale Zellen, in vitro und in vivo (Ratten) Auswirkungen: Wachstumshemmung durch Glycin-Mangel Gehirnfunktion: erhöhte Erregung? Attention Deficit Disorder (ADD)?, Embryotoxizität (Neuralrohr) 2. Bildung von Chelatkomplexen mit Elektrolyten ☐ Komplexbildung mit 2-wertigen Metall-KatIonen: Cu ++, Mn++, Co++, Fe++, Zn++, Ca++, Mg++ Betroffen: Alle Lebewesen				

Auswirkungen: Spurenelement- Mangelerscheinungen z.B. bei Rindern durch G mit Adjuvantien im Futter ☐ Erhöhung der Zell-Membranpermeabilität für Kalzium Betroffen: insbesondere Mitochondrien der Leberzellen Auswirkung: erhöhter oxidativer Stress, Bildung reaktiver Sauerstoffradikale (ROS) durch Veränderungen der inneren Mitochondrienmembran, Zellschäden: AP, ASAT u. ALAT ↑ 3. Epigenetische Veränderungen ☐ Störungen im Programm der Ablesung der zellspezifischen Bereiche der DNA Angriffsorte: Zellkern und Mitochondrien während der Zellteilung Betroffen: alle sich teilenden Zellen, insbesondere Gewebe mit hoher Mitoserate, hoher Stoffwechselaktivität und hohem Sauerstoffbedarf Auswirkungen: primär: irreversible Veränderung des Transkriptoms (Gesamtheit der RNA), sekundär: pathologische Veränderungen der zellulären Feinstruktur, tertiär: zelluläre Funktionsstörungen (Endokrine Drüsen: Hormonspiegel, Nieren: gestörte Elektrolytbalance, Leber: verminderte Synthese- und Entgiftungskapazität) Auf Grund seines Wirkungsmechanismus gehört G als aktive Wirksubstanz von Roundup® und anderen Herbiziden zur Gruppe der so genannten endokrinen Disruptoren (Pestizide mit Hormon-ähnlicher Wirkung). Ihr generelles Verbot wird seit vielen Jahren gefordert, aber von den Chemie-Konzernen blockiert. Ärzte und Epidemiologen verbinden seit langem die Zunahme bestimmter Krankheits-symptome bei Menschen und Tieren mit der zunehmenden Allgegenwart von G. Dazu gehören u. a. Missbildungen während der Embryonalentwicklung, Botulismus sowie die Häufung von Fettsucht, Parkinson und Diabetes in der Bevölkerung und Krebs. Ihr Ursprung und die Entstehungsweise lassen sich in eine **mutmaßlich** kausale Verbindung bringen, wobei durchaus auch andere Umweltrelevante Chemikalien eine wichtige Rolle spielen könnten. Diese Arbeit von hohem wissenschaftlichem Standard stellt eine zusätzliche Basis für die grundlegende Neubewertung des Risikoprofils dar, insbesondere auf Grund seiner ubiquitären Verbreitung. Aus toxikologischer Sicht ist die Verharmlosung von Glyphosat der bisher folgenschwerste Behördenirrtum der Geschichte.
Dossier Submitter's Response
In contrast to the opinion expressed in this comment, the suspected effects would have been revealed in the many toxicological studies which were performed with glyphosate. Apparently, this was not the case even though the administered doses were magnitudes higher than human exposure. In particular, there was no evidence of ED properties. This was also demonstrated in the ED screening programme of the U.S. EPA. In any case, the comment seems to address risk assessment rather than classification and labelling. No respective proposals are made. Thus, unfortunately no information was provided in the comment which could be used to assess the classification and labelling of glyphosate.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Finland		MemberState	2
Comment received				
The Finnish CA has focused on the data related to carcinogenicity and commented only this part in the CLH report.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	3
Comment received				
je vous invite fortement a faire preuve de la plus grande intégrité quant à cette étude. les enjeux dépassent largement votre organisation ou les bénéfices d'une entreprise : c'est l'avenir de l'humanité qui est en jeu et je pense sincèrement que ce terme n'est pas exagéré.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	4
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				

Dossier Submitter's Response
The hazard assessment and toxicological evaluation of carcinogenicity data was independently performed by the DS according to the technical guidance documents of the ECHA and not based on former evaluations on risk assessment or evaluations by other institutions. However, all relevant critical discussions of the past are considered in the assessment by the DS. All studies evaluated in the IARC monograph on glyphosate were discussed in the BfR addendum from August 2015, which was submitted together with the IARC monograph as addendum to the CLH dossier. There is agreement that all studies used in the IARC monograph on glyphosate will be considered in the final discussion of the CLH dossier. All relevant studies, including all studies submitted by industry as well as those published in the scientific literature, are assessed very carefully in compliance with common scientific principles. According to EU directives and national laws of EU member states the notifiers of pesticides are legally obligated to submit a range of studies which have to be performed in compliance with guidance documents. The quality of studies submitted by industry and of published studies of other origin is assessed by common criteria. If the studies provided by industry could or should become publically available in full, is a legal but not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC. At least, these studies are published by EFSA in great detail in Volume 3 of the RAR. All available studies in mice and also all studies in other animal species and in humans are taken into account for the decision on classification of glyphosate.
RAC's response
Noted. RAC has for the assessment of carcinogenicity, reproductive toxicity and STOT RE assessed the data included in the CLH report and the RAR. The data in the study reports were looked into when considered necessary. This was done when more details were considered necessary to include in the opinion for clarifications. The study results for all hazard classes included in the CLH proposal have been assessed according to the CLP criteria. A comparison with the evaluation by IARC for mutagenicity and carcinogenicity has been included in the opinion.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Sweden		Individual	5
Comment received				
Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				
Dossier Submitter's Response				
All the studies have been thoroughly reviewed according to the ECHA guidance documents. If they could or should become publically available in full, is a legal but not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC. It is emphasised that the studies themselves are published by EFSA in the RAR (Volume 3) in great detail. The findings which might be relevant for classification and labelling are also reported in the CLH dossier in sufficient detail. It is noted that this is a general comment and no proposals for classification and labelling are made.				

RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	6

Comment received
Je suis très préoccupé par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. En tout état de cause, vous devez également rendre publiques ces études d'industriels pour qu'elles soient soumises à l'évaluation d'autres scientifiques. Ce mode opératoire reste le principe de la démarche scientifique rigoureuse à même de nous garantir des études incomplètes, biaisées ou partiales. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Merci pour toute la rigueur scientifique, l'indépendance d'esprit et la transparence dont vous saurez faire preuve sur ce dossier particulièrement sensible et suivi par l'opinion publique. La confiance très dégradée entre les citoyens et les processus de décision dans les rouages de l'UE, a besoin d'être restaurée par un traitement irréprochable dans ce type de dossier sensible. Merci et recevez mes sincères salutations. [redacted]
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	7

Comment received
As a citizen, I am concerned by the possible carcinogenicity of glyphosate. Some experimental studies concluded that glyphosate can provoke cancers, these studies should be taken into account in your assessment.You should be particularly cautious with studies made or financed by industry businesses because of possible conflict of interest. Theses studies should be publicly available so that other experts could examine and assess their results. Our health should not be sacrified to the profits of some businesses.
Dossier Submitter's Response
All the studies have been thoroughly reviewed, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. If the studies could become publically available in full, is a legal but not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Italy		Individual	8
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter				
Dossier Submitter's Response				
All the studies have been thoroughly reviewed, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Thus, evaluation is not flawed. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	9
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	10
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	11
Comment received				
Glyphosat ist Krebserregend				
Dossier Submitter's Response				
All the studies have been thoroughly reviewed, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for				

Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.

RAC's response

The database for evaluation of glyphosate carcinogenicity is extensive and RAC has based their assessment on data from human epidemiological studies and a wide range of experimental carcinogenicity studies (7 rat and 5 mouse conventional cancer bioassays). 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 are no data that suggest that there are significant species differences and the studies performed and the tumour types evaluated are considered relevant to humans. The database includes studies of sufficient reliability and relevance to allow a robust evaluation following the criteria in the CLP.

Classification in category 1A concerns substances known to have carcinogenic potential in humans and is largely based on human evidence. Classification of glyphosate in category Carc. 1A is not justified.
Classification in category 1B concerns substances presumed to have carcinogenic potential in humans. The classification is largely based on animal evidence.

Following an overall evaluation of the human evidence and the tumour data from 7 rat and 5 mouse bioassays it is concluded that there is not sufficient evidence for carcinogenicity and a classification of glyphosate in category 1B is thus not warranted. The evaluation of strength of evidence and additional considerations including biological relevance of the tumour data is provided for each tumour type above. The main arguments are briefly summarised below.

Classification in category 2 concerns substances that are suspected human carcinogens. Classification is based on evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. RAC notes the following in relation to glyphosate:

Epidemiological data:

- No association between exposure to glyphosate and cancer was found in the AHS, which is the only prospective cohort study available. A weak positive association has been observed in some case-control studies, and in meta-analyses between exposure to glyphosate and cancer, especially NHL, as concluded in the meta-analyses by Chang and Delzell (2016) and Schinasi and Leon (2014), and also in the IARC monograph 112. 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. The increased risk observed in some case-control studies was not consistently observed in all case-control studies nor in the only cohort study available. When the whole database of epidemiology is taken into consideration RAC concludes that the criteria for assigning glyphosate to category 2 are not fulfilled.

Animal bioassays:

- There is insufficient evidence to support classification in category 2 based on the evaluation of six rat studies. A significant increase in benign pancreatic tumours, was observed in males in the low dose groups of two studies (Lankas, 1981, Stout and Ruecker 1990), 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 tumors was observed in any of the five other long-term studies for either males or females. The same holds true for liver adenomas and thyroid C-cell adenomas that were incresed only in the study by Stout and Ruecker (1990). The incidences of liver adenomas were within, whereas the incidences of thyroid tumours were slightly above, the range of the historical controls. 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.
- In the mouse studies, 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 in haemangiosarcoma was reported in CD-1 males at the top dose in two studies, and 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 pair wise 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 with historical control data (HCD) and differences in findings between the sexes. Increased tumour incidences observed at doses above 4000 mg/kg bw/day were given less weight by RAC because the doses used were excessive and exceeded the MTD. Looking at the overall pattern of tumor 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 control 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.
- Mode-of-action (MoA) data: Glyphosate is not reactive and no structural similarity to a substance(s) for which there is good evidence of carcinogenicity has been suggested. RAC does not find sufficient evidence to support a genotoxic MoA for glyphosate. Furthermore, the available data do not support non-genotoxic modes of action such as growth stimulation or tissue necrosis. Immunosupression is a recognised risk factor for NHL, but the data for glyphosate is regarded as insufficient for evaluation of this endpoint.

RAC concludes 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 classification for carcinogenicity is warranted for glyphosate according to the CLP criteria.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	12
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	13
Comment received				
Je suis très préoccupé par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte alors que vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
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RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	14
Comment received				
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RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	15
Comment received				
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RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	16
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	17
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment				

according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	18
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	New Zealand		Individual	19
Comment received				
This submission is about sub-lethal effects of the herbicide on bacteria. The sub-lethal effect is to change susceptibility to clinical antibiotics, with the potential to change the efficacy of treatment of humans or animals. This effect was not considered in the risk assessment. Failing to do so leaves as possible that the risk is non-negligible and not managed. Looking at the list of categories of "Specific comments: Carcinogenicity: Mutagenicity: Reproductive toxicity: Respiratory Sensitisation:" further confirms that the risk assessment was not informed by the sub-lethal effects, because there was no provision for these effects in the specific comments. I attach a separate file to assist the regulator in consider sub-lethal effects on microbes. ECHA note - The following attachment was submitted with the comment above: *echa consultation glyphosate.pdf*				
Dossier Submitter's Response				
Due to its unique mode of herbicidal action, some antibiotic activity of glyphosate may be assumed. In fact, there were effects of this compound on bacteria and some other micro-organisms, in particular when tested in				

isolation *in vitro*. Even an U.S. patent covering antimicrobial use of glyphosate was granted even though the doses suggested to control certain infections in humans were very high. It has been also shown that the vulnerability of various bacteria species is different. These findings have been taken into consideration in the RAR (Volumes 1 and 3) and, thus, for risk assessment but in the sections dealing with possible effects on animal health. The point of concern were potential dysbalances in the microbial communities in the digestive tract of ruminants. The DS even commissioned additional research activities to investigate a possible impact of glyphosate (i.e., a glyphosate-containing herbicide) on complex microbial communities in cattle at realistic dietary concentrations but no adverse effects were detected (Riede *et al.*, 2016, see attached article).
A possible impact of glyphosate on the susceptibility of clinically important pathogens to antibiotics is a different and newly raised issue which is considered not relevant for classification and labelling.
Effects of glyphosate on micro-organisms have not been considered in the CLH dossier since they are not covered by the health-related classifications of chemicals according to CLP and therefore not relevant for classification and labelling.

RAC's response

RAC concurs with the response from the dossier submitter that the effect of glyphosate on microorganisms are not relevant for the evaluation of the classification.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	20

Comment received

Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.

Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation.

Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.

Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.

Dossier Submitter's Response

Thank you for your comments which will be considered in the final discussion of the CLH dossier.
A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action

for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
	Ireland		Individual	21
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I urge you to include all independent studies used in the IARC monograph in your assessment. Also please review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
The hazard assessment and toxicological evaluation of carcinogenicity data by the dossier submitter has been performed independently according to the ECHA guidance documents and was not based on the former risk assessment for the approval of glyphosate or evaluations by other institutions. However, all relevant critical discussions of the past are considered in the assessment by ECHA. All studies evaluated in the IARC monograph on glyphosate were discussed in the BfR addendum from August 2015, which was submitted together with the IARC monograph as addendum to the CLH dossier. There is agreement that all studies used in the IARC monograph on glyphosate will be considered in the final discussion of the CLH dossier. All available studies including all studies submitted by industry as well as those published in the scientific literature are assessed very carefully in compliance with common scientific principles. According to EU directives and national laws of EU member states the notifiers of pesticides are legally obligated to submit a range of studies which have to be performed in compliance with guidance documents. The quality of studies submitted by industry and of published studies of other origin is assessed by common criteria. Whether the studies provided by industry could or should become publically available in full, is a legal not a scientific question. This decision is not up to the competent authorities of the DS nor up to ECHA's RAC. As a minimum, these studies are published by EFSA in great length in Volume 3 of the RAR. All available studies in mice and also all studies in other animal species and in humans are taken into account for the decision on classification of glyphosate. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				

Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	22
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Brazil		Individual	23
Comment received				
Discussion on the carcinogenic potential of glyphosate has been blurred by misunderstandings on hazard and risk, by acritical inferences due to mixing results from active ingredient (a.i.) and glyphosate-based formulations (GBF) studies and by complete absence of a state-of-art scientific approach on chemical carcinogen identification which should be based on systematic weight-of-evidence evaluation, on mode of action (MOA) and on criteria for assuming causality.				
Dossier Submitter's Response				
Noted. We have submitted a science-based weight-of-evidence approach for the risk assessment within the RAR, published by EFSA, to support the approval of glyphosate according to Regulation (EC) No 1107/2009. Additionally a science-based weight-of-evidence approach for the hazard assessment was submitted to ECHA in the CLH dossier for classification and labelling according to Regulation (EC) No 1272/2008. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an				

additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	24
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	25
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	26
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Please make sure to Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. All studies have been thoroughly reviewed by the DS according to the ECHA guidance documents, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Thus, evaluation is not flawed. The "independent studies" have been taken into account if the active substance glyphosate was in fact the test item. If the studies provided by industry could or should become publically available in full, is a legal but not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC. At least, these studies are already published by EFSA in great detail in Volume 3 of the RAR.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	27
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				

Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	28
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	29
Comment received				

Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	30
Comment received				
Je suis très préoccupée par les diverses études indépendantes effectuées sur le glyphosate et autres substances du même genre. Il faut absolument faire passer la santé des citoyens avant l'intérêt des fabricants, c'est un devoir. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	31
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				

Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Sweden		Individual	32
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I urge you to: - Include all independent studies used in the IARC monograph in your assessment. - Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. - Ensure that you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	33

Comment received
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Denmark	The Danish Society for Nature Conservation	BehalfOfAnOrganisation	34
Comment received				
Seeing that Glyphosate in various make ups is the most used pesticide globally and seeing that it not only gets used as a herbicide on agricultural and horticultural crops, but also in private gardens, in public areas and for pre-harvest use in many countries, it is obvious that it should be put under extra diligent scrutiny for its hasardous properties. We recognise that glyphosate does not have toxic properties equalling acting as immediately as some other pesticides, it is however of great concern to us that the IARC has labelled glyphosat as "proably carcinogenic. Nonwithstanding that EFSA does not concur with this evaluation, we would all the same implore ECHA for glyphosate to be banned from any private use in gardens and in public spaces like parks, sport facilities, playgrounds etc. and also banned as a substance used pre-harvest in cereals and other arable crops. Pending the scutiny of glyphosate over the coming year, we would also strongly encourage for glyphosate to be banned altogether. A healthy crop rotation can solve most of the problems that glyphosate solve today, because arable crop rotations are far to narrow in their scope. Just look at the success of organic agriculture. ECHA note - The following attachment was submitted with the comment above: *Glyphosate pathways to modern diseases.pdf*				

Dossier Submitter's Response
Noted. In this comment, management decisions due to certain concerns are suggested. That is a separate issue with no direct link to classification and labelling. Thus, the comment is not relevant for discussion on the CLH dossiers and the proposals made herein.
RAC's response
RAC concurs with the response from the dossier submitter that this is not relevant for the evaluation of the classification as classification is based on the evaluation of the intrinsic properties of the substance.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	35
Comment received				
I believe there is enough poison in the air, the water and especially in the fields ; glyphosate as well as others... I am concerned by staying healthy and chemicals on my food is not the right solution. Flora, fauna and the climate suffer and big firms like Monsanto are only concerned by making more and more money ! Disgusting business !				
Dossier Submitter's Response				
Noted. A personal opinion is expressed which is considered not relevant for classification and labelling.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	36
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				

RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	37
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	38
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	39
Comment received				
•Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. •Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	40
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. •Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier.				

A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	41
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Germany		Individual	42
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when				

you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	43
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenity data pointed out By top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted By industry with extreme caution because of the potential conflict of interest and make sure they become publicly available for scrutiny By other scientists.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	44
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que				

le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	45
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Please, we need you listen to us, and to be carefully				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	46
Comment received				
Mesdames, Messieurs, je tiens à attirer votre attention sur plusieurs points dans la mission que vous lancez sur le glyphosate.				

Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Avec mes remerciements [redacted]
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Italy		Individual	47
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. So I urge you to include all independent studies used in the IARC monograph in your assessment and review the studies submitted by industry with extreme caution because of their potential conflict of interest. Please make sure they become publicly available for scrutiny by other scientists and ensure you take into account studies from mice that show that Glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify Glyphosate. Thank you.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	48
Comment received				
Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	49
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Denmark		Individual	50
Comment received				
Dear Mr. Dancet, The glyophosate question is delicate because of the extraordinary interests of the industry. However, money cannot buy neither time nor health, should it turn out that gluophosate is a carcinogen. This is the reason why I expect you and the ECHA to conduct a thorough and scutinizing review. I expect that your assessment will follow the highest scientific standards including transparency regarding your decicions. Yours faithfully [redacted]				
Dossier Submitter's Response				
Thorough evaluation of all the data according to scientific "state of the art" has been made before and will be made by ECHA once more.				
RAC's response				
Noted. See response to comment no 4 and 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	51
Comment received				
Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	52
Comment received				
I am very worried by the deficient evaluation of the data of carcinogenicity, pointed by high-level scientists in an open letter. You have to include all the studies mentioned by the monograph of the IARC in your evaluation. You have				

to estimate the studies presented by the industrialists with a great deal of care, because of possible conflicts of interests. You also have to make them public so that they can be studied by other scientists. Thank you.
Dossier Submitter's Response
All studies have been thoroughly reviewed, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Thus, evaluation is not deficient. The studies mentioned in the IARC monograph have been taken into account if glyphosate was in fact the test item. If the studies provided by industry could or should become publically available in full, is a legal but not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	53
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2016	Germany		Individual	54
Comment received				
Kein allgemeiner Kommentar				

Dossier Submitter's Response
No response possible or needed.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	55
Comment received				
I base my objection to glyphosates on the evidence adduced and conclusions reached by the WHO's IARC, to whit that glyphosate is a probable human carcinogen.				
Dossier Submitter's Response				
All studies evaluated in the IARC monograph on glyphosate were discussed in the BfR addendum from August 2015, which was submitted together with the IARC monograph as addendum to the CLH dossier, which is attached at the end of this document. There is agreement that all studies used in the IARC monograph on glyphosate will be considered in the final discussion of the CLH dossier for hazard assessment of glyphosate. It should be acknowledged that the assessment by IARC is related to hazard assessment and not agreed with the risk assessment by, e.g., the EFSA, the most Member States of the EU, the U.S. EPA, the Canadian PMRA, the responsible authorities in Australia and New Zealand, or the JMPR (also belonging to WHO). Thus, it is at least not so clear-cut whether glyphosate is a probable human carcinogen. All studies have been thoroughly reviewed for hazard identification according to the ECHA guidance documents in the CLH dossier, as can be seen in the CLH dossier. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen by the DS.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	56
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. [redacted]				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2016	Germany		Individual	57
Comment received				
- PMID 27015139 "A causal relationship has not been established between glyphosate exposure and risk of any type of LHC" The carcinogenicity has - in contrast to alcohol or even unstable isotope potassium-40 containing bananas - not been proven. Take into consideration that a safe and effective herbicide cannot be replaced with not-so-safe herbicides. Take into consideration that forbidding glyphosate many people will starve because of lacking alternatives which are safe.				
Dossier Submitter's Response				
Noted. However, it is not clear what is meant with "LHC". It seems that this comment agrees with the opinion of the DS that glyphosate was not carcinogenic. Possibilites for replacement of glyphosate and their advantages or disadvantages (i.e., the economic benefits of glyphosate, when it comes down to it) is not considered relevant by the DS for the science-based decision on classification and labelling.				
RAC's response				
Noted. This evaluation is only looking at the intrinsic hazardous properties of glyphosate in relation to the criteria for classification according to CLP.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	58
Comment received				
Please be sure to take all aspects into consideration, especially the ones backed by studies that have NOT been paid for by parties with commercial interests in the product. Studies sponsored by the manufacturer MUST be made PUBLIC and checked thouroughly according to good scientific practice, in order to be taken into consideration. Public interest and health prevail against non disclosure				

concerns from manufacturers. You were made aware of serious studies with evidence of cancerigenic action. They must be taken into account.
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	59
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	60
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				

Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	61
Comment received				
Bonjour. Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. En espérant que ces inquiétudes largement partagées dans nos pays européens, trouveront un réel et indispensable écho. Respectueusement				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment				

according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	62
Comment received				
Reason for cancer				
Dossier Submitter's Response				
In the CLH dossier including the addendum, it is extensively explained why the DS does not consider glyphosate a carcinogen.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	63
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	64

Comment received
Assez de ces pesticides, insecticides et autres herbicides qui nous empoisonnent, nous et nos enfants, et vos enfants. faites barrage au glyphosate en supprimant sa mise sur le marché, et sans délai. Il y va de notre santé à tous, et celle de votre famille.
Dossier Submitter's Response
Noted. Again, this is a personal opinion which has no impact on classification and labelling.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	65
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. N'oubliez pas qu'en cas de doute avéré, le principe de précaution prévaut et qu'il ne faut pas risquer la santé des générations futures. On peut très bien se passer du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	66
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	67

Comment received

This is a follow-up comment to my previous comment, submitted 11 July '16.

A) I then stated RAC should be consistent in its use formulation studies in classifying pesticides.

To support that I just searched 20+ CLH dossiers on EChA's web pages whose chemical names obviously were pesticides for the word 'formulation (excluding uses such as formulating the feed of an animal experiment, etc.) (this is perhaps half of all CLH that are pesticides). About 40% (9) accepted at least one study using the pesticide's formulation; a couple had several studies (list follows); at least one (fenpyrazamine) used a formulation study to decide no classification of Sensitivity was needed.
The ~40% (9) CLH dossiers found using formulation study/ies:
DEET, chlorsulfuron, imazalil, fenpyrazamine, tebufenpyrid, isoproturon, metazachlor, indoxacarb isomers, epoxyconazole

As you have used formulation studies as the key study for C&L, it is logical to have a moderate policy: accept formulation studies, but only as 'supportive evidence (the CMR guidelines already do this for some other types of evidence). Start with glyphosate, since if you agree this is a sensible step, glyphosate need it the most (so many formulation findings!).

B) For the glyphosate re-authorisation COM vote I had analysed the RAR (which the CLH report is relying on heavily) for dismissals of chronic toxicity findings it reported (in its summaries of experiments). I now insert my findings of UNJUSTIFIED DISMISSALS OF TOXICITY RESULTS into the below comment boxes for the relevant endpoint (page numbers referenced are the glyphosate RAR's vol. B-6.

This is to convince you that even the usual insensitive industry tests are dismissed when they have an inconvenient (to the ADI) finding; so the evidence you are rely on so heavily is not accurate.

Dossier Submitter's Response
It should be highlighted that no proposals relevant for classification and labelling are made in this comment. However, the following comments should be considered: A) It should be always clearly distinguished if a study was performed with an active substance or a formulation. This has been done in case of glyphosate by the DS, in the CLH dossier. For purposes of classification and labelling of a compound, studies with formulations are less relevant. In case of glyphosate, the database obtained with the active substance is large enough. Nontheless, studies with formulations have been taken into account in the CLH dossier. There is no need for revision or amendment. B) The DS is not aware of the list of "unjustified dismissals of toxicity results". The studies and their results are published by EFSA in great detail in Volume 3 of the RAR. For mentioning of an effect in Volume 1, it should be consistent with regard to dose response, strength, and statistical significance. However, we have reported findings even if they were observed to occur in one study or in one laboratory only. By the way, we do not agree with the comment that "industry tests" (most likely those which comply with OECD guidelines) were "usually insensitive". It should be remembered that even the tumours in mice which are now so heavily discussed have been discovered in studies provided by the manufacturers.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	68
Comment received				
This "harmonised classification and labelling (CLH) of substances" will be valuable ONLY if the ECHA disregards the FLAWED EFSA finding on glyphosate in the formulation of glyphosate health and environmental policy for Europe and calls for a TRANSPARENT, OPEN and CREDIBLE review of the scientific literature.				
Dossier Submitter's Response				
Noted. This comment has no impact on classification and labelling. No proposals are made.				
RAC's response				
Noted. Please refer to information on the ECHA website regarding hazard classification of Glyphosate.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Umweltinstitut München e. V.	BehalfOfAnOrganisation	69
Comment received				
Beitrag zum Konsultationsverfahren der Europäischen Chemikalienagentur Vorsorgeprinzip anwenden – Glyphosat verbieten				

Zahlreiche wissenschaftliche Studien liefern Nachweise für eine humantoxische Wirkung von Glyphosat und glyphosathaltigen Pestiziden. Festgestellt wurden karzinogene, reproduktionstoxische, genotoxische und endokrine Wirkungen. Glyphosat wirkt außerdem negativ auf die Biodiversität. Insekten und Vögeln wird Nahrung und Lebensraum entzogen, das Bodenleben wird geschädigt. Besonders giftig ist Glyphosat für Amphibien, Fische und andere Wasserorganismen.
Im Glyphosat-Bewertungsverfahren der EFSA und des deutschen Bundesinstituts für Risikobewertung (BfR) im Rahmen einer Neuzulassung des Wirkstoffs wurden gravierende Fehler gemacht. Die Behörden wurden auf die Mängel hingewiesen. Dennoch blieben sie bei ihrer Empfehlung, Glyphosat als nicht krebserregend einzustufen. Sie berufen sich dabei auf Industriestudien, die Glyphosat entlasten sollen. Diese Studien sind aber nicht öffentlich einsehbar. Die Europäische Chemikalien-Agentur wird in den nächsten Monaten eine Einstufung von Glyphosat vornehmen und damit eine wichtige Grundlage für die Entscheidung liefern, ob der Stoff erneut zugelassen werden soll. Wir bitten die ECHA, diese Gelegenheit zu nutzen, um das Vertrauen der Bürgerinnen und Bürger in die Bewertung von Chemikalien auf EU-Ebene wiederherzustellen. Damit dies gelingt, dürfen die Fehler von BfR und EFSA nicht wiederholt werden. Die von NGOs und unabhängigen WissenschaftlerInnen vorgebrachten Kritikpunkte müssen in die Bewertung durch die Europäische Chemikalienagentur miteinbezogen werden. Dies betrifft insbesondere die Fehler bei der statistischen Auswertung bei Krebsstudien an Mäusen und die zu Unrecht verworfenen epidemiologischen Studien.

Studien mit Hinweisen, dass Glyphosat als endokriner Disruptor wirkt, müssen bei der Bewertung ebenfalls dringend miteinbezogen werden. Wirkstoffe, die das Hormonsystem schädigen, sind gemäß der Verordnung über die Bereitstellung auf dem Markt und die Verwendung von Biozidprodukten (Verordnung EG/528/2012) von einer Zulassung ausgeschlossen. Die Kommission hat trotz eindeutiger, präziser und unbedingter Handlungsaufforderung aus der Verordnung die Benennung von Kriterien für die Einstufung von Stoffen als endokrinschädigend über drei Jahre lang verschleppt. Infolgedessen sind bis heute keine Kriterien beschlossen. Dennoch wäre es ein grober Fehler, wenn die ECHA sich diesem Thema nicht widmet. Studien geben zahlreiche Hinweise darauf, dass Glyphosat das menschliche Hormonsystem beeinflusst. Auch die EFSA konnte eine hormonelle Wirkung von Glyphosat nicht ausschließen.

Für die Einstufung von Glyphosat durch die Europäische Chemikalienagentur (ECHA) muss eine gefahrenbasierte Bewertung vorgenommen werden, so wie es die CLP-Verordnung (Verordnung über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen [CLP] 1272/2008, 3.5.2.2.) und die Pestizidverordnung vorsehen. Ausschlaggebend für die Bewertung muss sein, ob Glyphosat krebserregend ist und welche anderen Gefahren von dem Wirkstoff ausgehen, und nicht wie hoch die Schadenswahrscheinlichkeit bei der normalen Aufnahmemenge ist.
Quellen zur endokrinen Wirkung
•IARC (2015): Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology, 20 March 2015, http://dx.doi.org/10.1016/S1470-2045(15)70134-8

http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf •Gasnier C, Dumont C, Benachour N, Clair E, Chagnon MC, Séralini GE. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines.http://www.gmoseralini.org/wpcontent/uploads/2013/01/Gasnieral.TOX_2009.pdf •Dallegrave E, Mantese FD, Oliveira RT, Andrade AJM, Dalsenter PR, Langeloh A. Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats http://link.springer.com/article/10.1007/s00204-006-0170-5#/page-1 •Richard S, Moslemi S, Sipahutar H, Benachour N, Seralini GE. Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257596/ ECHA note - The following attachment was submitted with the comment above: *Analysen und Studien.zip*
Dossier Submitter's Response
Also in this comment, no proposals for classification and labelling are being made to which the DS might respond. Apparently, the evaluation of glyphosate by the DS is not agreed with by the German "Umweltinstitut". However, this evaluation is sufficiently explained in the CLH dossier and there is not much use in repeating it here once more at length.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	70
Comment received				
I am very preoccupied by the mass use of any chemical products, whatever its degree of toxicity on Earth and on living beings. Toxic products should be the exception, not the normal way.				
Dossier Submitter's Response				
The comment is not directly linked to the assessment of glyphosate with regard to classification and labelling.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	71
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				

Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	72
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	73
Comment received				
Prendre soins dès générations futur est un de vos devoir! Alors quand vous ferai vos études prennez bien tout les paramètres : CIRC, études independente, ect.. On s'est tous que le glyphosphate est cancérigène alors faite le bon choix pour les citoyens européens, pourvois et vos enfants !				
Dossier Submitter's Response				
All studies have been thoroughly reviewed including those mentioned in the IARC monographs. The studies and their results are reported in detail. Taking a weight of evidence approach, the DS is still convinced that glyphosate is not carcinogenic. For justifications, see the CLH dossier, please!				

In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Netherlands		Individual	74
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Please make sure you include all independent studies used in the IARC monograph in your assessment. And please review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. I would also like to ask you to ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	75
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	76
Comment received				
e suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	77
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				

Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	78
Comment received				
Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate				
Dossier Submitter's Response				
The studies in mice are reported in detail in the CLH dossier and an extensive explanation is given for all three tumour types of concern why glyphosate is not considered a carcinogenic substance. In the addendum, re-evaluation was performed using the OECD framework. The same conclusion was reached.Also the (epidemiological) studies on cancer in humans have been taken into account. See also our response to comment 26, please!				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	79
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				

RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	80
Comment received				
•Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	81
Comment received				
Je suis très préoccupée par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	82
Comment received				
Glyphosate is now well knowned to cause cancer, that a good reason why we don't need it. Remember that first application of glyphosate was war. Moreover it significantly slow the process of metamorphosis that agriculture is living right know by promoting an old vision of agriculture (GMO, huge exploitations, monoculture, etc) it kills human and bio organisms that feed the plants in normal conditions. What do we need today is to study interction between plants, micro organisms, habitat, not to kill it with glyphosate.				
Dossier Submitter's Response				
The DS has still the opinion that glyphosate does not cause cancer. Apart from that, this comment is a personal opinion that may be shared or not. It has not impact on the classification and labelling.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	83
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Netherlands		Individual	84
Comment received				
I believe we a further investigation of glyphosate is necessary. May you find out what is good for all living creatures.				
Dossier Submitter's Response				
One will hardly find a chemical for which such a huge toxicological database is available as for glyphosate. There is certainly enough data to draw a conclusion with regard to classification and labelling. No proposals are made in this comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	85
Comment received				
The amount of glyphosate used in agriculture has increased due to increased production of genetically modified flora that is made resistant to the substance. Additionally several cities use glyphosate to remove weeds from roadsides and parks. Recent findings in IARC study should be seriously taken in to account when forming regulations for herbicides.				
Dossier Submitter's Response				
Noted. As can be seen from the CLH dossier, the IARC monograph has been seriously taken into account. It must be emphasised, however, that there is no such thing like a "study" by IARC even though this is a misunderstanding. Instead, IARC reviewed only published, previously known information without having access to most original studies. The comment itself has no impact on classification and labelling.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	86
Comment received				
•I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. •Include all independent studies used in the IARC monograph in your assessment. •Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. •Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	87
Comment received				
Die Konsultation ermöglicht keine spezifischen Kommentare zu den Auswirkungen von Glyphosat auf die Artenvielfalt. Gleichwohl sei an dieser Stelle angemerkt, dass Glyphosat laut Umweltbundesamt nachweislich schädliche Auswirkungen auf die Biodiversität hat. So zerstört Glyphosat als Breitbandherbizid die Nahrungsgrundlage für zahlreiche Insekten, womit wiederum durch den Rückgang der Insektenpopulationen auch vielen Feldvögeln die Nahrungsgrundlage entzogen wird. Vgl. https://www.umweltbundesamt.de/themen/chemikalien/pflanzenschutzmittel/glyphosat				
Dossier Submitter's Response				
Thank you for comment. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on direct effects of substances on the aquatic environment. There is no hazard class in the CLP regulation to classify glyphosate for indirect effects on biodiversity.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	88
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when				

you decide how to classify glyphosate. In any case. Please keep in mind you and your family are as concerned as by what these products do...
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Denmark		Individual	89
Comment received				
Yours truly is extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Sweden		Individual	90
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Therefore, I have 3 points you must make sure is part of further inquiries into this probably carcinogenic product:				

* Include all independent studies used in the IARC monograph in your assessment. * Review the studies submitted by industry with EXTREME caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. * Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Netherlands		Individual	91
Comment received				
Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Ireland		Individual	92
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I would request that you please include all independent studies used in the IARC monograph in your assessment.				

Please review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Please ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	International Agency for Research on Cancer (IARC)	BehalfOfAnOrganisation	93
Comment received				
The IARC Monographs' programme will be readily available to provide clarifications requested by ECHA and or RAC regarding the completeness and interpretation of scientific data with regards to the carcinogenicity of glyphosate.				
Dossier Submitter's Response				
Noted. No need for response by DS.				
RAC's response				
Noted, thank you for the offer to provide clarifications. See also responses to comment no. 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium		Individual	94
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Netherlands		Individual	95
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Sweden		Individual	96
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Please include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				

Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate. Kind regards from a concerned citizen, mother and daughter of a woman who died too early in cancer. [redacted]
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Ireland		Individual	97
Comment received				
I do not want chemicals in my food that profit companies and multinationals. I would agree if a chemical was proven to be necessary by an independent body overseen by a people's jury. I call for all food additives to be proven safe before production at the producers expense.				
Dossier Submitter's Response				
In this comment, a personal opinion is expressed. It has no impact on classification and labelling of glyphosate.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Portugal		Individual	98
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				

Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Hungary		Individual	99
Comment received				
For the healthy wellbeing of my and your and everyone's children PLEASE REPRESENT US AND ACT ACCORDING THE FOLLOWING POINTS: I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results. I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest". Thanks in advance with best wishes				
Dossier Submitter's Response				
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Poland		Individual	100
Comment received				

•I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter and I calling you to: •Include all independent studies used in the IARC monograph in your assessment. •Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. •Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Bulgaria		Individual	101
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter so I ask all independent studies used in the IARC monograph to be included in your assessment. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Bulgaria		Individual	102
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Romania		Individual	103
Comment received				
Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number

16.07.2016	Italy	Food and Veterinary Toxicology section - Istituto Superiore di Sanità	BehalfOfAnOrganisation	104
Comment received				
It is advisable to reconsider the classification of Glyphosate for carcinogenicity: based on the evidence on malignant lymphomas in mice, the substance may meet the criteria for Cat.2 classification. It is, therefore, advisable a detailed appraisal at ECHA level (see Specific Comment on Carcinogenicity). In addition, limited evidence is provided to rule out endocrine disruption. Apparently, endocrine disrupting effects are ruled out mainly on the basis of two short summaries provided by US EPA (Levine et al., 2012; Bailey et al., 2013). Before taking any final conclusion, and due to the relevance of endocrine disrupting effects in the REACH framework,full reports should be available in order to allow an independent assessment by EU authorities. Therefore, in order to confidently rule out endocrine disruption, more details should be obtained about the studies (protocols, concentrations/dose levels, endpoints, and results)assessed by US EPA,				
Dossier Submitter's Response				
In the CLH dossier and the addendum, justification is given why no proposal for classification and labelling was made on basis of malignant lymphoma in mice. One of the main reasons was the extremely variable but often very high spontaneous incidence of this tumour type. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. With regard to ED properties, it must be clarified that ED properties will not be classified by ECHA according to the CLH dossier. Therefore the fact of a substance exhibiting ED properties would not lead automatically to classification and labelling. Instead, it would rather depend on the occurrence of adverse effects due to ED in the apical toxicological studies. Thus, even the submission of the new studies in full from the U.S. EPA would not have an impact on the proposals for classification and labelling. The EU Commission has recently published a draft on criteria for identification of endorine disrupters.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	105
Comment received				
I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of				

interest". I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Netherlands		Individual	106
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I urge you to include all independent studies used in the IARC monograph in your assessment. Please review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Spain		MemberState	107
Comment received				
We would like to thank the author(s) of this report for a very thorough, well structured, comprehensive and well-written document. Besides, Spain acknowledges the excellent quality of the scientific analysis provided in it.				
Dossier Submitter's Response				
Noted. Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	108
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	United Kingdom		Individual	109
Comment received				
Carcinogenicity data seems to have been improperly interpreted. Studies used should be widened to include all those in the IARC monograph. Industry				

studies compromised by vested interest. Mice studies have shown carcinogenic effects.
Dossier Submitter's Response
All studies underwent thorough review and evaluation including those mentioned in the IARC monograph. In the CLH dossier, it is explained in length why no classification and labelling for carcinogenicity is proposed. A more comprehensive answer is submitted in the response to comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Hungary		Individual	110
Comment received				
Being an inhabitant of the European Union member country, I would like to bring the following to your attention:- I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Denmark		Individual	111
Comment received				

Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4 and 11.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Ireland		Individual	112
Comment received				
Include all independent studies used in the IARC monograph in your assessment.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Ireland		Individual	113
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				

Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Netherlands		Individual	114
Comment received				
- A large numder of top scientists has written an open letter in which they express their concern about the flawed evaluation of the carcinogenicity data on glyphosate - Studies that are payed for by the industries that have a business interest in the production and use of glyphosate and that are kept secret, cannot be seen as independent scientific studies. This is self evident. The ECHA should base its conclusions only on scientific studies that have been open to peer review and that have been published.				
Dossier Submitter's Response				
The claim that the evaluation was flawed is rejected since all studies have been subject to thorough critical assessment as can be readily seen in the CLH dossier. Published studies have been taken into consideration but the comprehensive studies performed by the manufacturers must not be disregarded only because of their source. The companies are legally obliged to provide such studies. They have to perform them according to OECD guidelines and under GLP conditions. Such studies provide the basis for health evaluation of most pesticides. There is no reasonable justification for making an exception just for glyphosate.				
RAC's response				
Noted. See response to comment no 4 and 11.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Germany		Individual	115
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when				

you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	116
Comment received				
Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	France		Individual	117
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				

Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	[redacted]	BehalfOfAnOrganisation	118
Comment received				
Much of the scientific review and rationale presented in the CLH report by BAuA is sound and endorsed by the Glyphosate Task Force (GTF), with the exception of the new proposed classification for STOT-RE category 2. The rabbit model cited as a basis for the proposed STOT-RE (CLH report page 42) is not relevant to humans in cases where nutritional integrity of orally dosed rabbits is compromised by gastrointestinal effects which result in loose stools. Such scenarios prevent the animals from performing the necessary act of coprophagy. If coprophagy is not feasible in rabbits, poor nutrition due to reduced vitamin nitrogen, protein and sulfur intake results in weight loss, compromised health and even mortality. Maternal toxicity findings is rabbits is not consistent with multiple studies conducted in mice, rats and dogs, which do not rely on coprophagy for a balanced diet. It is also important to note that the maternal toxicity findings in orally dosed pregnant rabbits is not a consequence of systemic toxicity, as reflected in the complete absence of toxicity in repeat dose dermal toxicity studies in rabbits themselves. Multiple rabbit dermal toxicity studies consistently report the highest dose tested as the NOAEL. Systemic glyphosate exposures up to 133 mg/kg/day were calculated based on a dermal NOAEL of 5000 mg/kg bw/day and measured dermal absorption of 2.66% from an in vitro rabbit skin study. Accounting for the established 20% oral absorption of glyphosate, the equivalent oral dose of 665 mg/kg bw/day to reach this systemic dose yields no systemic toxicity via the dermal route. Since glyphosate is essentially unmetabolized in mammals, systemic toxicity is independent of the route of exposure and therefore the maternal toxicity noted in lower dosed oral gavage studies is attributable to a local GI tract effect, and should not be considered systemic toxicity to a specific organ. A thorough and systematic scientific evaluation of the regulatory toxicology studies following internationally accepted study guidelines and scientific literature demonstrates that glyphosate is not a carcinogenic, mutagenic, reproductive or endocrine disruption hazard for humans. This position is also endorsed by several decades of detailed regulatory reviews across the globe including the Australian Pesticides and Veterinary Medicines Authority (APVMA), Canadian Pest management Regulatory Agency (PMRA), Rapporteur Member State Germany – Renewal Assessment Report (RMS Germany - RAR), European Food Safety Authority (EFSA, 2015), United States Environmental Protection Agency (US EPA, 2012) and the Joint FAO/WHO Meeting on Pesticide Residues (JMPR, 2016). More specific details are outlined below and				

in the appended documentation. ECHA note - The following attachments were submitted with the comment above: *Glyphosate-Confidential.7z and Glyphosate-Public.7z*
Dossier Submitter's Response
The proposal (STOT RE 2) is kept since mortality is the most severe maternal effect which may occur in a study of this type. The pregnant rabbit turned out to be the most sensitive animal model. There is no reason to disregard these findings. Whether the mechanism causing the observed effect is local rather than systemic is not relevant for classification.
RAC's response
Noted. See response to comment no 278.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	United Kingdom		Individual	119
Comment received				
ECHA submission for the reassessment of glyphosate The German Rapporteur Member State (BfR) claimed that glyphosate has minimal effects on biodiversity. I challenged EFSA's Dr José Tarazona and Dr Bernhard Url about this between November 2015 and February 2016. I sent them evidence to the contrary. [redacted] Yet, despite these data gaps, the unelected European Commission re-licensed glyphosate for 18 months while the European Chemical Association (ECHA) produced its verdict. We have done a 10-year (2006-2016) observational study of biodiversity on a small Nature Reserve exposed to ultra-low dose Roundup® sprayed on Japanese knotweed outside our area. Japanese knotweed has become a Roundup-resistant super-weed and just grows more strongly each year spray is applied (like super-weeds in GM cropping systems in the US). From 2006 to 2010 we documented 143 different species of moth, four species of bush-cricket, 20 species of butterfly, six species of bumblebee and numerous dragonflies, damsel flies, grass-hoppers, many beetles including ladybirds and the rare oil-beetle, bats, many forms of hover flies and solitary bees, vigorous pond life including whirligig beetles, water boatmen and giant diving beetles. In 2013 biodiversity began to decline both in species and in number. This was documented in a paper in 2014. Moths have almost vanished. http://www.i-sis.org.uk/How_Roundup_Poisoned_My_Nature_Reserve.php Declines in biodiversity continued in 2015 and 2016 because Swansea City and County Council had employed a commercial national contractor Complete Weed Control, to embark on a 3-year-programme of eradication of Japanese Knotweed with Dakar Pro, (a commercial form of Roundup) in the Ilston Valley not far from our reserve (as well as the Clyne Valley). They said they would continue 'while Roundup is still legal'. Photographs of our bee hotel taken on				

29/06/2015 and on 06/07/2016 show the disappearance of our solitary bees. By 2017 when ECHA has finally decided, our Nature Reserve will be a biological desert as described by Craig Childs in his book Apocalyptic Planet: Field Guide to the Future of the Earth. The state of Iowa was just one area in which the US Geological Survey reported widespread contamination of soil, air, rainwater and river water with glyphosate and its longer-acting metabolite AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid). Grundy County, Iowa was where Craig Childs spent a long weekend in a monoculture of GM "Roundup® Ready" corn looking for wildlife. "In this cornfield, I had come to a different kind of planetary evolution. I listened and heard nothing, no bird no click of an insect … Mr Owen was the farmer who had given us permission to backpack across his cornfields. He grew a combination of DuPont and Monsanto stock. We were in DuPont now. It didn't look any different to me." When ECHA endorses the European Commission's verdict of safety of glyphosate to satisfy farmers and protect the profits of Agrochemical Corporations, your children and grandchildren might well ask you this question: "Where have all the moths, bush-crickets, butterflies, bumblebees, dragonflies, damsel flies, grass-hoppers, beetles, ladybirds, bats, hover flies and solitary bees gone? Why are our vegetables not being pollinated? Were you responsible? Did you kill them?" To which you will have to answer: "Yes, we killed them."
Dossier Submitter's Response
Thank you for comments Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on the direct effects of substances on the aquatic environment. There is no hazard class to classify glyphosate for indirect effects on biodiversity according to the CLP regulation.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Norway		MemberState	120
Comment received				
IARC evaluated glyphosate in 2015 and concluded that the substance is probably carcinogenic to humans. However EFSA concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans. More recently the JMPR concluded that the substance is not carcinogenic in rats, but pointed out that a tumorigenic effect could not be excluded at high doses based on studies on mice. http://www.fao.org/3/a-i5693e.pdf				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	United Kingdom		Individual	121
Comment received				
My group is investigating potential low dose pesticide toxicity including that of glyphosate-based herbicides. Our work has demonstrated kidney and especially liver damage in rats chronically (2-year) exposed to Roundup herbicide. We have also shown that glyphosate possesses estrogenic properties and thus can be classified as an endocrine disruptive chemical. Thus my group's work makes a direct contribution to the evidence base for regulating this class of pesticide. ECHA note - The following attachment was submitted with the comment above: *Mesnage2015.pdf* Journal articles are not confidential as such, however, ECHA does not publish them on the website due to Intellectual Property Rights.				
Dossier Submitter's Response				
Thank you for your contribution. However, to our knowledge, the tissue samples have been obtained from a study that was widely considered as not reliable. Thus, the relevance of the new findings may be doubted. Furthermore, results of a study with Roundup cannot be directly used for classification and labelling of glyphosate. With regard to ED properties of glyphosate, there were no adverse findings pointing into that direction in the apical toxicological studies and no evidence for endocrine-mediate effects was obtained in the research programme commissioned by U.S. EPA.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Switzerland		Individual	122
Comment received				
These comments completely replace my previous comments which had a problem with the Figure numbering. The previous submission has Reference Number 702fd2a8-3afd-41ea-ac94-fc89eb76cbd5.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
21.06.2016	France		Individual	123
Comment received				

From what I read, it would be logical to include carcinogenicity, germ cell mutagenicity and reproductive toxicity.
Dossier Submitter's Response
All these endpoints have been addressed in the CLH dossier. Justifications for not proposing classification and labelling are given.
RAC's response
Noted. See response to comment no 11, 228 and 259.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Czech Republic		Individual	124
Comment received				
I am a member of an organisation of millions of concerned private individuals. Our organisation has, and is, actively campaigning to ban the use of all glyphosate. We would like the truth, independent of all pressure groups.				
Dossier Submitter's Response				
Noted. No proposal with regard to classification and labelling is made in the comment.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	Denmark		MemberState	125
Comment received				
The proposal to classify glyphosate as STOT RE cat 2 is based on the observation of increased mortality in pregnant rabbits in several developmental toxicity studies. Increased mortality is a very severe effect which is not taken into account in other parts of the classification proposal. Applying Haber's rule to adjust the standard guidance values for exposure duration of about 14 days, gives a guidance value of approximately 60-600 mg/kg bw/day for STOT RE category 2 classification. Below the adjusted standard guidance value of 600 mg/kg bw/day, increased mortality is observed in 5 out of 7 studies in pregnant rabbits (with an "overall" maternal NOAEL of 50 mg/kg bw/day being established based on the 7 developmental studies). We therefore find that a classification of glyphosate as STOT RE cat 2 is indeed justified. Thus the classification proposal – including the proposal for Eye dam. 1 and Aquatic chronic 2 - is supported and we agree that further classification is not necessary.				
Dossier Submitter's Response				
Noted. Thank you for the support.				
RAC's response				
Noted. See response to comment no 278.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France		Individual	126

Comment received
Levels of glyphosate are being found in human urine that are at levels higher than that permitted in the water supply. If a designated 'safe' level is being exceeded then how can this be safe and of no health concern? If levels in water are legislated for, where is the legislation for permitted levels in food and why is it translating into high levels in urine. FUrther, Why are glyphosate levels controlled and monitored in water supplies and appear to be irrelevant in food? One more thing, given Monsanto's reputation for producing chemical treatments that are later found to be detrimental to health and are banned, what evidence exists that indicates can we realistically expect their testing and prognosis of one of their products to be open and truthful?
Dossier Submitter's Response
It should be understood that the permitted drinking water limit value of 0.1 µg/L (98/83/EC) is a legal value. That is based on the scientific knowledge and taking into account the precautionary principle For permitted residues in food and feed, the toxicological properties of a compound are taken into account, in contrast. It has been shown that urinary concentrations of glyphosate as measured in people in Europe and North America suggest a previous (dietary, environmental or occupational) exposure which is by magnitudes lower than the health-based reference values (see Niemann et al., 2015). Really high urinary concentrations have been reported only after suicidal or accidental oral intake of large volumes of glyphosate-containing herbicides (see Zouaoui et al., 2012).
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Portugal		Individual	127
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				

RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Germany		Individual	128

Comment received

The discussion about Glyphosate in the EU is not a scientific discussion, but the result of lobbying for the chemical industry, and in particular by the glyphosate producers: Monsanto, Syngenta, BAYER AG, BASF and others. This is not a secret but a well-known and researched fact in the public media. I am not a scientist nor a member of a NGO or in any way related to the chemical industry but a very concerned consumer from Germany who researched a lot about this topic. I am not a biologist nor a natural scientist and probably don't use the toxicological or scientific terms correctly, but I have attached and cited all the resources for my arguments and complaints.

Table of Content:

1. Over 750 studies prove the toxic effects of glyphosate

It is already well researched in over 750 scientific studies and publications that glyphosate is toxic for humans, animals and the ecosystems.

These 750+ studies are available via the NGO platform GMO Free USA:

http://www.gmofreeusa.org/research/glyphosate/glyphosate-studies/

These glyphosate studies and articles are published and peer-reviewed by other scientists.

The IARC has evaluated these independent (not-paid by the glyphosate producers) studies from international researchers with 17 scientists for one year just in search of proof of the carcinogenic effects of glyphosate on the human body.

2. The vague academic methods of the German BfR

The German BfR in contrast just – or mainly – reviewed unpublished secret glyphosate studies from the glyphosate producers.

The BfR also used letters to the editors from glyphosate users as scientific studies, as the German newspaper Die Sueddeutsche revealed: (Only in German available) http://www.sueddeutsche.de/wirtschaft/kampf-um-glyphosat-wenn-leserbriefe-von-monsanto-als-studien-gelten-1.2570374

Furthermore, the BfR marked a lot of studies that prove the carcinogenic effects of glyphosate as irrelevant, not reliable or false.

These are mistakes by the BfR in favor of the chemical industry, because these studies use correct scientific methods and are actually relevant.

This is also documented in various TV reports (only in German available):
The German ZDF Frontal 21 report via youtube:
https://www.youtube.com/watch? v=GdZ4b_5cDRQ

And the German ARD report:
http://www.ardmediathek.de/tv/Europamagazin/Das- Gescha¨ft-mit-dem-umstrittenen-Herbiz/Das-Erste/Video?bcastId=342024&documentId=31161846

The German BfR admitted in their secret study that they didn't review all of the 1200 glyphosate studies from the glyphosate producers, but the BfR simply adopted the results of 850 studies without a re-evaluation.

And these studies are initiated and paid by the glyphosate producers. The details can be found in this interview with the German politician Harald Ebner (Bu¨ndnis 90 / Die Gru¨nen). Only in German available via Euronews:
http://de.euronews.com/2016/06/30/mdb-ebner-zu-glyphosat-risiko-der-krebsgefahr/

Also, 96 international scientists claimed in an open letter by Prof. Christopher J. Portier to the EU Commissioner of Health & Food Safety, Mr. Vytenis Andriukaitis, that the methods used by the German BfR are not academic comprehensible.

This letter can be found via Efsa Europe:

https://www.efsa.europa.eu/sites/default/files/Prof_Portier_letter.pdf

The 250 delegates from the 119. Deutschen A¨rztetages 2016 that represent all the doctors in Germany demand from the German government and the EU commission the ban of herbicides that contain glyphosate.

This info can be obtained via the official site of the German Bundesa¨rztekammer: http:// www.bundesaerztekammer.de/ueber-uns/landesaerztekammern/aktuelle- pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/

Dr. Peter Clausing from the Pestizid Aktions-Netzwerk e.V. (PAN Germany) also analyzed and criticized the method adopted by the BfR to examine the carcinogenic effects on mice, which the BfR marked as irrelevant.

This report, which is only available in German, can be obtained via the official site of the Austrian NGO Global2000:
https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf

And Prof. Dr. Eberhard Greiser criticized the methods used by the BfR and Efsa too: This report, which is only available in German, can be obtained via the official site of the Austrian NGO Global2000:
https://www.global2000.at/sites/global/files/
Gutachten_Prof.Greiser_Glyphosat_Studien.pdf

Another group of eight scientists, namely, Michael Antoniou, Mohamed Ezz El-Din Mostafa Habib, C. Vyvyan Howard, Carlo Leifert, Rubens Onofre Nodari, et al. have published a 52-page long scientific in-depth review of the non-scientific methods of the BfR.

The group reviewed also the independent glyphosate studies in search of birth defects and found evidences:
This full-report, Roundup and Birth Defects, can be obtained via the publication website Scribd:
https://de.scribd.com/doc/57277946/RoundupandBirthDefectsv5

3. The WHO under the influence of the glyphosate producers

The World Health Organization (WHO), which also claimed that glyphosate is non- carcinogenic, non-toxic for humans, animals and the eco-system works and acts under industry influence.

A German TV report revealed that the WHO got 75% of their annual budget, which is 3 billion dollar from the industry in 2011, and in particular directly from glyphosate producers like Syngenta, BAYER and others.

The German ZDF TV reportage can be watched here via youtube (only in German):
https://www.youtube.com/watch?v=vtuFi0O5rjQ

The WHO is also funded indirectly by Monsanto because the Bill and Melinda Gates Foundation Trust owns a big share of the glyphosate producer Monsanto.

This info can be obtained via the NGO Wiki: Source Watch
http://www.sourcewatch.org/index.php/Bill_%26_Melinda_Gates_Foundation

And the Gates Trust paid the WHO over 400 million dollars in 2011. This info can be found via Global Health Policy:
http://www.globalhealthpolicy.net/?p=826

Also in 2015, the WHO still got funded from the:

Bill and Melinda Gates Foundation Trust: 185 million dollars

Glyphosate Producer Bayer AG: 0.6 million dollars

Glyphosate Producer Syngenta : 160, 000 dollar Glyphosate Producer BASF: 130, 000 dollar

All Infos via World Helath Organization: http://www.who.int/about/finances-accountability/reports/A69_INF3-en.pdf?ua=1

And when acknowledging the many decisions the WHO made in the past in favor of some industry companies, as Soren Ventegodt revealed in this article in the Journal for Integrative Medicine & Therapy:
http://www.avensonline.org/wp-content/uploads/JIMT-2378-1343-02-0004.pdf

or the journalist, Anne Kleinknecht, in this German TV report:
http://www.br.de/nachrichten/who-pharma-industrie-100.html

all the above fundings by the glyphosate producers are in fact not in compliance with the ethical standards of the WHO which states:
"Funds may be accepted from commercial enterprises whose business is unrelated to that of WHO, provided they are not engaged in any activity that is incompatible with WHO's work."

Why, because the WHO actually does judge and has judged in favor of particular companies and not in favor of the health of the people in the world.

These infos about the WHO have been revealed by this German ZDF TV report: (Only available in German):
https://www.youtube.com/watch?v=vtuFi0O5rjQ

4. The JMPR and its experts under the influence of the glyphosate producers

The WHO expert committee, JMPR, which claimed that glyphosate is harmless to the human body is also heavily influenced by the industry as this German ARD TV report revealed: (Only available in German)
https://www.youtube.com/watch?v=gB3pFQQHJiI

Furthermore, the JMPR has seven experts who get paid – directly or indirectly – by the glyphosate producers, as this article by Stéphane Horel reveals, via Environmental Health News:
http://www.environmentalhealthnews.org/ehs/news/2016/june/endocrine-disrupters-final- maneuvers-by-brussels2019-industry-linked-scientific-community

Here are a few examples from the article:
[redacted]

The members of the ECOTEC that are paid for their work as experts and consultants are the glyphosate producers: Syngenta, BAYER, BASF, Dow Chemical and others.

This info can be obtained via the ECOTEC website:
http://www.ecetoc.org/ecetoc-membership/member-companies/

[redacted]

[redacted]
http://www.ecetoc.org/wp-content/uploads/2014/08/ ECETOC_WR_27._Expert_panel_to_better_understand_endocrine_disrupter_low_doses_ effects.pdf

[redacted]
http://ilsi.eu/task-forces/food-safety/packaging-materials/

And the ILSI Europe is funded by Monsanto, and in addition by the Croplife International group and their members, which are the glyphosate producers: Monsanto, BASF, DuPont, Dow Europe (Dow Chemical) et al.

This info can be obtained via the official ILSI website:
http://ilsi.eu/about-us/

The British newspaper, The Guardian, revealed in May 2016 how the ILSI is influenced by the payments from the chemical industry:
https://www.theguardian.com/environment/2016/may/17/unwho-panel-in-conflict-of- interest-row-over-glyphosates-cancer-risk

[redacted]
This info can be obtained via the Monsanto news site:
http://www.monsanto.com/global/in/ourcommitments/pages/monsanto-beachell-borlaug- international-scholarship-program.aspx

And Syngenta cooperates with the Leicester University in projects or provides their students with job opportunities.

This info can be obtained via the official Leicester University website: https://le.ac.uk/search?q=syngenta

5. The FAO under the influence of the glyphosate producers

Also, the FAO that judged glyphosate as non-toxic to the human body received in fall 2015 a voluntary financial contribution of € 300,000 by the European Seed Associations (ESA): This info can be obtained via the official ESA website: https://www.euroseeds.eu/esa-hands-300000€-voluntary-financial-contribution-fao-it

And the paying members of the ESA are glyphosate producers: Monsanto, Syngenta, Bayer, and BASF. This info can be obtained via the official ESA site: https://www.euroseeds.eu/esa_members/Individual-Members

6. Efsa experts paid by the glyphosate producers

Eight members of the Efsa expert group that judged glyphosate as non-toxic to the human body are under the influence of the glyphosate producers.

In addition, 4 of the 18 experts never worked on endocrine disrupters as the German NGO Lobbycontrol revealed:

https://www.lobbycontrol.de/2015/06/efsa-bfr-gefaehrden-unsere-gesundheit-zugunsten-
der-industrie/

Also, the PAN Europe Network came to a conclusion in its analysis that nearly all Efsa experts are industry-biased. This info can be obtained via the PAN Europe report: A Toxic Mixture? Industry bias found in EFSA working group on risk assessment for toxic chemicals: http://www.pan-europe.info/old/Resources/Reports/PANE%20-%202011%20-%20A%20Toxic%20Mixture%20-%20Industry%20bias%20found%20in%20EFSA%20working%20group%20on%20risk%20assessment%20for%20toxic%20chemicals..pdf

The Efsa staff is also under the influence of the chemical industry:

This info can be obtained via this Danish website (Only available in Danish): http:// www.danskgartneri.dk/nyheder/2015/september/handlingsplan-for-

prosulfocarb-i-2015

[redacted]

This info can be found via the website of The Parliament Magazine: https://www.theparliamentmagazine.eu/articles/news/no-place-food-lobby-efsa-board-says-ngo

7. Monsanto hides his secret glyphosate studies with the help of the authorities

As mentioned before, the German BfR reviewed only glyphosate studies by the glyphosate producers which are not publicly available and are labeled as confident and trade secret.

This is strange because the patents for Monsanto's glyphosate are expired in most of the countries.

This is also strange because the European Court has judged in 2013, in the law case, Greenpeace against Monsanto (Case T-545/11), that Monsanto has to make his glyphosate studies public because the health of over 600 million people in the European Union depend on the trade secret of the company.

This judgment can be obtained via the official European InfoCuria website: http://curia.europa.eu/juris/document/ document.jsf;jsessionid=9ea7d0f130d589f04532581f4b588a7cc2074f2fd759.e 34KaxiLc3e Qc40LaxqMbN4Pa3aPe0? text=&docid=142701&pageIndex=0&doclang=EN&mode=lst&dir=&occ=first&p art=1&cid=2 44708

Despite this European Court judgement, the EU food safety institutes, BfR and Efsa, are not forcing Monsanto to publish their glyphosate studies.

Not only this, the BfR defends Monsanto strategy to hide the glyphosate studies by saying that Monsanto is authorized to do so.

And there are more reasons why the BfR is influenced by the glyphosate industry.

8. The German BfR and its experts under the influence of the glyphosate producers

Many of the BfR commissioners for pesticides get also paid directly by the glyphosate producers or are closely connected to them.

This info can be obtained via the official BfR website:
http://www.bfr.bund.de/de/mitglieder_der_bfr_kommission_fuer_pflanzenschutzmittel_und_ihre_rueckstaende-189320.html

[redacted]

[redacted]

BfR - Syngenta cooperations and projects:
http://www.jki.bund.de/index.php?id=1075&q=Syngenta

BfR - BASF cooperations and projects:
http://www.jki.bund.de/index.php?id=1075&q=BASF

BfR - Monsanto cooperations and projects:
http://www.jki.bund.de/index.php?id=1075&q=Monsanto

BfR - Bayer Cropscience cooperations and projects:
http://www.jki.bund.de/index.php?id=1075&q=Bayer%20cropscience

[redacted]

[redacted] This means that the Fraunhofer Institute receives scientific advice from the glyphosate producers.
These infos are available in the Fraunhofer Institute annual report:
http://www.ime.fraunhofer.de/content/dam/ime/de/documents/Publikationen/Fraunhofer_IME_Jahresbericht_2013_2014.pdf

[redacted]

This info can be found via Wikipedia Germany:
https://de.wikipedia.org/wiki/Bundesverband_Deutscher_Pflanzenzu¨chter

[redacted]

This info can be obtained via the NGO website Corporate Europe Observatory:
http://corporateeurope.org/agribusiness/2013/04/pesticides-against-

pollinators

[redacted]

This info is available via the official website of Eurofins: http://www.eurofins.com/agroscience-services/about-us/latest-news/new-md-bu-head-for- ecotoxicology-eas-germany/

In summary, 7 of the 13 BfR experts get paid or are influenced by the glyphosate producers.Another BfR expert works not directly for the chemical industry, but his institution has been criticized for its chemical industry friendly decisions.

[redacted]

This info is only available in German via the independent media website NEOPresse: http:// www.neopresse.com/umwelt/bienensterben-syngenta-zahlt-unbedenklichkeits-studien- selbst/

And even the Austrian chamber of agriculture, the Landwirtschaftskammer O¨sterreich (LKO¨), offered the apiarists (hush-) money when they are not talking in public about the mass death of their honeybees, as the Austrian media revealed.

This article is only available in German via the official ORF website: http://www.orf.at/stories/2182223/2181992/

[redacted]

[redacted]

This info (only availably in German) can be obtained via the independent and investigate Swiss journalists platform Investigativ: http://www.investigativ.ch/aktuell/detail/bundesamt- fuer-landwirtschaft-gegen-unbequeme-journalistin.html

9. FAO experts are paid by the glyphosate producers

Furthermore, the individual FAO experts who reviewed the glyphosate studies

and/or the BfR glyphosate review, are also under the influence of the glyphosate producers:
http://www.who.int/foodsafety/areas_work/chemical-risks/JMPR_2016_ListOfExperts.pdf

In particular, the following experts get paid by the glyphosate producers:

[redacted]
http://www.environmentalhealthnews.org/ehs/news/2016/june/endocrine-disrupters-final- maneuvers-by-brussels2019-industry-linked-scientific-community

[redacted]

These infos can be obtained via the official TNO website:
https://www.tno.nl/en/focus-area/healthy-living/food-nutrition/food-innovations/high-scale-and-high-level-protein-purification/

[redacted]

This info can be obtained via this list of Monsanto Employees in Government, by Mathias Olsen via Metabunk: https://www.metabunk.org/partially-debunked-list-of-monsanto- employees-in-government.t3664/

And via Global Research Canada: http://www.globalresearch.ca/monsanto-controls-both- the-white-house-and-the-us-congress/5336422

[redacted]

[redacted]

This info can be found via the website Synbio Watch by Jeff Conant:

http://www.synbiowatch.org/2013/02/uc-berkeley-joins-monsanto-in-fight-against-farmer/

Monsanto also paid the University of California 100 million dollar for their patent for Posilac. And in addition, every year a minimum of $5 million annual royalty will be paid until the year 2023: http://news.monsanto.com/press-release/monsanto-company-university-california-resolve- dispute-over-technology-used-produce-bo

[redacted]

These infos are available only in German via the official website of the German party Die Gru¨nen: https://www.gruene-bundestag.de/fileadmin/media/ gruenebundestag_de/themen_az/agrar/PDF/160512-brief-glyphosat-ueberpruefung- beteiligung-von-dr-Andrea-hartwig.pdf

[redacted]

This info can be found in the British newspaper, The Guardian: https://www.theguardian.com/society/2015/sep/15/experts-criticise-public-health-england- e-cigarettes-review

And via the British newspaper, The Independent: http://www.independent.co.uk/voices/editorials/by-failing-to-release-a-report-on-reducing- sugar-consumption-tories-hamstrung-their-own-obesity-a6700541.html

And here, via an open letter to the CMO (England): http://www.moraybeedinosaurs.co.uk/neonicotinoid/mason/ Open_letter_to_the_CMO(England)_the_Wellcome_Trust_and_Public_Health_England.pdf

[redacted] This info can be obtained via the official UK government website Public Health Matters: https://publichealthmatters.blog.gov.uk/author/david-rhodes/

[redacted]

This info is available via the NGO website of the activist lawyers ClientEarth: http://www.clientearth.org/industry- influence-throws-doubt-pesticide-safety-claim-ahead-eu-vote/

[redacted]

This info can be found via the official website of the Utrecht University: http://www.uu.nl/en/research/future-food-utrecht/results
Also Syngenta cooperates closely with the Utrecht University and provides job opportunities for their students: http://www.uu.nl/masters/en/environmental-biology/career-prospects

[redacted]
http://www.nacrw.org/2011/11Presentations/O-17_JaneStewart.pdf

[redacted] This info can be found on the official website of the Australian department: http://www.agriculture.gov.au/ag-farm-food/food/publications/ national_food_plan/issues-paper/submissions-received/syngenta? wasRedirectedByModule=true

[redacted]

This info can be found via the website of the NGO Earth Open Source, by Claire Robinson: http://earthopensource.org/wp-content/uploads/Eu_pesticidefoodsafety.pdf

[redacted] This info can be obtained via the British newspaper, The Guardian: https://www.theguardian.com/environment/2016/may/17/unwho-panel-in-conflict-of-interest-row-over-glyphosates-cancer-risk

[redacted]

This info can be found via the online magazine Farm Weekly: http://www.farmweekly.com.au/news/agriculture/general/news/court-ruling-on-apvma- backs-farmers/2752888.aspx?storypage=0

[redacted] These infos are available via the official website of the ABC Australia media network: http://www.abc.net.au/news/2016-06-10/opposition-to-apvma-relocation/7498820

The members of The Crop Life Australia are the glyphosate producers: Monsanto, Syngenta, BAYER, BASF, and DuPont. These infos are available via the official website of Crop Life Australia: http://www.croplife.org.au/members/

[redacted]

These infos can be obtained via the website of the NGO GM Watch: http:// www.gmwatch.org/news/latest-news/16939-conflict-of-interest-concerns-cloud-meeting-as- experts-review-glyphosate-risks

[redacted] And Hoffmann-La Roche Inc. works in a joint venture with the Glyphosate producer, BAYER. Info via Wikipedia Germany:
https://de.wikipedia.org/wiki/Hoffmann-La_Roche#cite_note-14
Hoffmann-La Roche also cooperates with glyphosate producer, Syngenta in the ProRheno AG in Basel.

This info can be found via the official website of ProRheno:
http://www.prorheno.ch/ Organisation-Traegerschaft-19

Hoffmann-La Roche works also together with the glyphosate producers - Syngenta, Bayer, BASF, and Dow Europe in the Swiss lobby organization, InterNUTRITION.
These infos can be obtained via the official website of Science Industries Swiss:

https://en.scienceindustries.ch/involvement/internutrition
https://en.scienceindustries.ch/association/our-members

[redacted]

This info can be obtained via the official website of the MRC-PHE, Environmental Health UK:
http://www.environment-health.ac.uk/researchers-society-committee

[redacted]

This info can be obtained via the official website of the U.S. FDA:
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm219482.htm

The U.S. Food and Drug Administration (FDA) has been in the critics for lobbying for the chemical industry and in particular for Monsanto.
This info can be found via the website EcoWatch:
http://ecowatch.com/2012/01/30/action-why-is-a-monsanto-lobbyist-serving-as-the-fdas- food-safety-czar/

Also, the U.S. Environmental Protection Agency (EPA) has been accused for lobbying for the glyphosate producers - Monsanto and Dow Chemical in several cases.

This info can be obtained via The Huffington Post:
http://www.huffingtonpost.com/andrew- kimbrell/dow-chemical-and-monsanto_b_6041802.html

[redacted]

A few examples are the GMOs' maize MIR604 and GA21 by Syngenta and Monsanto.

This Info can be found via the official site of the Japanese administration:
https:// www.fsc.go.jp/hyouka/hy/hy-summary-gmfood-mir604xga21.pdf

Also, Dow Chemical's and Monsanto's cross-breeding cotton 281, cotton 3006, and roundup ready cotton1445 have been approved by the FSCJ without any further research.
This Info can be found via the official site of the Japanese administration:
https://www.fsc.go.jp/english/evaluationreports/newfoods_gm/fs1191_cotton281_1445.pdf

Also, the GMOs Bt Cry34/35Ab1 Event DAS-59122-7 and roundup ready maize NK603 by Du Pont and Monsanto have been approved by the FSCJ with the remark: "...does not require safety confirmation." cited via the official site of the Japanese administration:
https://www.fsc.go.jp/english/evaluationreports/newfoods_gm/fs1164_cry34_nk603.pdf

FSCJ also approved Monsanto's genetically modified maize varieties, which have been developed by crossing its high lysine maize line, LY038, with the maize line MON810, which is resistant to Lepidoptera pest. The FSCJ stated in its approval, without any further studies on the breed, that Monsanto's GMO breed maize has no adverse effects on human health.

This Info can be found via the official site of the Japanese administration:
https://www.fsc.go.jp/hyouka/hy/hy-summary-gmfood-ly038xmon810.pdf
And while the FSCJ approved all products by Monsanto, Syngenta, DuPont and Dow Chemical without any additional studies,
see here: https://www.fsc.go.jp/hyouka/hy/hy-summary-gmfood-ly038xmon810.pdf , many international scientists proved in their studies how harmful these particular products are.

The GMOs MIR604 and GA21 for instance.This info is only available in German via the NGO website Testbiotech:
http://www.testbiotech.org/sites/default/files/TBT%20Comment_%20Bt11_MIR162_MIR604_GA21.pdf

or Monsanto's GMO maize Mon810.
This info is available via the NGO website GMO Free USA:
http://www.gmofreeusa.org/?s=MON810&submit=Search

http://www.gmofreeusa.org/gmo_article/feeding-study-with-bt-corn-mon810-ajeeb-yg-on- rats-biochemical-analysis-and-liver-histopathology/

or with the GM maize variety LY038 x MON810.

This info is available via the NGO website GM Free Cymru:
http://www.gmfreecymru.org/news/Press_Notice9Nov2009.htm

[redacted]

10. Monsanto's past and actual lawsuits for hiding the toxic effects of their products

All these facts, scientifically and political, are just a few of the reasons why six European NGOs started a lawsuit against Monsanto, the BfR and the Efsa.
This info can be obtained the PAN Europe network website:
http://www.pan-europe.info/press-releases/2016/03/2-march-2016-glyphosate-re- authorisation-ngos-join-forces-demand-legal-action

And it is not the first time that Monsanto has been caught and sued for hiding health issues in their product studies:

[redacted]

These secret Monsanto studies reveal glyphosate's link to cancer and the fact that Monsanto has manipulated these studies by mixing data to hide these effects.
This info can be found via the website of the NGO GM Watch
http://www.gmwatch.org/news/latest-news/16515-monsanto-s-secret-studies-reveal- glyphosate-link-to-cancer

and via the website of the lawyer agency Levin Papantonio:
https://www.levinlaw.com/monsanto-roundup-litigation

Monsanto has been successfully sued for making a false claim that Roundup targets enzymes supposedly found only in plants, not in people.

This info can be obtained via the Monsanto Class Action website:
https://www.monsantoclassaction.org

Monsanto has been sued for hiding the danger in their studies for the polychlorinated biphenyls (PCB) they have produced between1930 and 1980.
This info is available via EcoWatch:
http://ecowatch.com/2016/05/26/monsanto-losses-pcb-lawsuit/

It was in 1975 that a Monsanto study found that PCBs caused tumors in rats. Monsanto simply "...ordered its conclusion changed from "slightly tumorigenic" to "does not appear to be carcinogenic."

The full article: "Monsanto Hid Decades Of Pollution" by Washington Post reporter, Michael Grunwald, can be found here, via Common Dreams: http://www.commondreams.org/headlines02/0101-02.htm

Monsanto has also been caught hiding the danger of their cow hormone product, Posiliac, in their studies.
This info is available via the website Organic Consumers:
https://www.organicconsumers.org/old_articles/rBGH/milkismilk20405.php

Monsanto is also promoting RoundUp with false scientific claims from studies they have outsourced to private scientists, which they have paid:

In 1996, Monsanto was sued for claiming that RoundUp's glyphosate is "biodegradable": This info can be found via The Huffington Post:
http://big.assets.huffingtonpost.com/fraud.pdf

Monsanto has also been successfully sued for claiming that "Glyphosate is less toxic to rats than table salt acute oral ingestion"! The scientist and president of the German BfR, Andreas Hensel, repeated Monsanto's false marketing claim 20 years later in Germany, in 2016, by saying that glyphosate and salt have the same toxicology. Andreas Hensel said in an interview with the German news magazine Der Spiegel, "Die To¨dliche Dosis von Glyphosat liegt in der gleichen Dimension wie Kochsalz."

This quote can be found online via the German news magazine Der Spiegel:
http://www.spiegel.de/spiegel/vorab/behoerdenchef-wirft-umweltverbaenden-und-gruenen- panikmache-vor-a-1081815.html

11. Monsanto's vague claims about glyphosate

Monsanto makes false claims on its German glyphosate info site. Monsanto writes that glyphosate has an average half-value time in the ground / soil of 16.5 days.In contrast, independent studies with real field tests found that the average half-life time of glyphosate in the ground / soil is 47 days.
This info is available via the the website of the National Pesticide Information Center:
http://npic.orst.edu/factsheets/archive/glyphotech.html#references

Monsanto also claims on their European glyphosate product info site that glyphosate rarely can't be found in groundwater: "For the same reason, glyphosate residues are not likely to leach into groundwater and only limited amounts of glyphosate are found in surface water as a result of runoff."

The fact is that Horth found in 23% of the ground water samples glyphosate residues, and in 43% of the water samples AMPA residues, in his glyphosate water monitoring study between 1997 - 2011 (Only available in German), and according to this presentation by Steffen Matezki, German Umweltbundesamt (UBA) via Agrarkoordiantion. This info is only available in German via the website Agrar Koordination: http://www.agrarkoordination.de/

fileadmin/dateiupload/Roundup___Co/2014-12-02_PAN-Vortrag_Matezki_Kurzversion.pdf

Monsanto also claims on their German glyphosate product info site that less than 1% of glyphosate residues can be found in surface water.
This info is based on a 36-year-old study by W.M Edwards in 1980. Actual studies by Chang (et al., 2011), Battaglin (et al., 2011) and Daouk (et al., 2013) found glyphosate residues in 50% of the creeks and in 20% of the seas in Mississippi and Iowa in 2007 and 2008 respectively.

The German testbiotech organization published a summery on glyphosate residues in waters, which is only available in German via:
https://www.testbiotech.org/sites/default/files/Basistext_Glyphosat_Testbiotech__0.pdf

Monanto claims on their European glyphosate info site that glyphosate has no effect on plant roots.

The German plant scientist, Prof Dr. Gu¨nter Neumann proved in various studies that glyphosate do have negative effects on non-targeted plant roots. These infos are only available in German via:
The BR TV news http://www.br.de/mediathek/video/sendungen/unser-land/glyphosat- forschung-hohenheim-100.html

via the website for sustainable agriculture:
http://stopogm.net/files/RGTNTPVR.PDF

via the website for sustainable agriculture:
http://stopogm.net/sites/stopogm.net/files/ GlyphosateBott.pdf

German University Hohenheim:
https://opus.uni-hohenheim.de/volltexte/2011/606/pdf/Dissertation_S._Bott_UH2010.pdf

12. The different maximum values of glyphosate in food are not scientifically verified

It's also not scientific comprehensible why the highest level of glyphosate residues in honey is 0.05mg/kg, in drinking water 1mg/kg, in corn 3mg/kg, in lentils 10mg/kg, in soy 20mg/kg and in mushrooms 50mg/kg.
See details via the EU Pesticides database for Plants:
http://ec.europa.eu/food/plant/pesticides/eu-pesticides-database/public/?event=pesticide.residue.CurrentMRL&language=EN

re there any actual long term studies on humans that prove that these maximum values have no effects on the human body, on pregnant women, on babies, on elderly and ill people?

It's also strange that the Efsa / BfR increased in 2012 the amount of glyphosate in lentils by the factor 100, from 0.1 mg/kg to 10 mg/kg, without

any studies or evidence of long term effects on the human body. See also this petition to the EU Parliament:
http://www.europarl.europa.eu/meetdocs/2009_2014/documents/peti/cm/1022/1022470/1022470de.pdf

This is also dangerous because there is no glyphosate in food monitoring in Germany: The German food and health authorities are testing 5 million food samples for dozens of different pesticide residues every year, but only 1,200 food samples for glyphosate.

The numbers are taken from this German ZDF TV report:
http://www.zdf.de/wiso/glyphosat-im-honig-44206590.html

13. Glyphosate residues found in over 75% of the population

In a glyphosate urine test from 2015/16, with more than 2000 citizens who took part in this survey, 99.6 percent had levels of glyphosate residues which are five to 42 times over the maximum value of glyphosate residues for drinking water in Europe.
This info can be found via EcoWatch: http://ecowatch.com/2016/05/12/mep-glyphosate- urine-test/

In 2013, in an European-wide glyphosate test of 82 urine samples received from 18 countries, scientists found glyphosate residues in 44% of the samples. This info is only available in German via the German NGO Der Bund: https://www.bund.net/fileadmin/bundnet/pdfs/gentechnik/130612_gentechnik_bund_glyphosat_urin_analyse.pdf

And there is no long term study on how these glyphosate residues affect the human body.

14. Some supposable glyphosate effects on wild animals

Also the effects of glyphosate on red deers, fawns, pheasant and rabbits seem to be deadly as the Fallwild Bericht 2013/2014 by the German Landesamt fu¨r Natur, Umwelt und

Verbraucherschutz NRW, Forschungsstelle fu¨r Jagdkunde und Wildschadenverhu¨tung revealed. This info is available only in German via the huntsman magazine Rheinisch- Westfa¨lischer Ja¨ger: http://www.rwj-online.de/rwj/forschungsstelle/wildkrankheiten/warum-rehe-krank-werden---und-wie-man-ihnen-helfen-kann_6_1284.html

The dangerous effects of glyphosate on honey bees is also scientifically verified and beekeepers demand the EU administrations to ban glyphosate:

This info is available only in German via the NGO website for honey bees Mellifera e.V.: https://www.mellifera.de/ueber-uns/presse/mitteilungen/glyphosat-beeintraechtigt-das-orientierungsverhalten-der-bienen.html

Details via M Boily et al „Acetylcholinesterase in honey bees (Apis mellifera) exposed to neonicotinoids, atrazine and glyphosate: laboratory and field experiments." http:// www.ncbi.nlm.nih.gov/pubmed/23443944

Info available only in German via the website of the law agency Gaßner, Groth, Siederer & Coll.: http://www.ggsc.de/aktuelles/aktuelle-meldungen/details/news/1015-glyphosat-in- honig-ggsc-fordert-von-der-eu-kommission-und-von-anderen-behoerden-schutzmassnah/

15. The effects of glyphosate on the biodiversity

The effects of glyphosate on biodiversity are also not considered by the final judgement of the EU administrations, BfR and Efsa. How glyphosate effects biodiversity is proven in these different studies, compiled by Rosemary Mason, in: Glyphosate: Destructor of Human Health and Diversity.
These infos can be obtained via GMO Evidence:
http://www.gmoevidence.com/wp-content/uploads/2013/09/Glyphosate-Destructor-of- Human-Health-and-Biodiversity.pdf

And on, Flavia Geiger et al. in "Persistent negative effects of pesticides on biodiversity and biological control potential on European farmland:" This study can be obtained via Science Direct:
http://www.sciencedirect.com/science/article/pii/S1439179109001388

16. The short and long term effects of the nearly 100 different herbicides formulas with glyphosate are not fully researched

This is important because the short and long term effects of the nearly 100 different herbicides formulas with glyphosate - and in particular in combination with dozens of different RoundUp additives, like the polyethoxylated tallow amine (POEA), propylenglycol, sodium sulfite, sodium benzoate, methyl p-hydroxybenzoate, 3-iodo-2-propynyl butyl carbamate, 5-chloro-2-methyl 3(2H)-isothiazolone and many others – on animals and the ecosystem are in the studies of the WHO, Efsa and BfR not evaluated and not considered for their decision of renewing the glyphosate admission.

17. Conclusion and claims
The European administrations, WHO, Efsa, FAO, BfR et al. and the scientists

who claim that glyphosate is non-toxic to humans, animals and the ecosystem are heavily under the influence of the glyphosate producers.

Monsanto has been sued several times successfully for hiding product studies that prove that their products are harmful to humans, animals and the ecosystem.

Therefore, Monsanto and the other glyphosate producers, Syngenta, BAYER, BASF, Dow Chemical, DuPont et al. must disclose their secret studies of glyphosate and their studies for their herbicide products containing glyphosate.

The studies for and paid by the glyphosate producers have to be carefully re-evaluated by a group of independent researchers. The independent glyphosate studies must be re- evaluated in search for all proven effects on the human body, animals and the ecosystem by an independent authority, where GMO and glyphosate experts and critics from environmental NGOs work together.

Because, and according to the EU precautionary principle, over 700 million people in the EU shouldn't be the testimonials, and the 4.325.000 km2 ecosystem shouldn't be the testing field for the chemical industry.

thanks

ECHA note - The following attachment was submitted with the comment above: *Glyphosate-ECHA-Comments-by-Consumer-Schraiber.pdf*

Dossier Submitter's Response
This is a very extensive comment that compiles many of the arguments and claims which are used to discredit the current re-evaluation of glyphosate in the hope of banning glyphosate. However, these points primarily concern risk assessment and risk management. Consequently, they are largely inconsequential with regards to the classification and labelling of glyphosate. Accordingly, this table is not the appropriate place to deal with them.
RAC's response
Noted. See response to comment no 4 and 68.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Spain		Individual	129
Comment received				
Please note that I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I also request that you include all independent studies used in the IARC monograph in your assessment. As scientists, I urge you to review the studies submitted by industry with **extreme** caution because of their very obvious potential conflict of interest, and make sure that all so-called "science" submitted becomes publicly available for scrutiny by other scientists, including all contractual obligations imposed on the scientists involved (non-disclosure, etc.). Please ensure you take into account studies from mice that show that				

glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate. Thank you very much for your time.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	130
Comment received				
Please make sure you evaluate all facts and studies, especially the indepent ones before drawing a conclusion. Studies paid for by the industry always involve the risk of a conflict of interest. It is better to err on the side of safety. Remember it's life on earth - plants, animals, people - that have to live with the consequences of your decision.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4 and 68.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	131
Comment received				
Die Konsultation erm&#xF;glicht keine spezifischen Kommentare zu den Auswirkungen von Glyphosat auf die Artenvielfalt. Gleichwohl sei an dieser Stelle angemerkt, dass Glyphosat laut Umweltbundesamt nachweislich sch&#xF;dliche Auswirkungen auf die Biodiversit&#xF;t hat. So zerst&#xF;rt Glyphosat als Breitbandherbizid die Nahrungsgrundlage f&#xF;r zahlreiche Insekten, womit wiederum durch den R&#xF;ckgang der Insektenpopulationen auch vielen Feldv&#xF;geln die Nahrungsgrundlage entzogen wird. Vgl.				

https://www.umweltbundesamt.de/themen/chemikalien/pflanzenschutzmittel/glyphosat
Dossier Submitter's Response
Thank you for comments Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on the direct effects of substances on the aquatic environment. There is no hazard class to classify glyphosate for indirect effects on biodiversity according to the CLP regulation.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	132
Comment received				
1) If RAC or other EU bodies have accepted evidence for classification/hazard communication of pesticide FORMULATIONS before, please be consistent with this glyphosate proposed classification. Studies on formulations can be supportive evidence. Regardless, I submit glyphosate-only studies and clearly denote any formulation studies. 2) A broad effects PubMed search for "glyphosate (toxic* OR risk* OR hazard*) " returns 7 glyphosate-only relevant published toxicity findings published in 2016 WHICH ARE NOT IN THE CLH REPORT TO COMMENT ON AND SO YOU ARE NOT CONSIDERING (no doubt there are a few more, e.g. in Web of Science, or with a broader PubMed search term). I reference these in specific endpoint comments below, and attach their PubMed abstracts. You must show you have properly evaluate the up to date findings in your classification decisions--not up 'to the last day, but being months out of date is unacceptable for a chemical so heavily studied. 3) Last I refer you Pesticide Action Network's 'Missed & Dismissed' report (http://www.pan-europe.info/old/Resources/Reports/PANE%20-%202014%20-%20Missed%20and%20dismissed.pdf), which compared (among six other pesticides) published technical glyphosate findings to its RAR; it contains a link to the PubMed page where I saved (numbered keyed to the report) the abstracts of the inde literature. I.e., the notations here, e.g. "#122", below, refer to the 122 abstract at the PubMed link (which is: www.ncbi.nlm.nih.gov/sites/myncbi/collections/public/1loH85XekdSXuno_Xemk0jK5h/). PS: I want to submit the attachement as no-confidential, but carelessly uploaded using the button for confidential (then I re-uploaded it as a public file). ECHA note - The following attachment was submitted with the comment above: *'16 glyphos-only tox-7 selected items - PubMed.rtf*				

Dossier Submitter's Response
Unfortunately, new research results can only considered for evaluation when released before a certain date. Otherwise, a decision could never be made. The regulatory agencies must not be blamed for not taking data that are published during the review and commenting phase into consideration. In addition, the selected 7 new references partly reflect environmental research without relevance for human health (Rissoli et al., 2016; Roy et al., 2016; Wang et al., 2016; Vannini et al., 2015; Vincent and Davidson, 2015). Dai et al. (2016) confirmed low (reproductive) toxicity of glyphosate. The paper of Coullery et al. (2016) does not provide convincing evidence of a critical effect against the huge background of neurotoxicological and other toxicological studies with glyphosate. As a consequence, these data would be unlikely to change the outcome of the assessment even if they were to be taken into consideration.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Denmark		Individual	133
Comment received				
[redacted] Glyphosate is under review again through your agency's consultation. As one of the millions who have signed the petition to request the consultation is transparent and independent, I would also request that the consultation considers invoking the precautionary principle, as recommended by the WHO and the EU itself. If there is any indication that this chemical is linked to cancer, this principle should apply.				
Dossier Submitter's Response				
The evaluation by RAC will be transparent and independent. There is enough data available to perform a comprehensive, science-based evaluation and a to draw a conclusion also with regard to carcinogenicity. The precautionary principle should be applied when the information on a substance is not sufficient which is not the case with glyphosate.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	134
Comment received				
Die Konsultation ermöglicht keine spezifischen Kommentare zu den Auswirkungen von Glyphosat auf die Artenvielfalt. Gleichwohl sei an dieser Stelle angemerkt, dass Glyphosat laut Umweltbundesamt nachweislich schädliche Auswirkungen auf die Biodiversität hat. So zerstört Glyphosat als Breitbandherbizid die Nahrungsgrundlage für zahlreiche Insekten, womit wiederum durch den Rückgang der Insektenpopulationen auch vielen Feldvögeln die Nahrungsgrundlage entzogen wird. Vgl.				

https://www.umweltbundesamt.de/themen/chemikalien/pflanzenschutzmittel/glyphosat
Dossier Submitter's Response
Thank you for comments. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on the direct effects of substances on the aquatic environment. There is no hazard class to classify glyphosate for indirect effects on biodiversity according to the CLP regulation.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	135
Comment received				
Die Konsultation ermöglicht keine spezifischen Kommentare zu den Auswirkungen von Glyphosat auf die Artenvielfalt. Gleichwohl sei an dieser Stelle angemerkt, dass Glyphosat laut Umweltbundesamt nachweislich schädliche Auswirkungen auf die Biodiversität hat. So zerstört Glyphosat als Breitbandherbizid die Nahrungsgrundlage für zahlreiche Insekten, womit wiederum durch den Rückgang der Insektenpopulationen auch vielen Feldvögeln die Nahrungsgrundlage entzogen wird. Vgl. https://www.umweltbundesamt.de/themen/chemikalien/pflanzenschutzmittel/glyphosat				
Dossier Submitter's Response				
Thank you for comments. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on the direct effects of substances on the aquatic environment. There is no hazard class to classify glyphosate for indirect effects on biodiversity according to the CLP regulation.				
RAC's response				
Noted. See response to comment no 68.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Slovenia		Individual	136
Comment received				
As someone who bakes bread I am very interested to use a flour which is *safe* to use from every aspect of human life and the whole life on the Earth. This reason is important enough to restrict the use of any chemical product produced by humans. There are reports that this one particular substance is more dangerous than most other – decision based on such reports should be easy to make.				

Dossier Submitter's Response
Residues of glyphosate are of no health concern if the permitted residue limits are not exceeded. In spite of the high public awareness, there is no scientific basis for the claim that glyphosate is more dangerous than most other chemicals.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	137
Comment received				
Reason for cancer				
Dossier Submitter's Response				
As explained in the CLH dossier, the DS has a different view.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	138
Comment received				
Reason for cancer				
Dossier Submitter's Response				
As explained in the CLH dossier, the DS has a different view.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	139
Comment received				
For correct display of all the comments: see public attachement The CLH report of glyphosate addressing the hazard assessments records only international agreed standard test guidelines which are then used for the comparison with the classification criteria. Not all of the available studies were reported in the CLH report itself but more studies are described in the annexed EFSA conclusion 2015 and the addenda of the Renewal Assessment Report (RAR). In general, we would have appreciated that at least an overview table on glyphosate itself had been inserted for each endpoint by extracting all available studies in the EFSA conclusion 2015 doc/RAR indicating guideline/non-guideline, GLP, results, deviations, reliability, … Standard testing, non-standard testing and non-testing methods shall be considered for classifying purposes (CLP regulation). We regret that for the classification of glyphosate, notwithstanding the different public available				

articles on glyphosate that are mentioned in the RAR and evaluated by the RMS, none of the non-standard scientific literature studies were considered in the CLH report. ECHA note - The following attachment was submitted with the comment above: *CLH - Glyphosate - BE CA.docx*
Dossier Submitter's Response
There are tables with the available studies, including those from open literature, in the CLH dossier for all endpoints. As compared to the RAR, even some more studies have been included which had been used for the first EU evaluation (1998-2002) but do not comply with current standards any longer. Studies which are referred to in the RAR but not in the CLH dossier were considered not relevant for classification and labelling.
RAC's response
Noted. See response to comment no 4 and 11.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Sweden		Individual	140
Comment received				
to classify glyphosate.				
Dossier Submitter's Response				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Denmark		Individual	141
Comment received				
I am very concerned about a flawed evaluation of carcinogenicity data which was pointed out by top scientists in an open letter.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4 and 11.				

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	Denmark		Individual	142
Comment received				

Necessary to forbid
Dossier Submitter's Response
Noted. This is personal opinion concerning risk management, not classification.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Switzerland		Individual	143
Comment received				
There is a cover letter and a pdf file of the submitted comments in the attached zip file. The Figures and Tables are in the attached zip file.				
Dossier Submitter's Response				
Unfortunately, it is not clear to which comment this information might be related.				
RAC's response				
It is not clear to RAC which attachments this refers to.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Austria		Individual	144
Comment received				
•I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. •Include all independent studies used in the IARC monograph in your assessment. •Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. •Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France		Individual	145
Comment received				

I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. I insist that all independent studies used in the IARC monograph be included in your assessment. It is important that the studies submitted by industry be reviewd with extreme caution because of their potential conflict of interest, and you must make sure that they become publicly available for scrutiny by other scientists. Studies from mice must be taken into account because that show that glyphosate is carcinogenic, as well as the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	146
Comment received				
Je suis très préoccupée par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				

Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	147
Comment received				
Glyphosate is				
Dossier Submitter's Response				
No response possible since the comment is not complete.				
RAC's response				
No response.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Czech Republic		Individual	148
Comment received				
Glyphosate is a non-selective herbicide which kills all herbage and acts by interfering with the so-called shikimate pathway, a pathway that is also present in algae, bacteria and fungi. Sub-lethal exposures of Escherichia coli and Salmonella enterica serovar Typhimurium to commercial formulations of glyphosate have been found to induce a changed response to antibiotics. All relevant scientific studies on exposure to glyphosate formulations in relation to antimicrobial resistance should be taken into account, in particular: Sublethal Exposure to Commercial Formulations of the Herbicides Dicamba, 2,4-Dichlorophenoxyacetic Acid, and Glyphosate Cause Changes in Antibiotic Susceptibility in Escherichia coli and Salmonella enterica serovar Typhimurium Authors: Brigitta Kurenbacha, Delphine Marjoshia, Carlos F. Amábile-Cuevasb, Gayle C. Fergusonc, William Godsoed, Paddy Gibsona, Jack A. Heinemanna				
Dossier Submitter's Response				
Due to its unique mode of herbicidal action, some antibiotic activity of glyphosate may be assumed. In fact, there were effects of this compound on bacteria and some other micro-organisms, in particular when tested in isolation *in vitro*. Indeed, a U.S. patent covering antimicrobial use of glyphosate was granted even although the doses necessary to control certain infections in humans were very high. It has been also shown that the vulnerability of various bacteria species is different. These findings have been taken into consideration in the RAR (Volumes 1 and 3) and, thus, for risk assessment, but in the sections dealing with possible effects on animal health. The point of concern was the potential imbalance of the microbial communities in the digestive tract of ruminants. The DS even commissioned additional research activities to investigate a possible impact of glyphosate (i.e., a glyphosate-containing herbicide) on complex microbial communities in cattle at realistic dietary concentrations, but no adverse effects were detected (Riede *et al.*, 2016, see attached article). A possible impact of glyphosate on the susceptibility of clinically important pathogens to antibiotics is a different and relatively recent issue which was indeed not considered in the RAR. Based on the U.S. patent, no such effects are expected at realistic exposure however research activities are under way nonetheless.				

Effects of glyphosate on micro-organisms have not been considered in the CLH dossier since they are not covered by the health-related classifications of chemicals according to CLP. Such effects would be clearly more an issue for risk assessment than for classification and labelling.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		Individual	149
Comment received				
I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest". I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.				
Dossier Submitter's Response				
Noted. All relevant studies have been and will be subject to thourough evaluation.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	150
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Merci.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier.				

A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	151
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.Vous devez notamment inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Switzerland	Avaaz	BehalfOfAnOrganisation	152
Comment received				
Dear members of the Committee for Risk Assessment, We welcome the review that you are undertaking on behalf of citizens across Europe to assess the hazards of glyphosate. We are writing to you to submit a comment on behalf of over 2 million Avaaz members who have called for an independent and transparent glyphosate evaluation following the classification of glyphosate as a possible carcinogen through the International Agency for Research on Cancer (IARC). We have reasonable doubt that glyphosate is safe for human health. We also believe it is a major threat to biodiversity. The question of glyphosate has inspired unprecedented interest and concern amongst those most directly affected by its use -- people from all across Europe. Their concerns have most recently been expressed in more than				

12.000 citizen comments directed at your agency, some of which we are attaching to this submission.

After careful consideration of the science on carcinogenicity presented in the Harmonised classification and labelling (CLH) report submitted by the Federal Institute for Occupational Safety and Health (BAuA), we believe there is no alternative than to classify glyphosate in category 1b, because it causes cancer in experimental animals.

We would like to make the following points on the carcinogenicity studies:

- We are extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists but not taken into account in the CLH report by BAuA and the wrongly-dismissed epidemiological studies
- Review the studies submitted by the industry with extreme caution because of their obvious conflict of interest. We further call on you to ensure these industry studies are made available to the public.
- We ask you to include all independent studies used in the IARC monograph in your assessment.
- By taking into account the five studies of mice (1) that show that glyphosate is carcinogenic with statistically significant evidence and the six studies from registers of human cancer cases, glyphosate must be classified into group 1b.

In detail, we strongly support Chris Portier's comments on the CLH report, with the conclusion that glyphosate should be classified into Group 1b. We also support the Environment Ministry of Lower-Saxony in Germany in demanding a reclassification to 1b in their comment to ECHA from 30th June 2016.

Furthermore, we also support the comment submitted by Peter Clausing on behalf of PAN Germany which comes to the following conclusion:

"Proper evaluation of the evidence provided in CLH Report, the RAR and its Addendum inevitably leads to the conclusion that glyphosate is carcinogenic in experimental animals, warranting a Category 1B carcinogenicity labelling of glyphosate."

We would like to underline our grave concern that the CLH report submitted by BAuA and written with the help of BfR is not aligned with the scientific rigour and standards held up by ECHA in general. On this matter we would like to remind you of Chris Portier's statement:
"What I found most disturbing with this submission is that, despite our previous concerns about the EFSA conclusions on carcinogenicity, the review continues to disregard guidance set forth by ECHA, OECD, IARC and others on how to evaluate carcinogenicity data, especially regarding the use of the limited evidence category for the human data, the appropriate use of historical controls and the proper use of findings of a positive trend in an animal cancer study."

We would also like to remind you that in its final assessment, the German Federal Institute for Risk Assessment (BfR) accepted that the IARC/WHO findings were correct, and admitted to having simply adopted the statistical evaluations presented by the industry. The industry descriptions thus

contained the industry's own assessment of the reliability and interpretation of each study, which wouldn't align with most people's understanding of an independent review. But still, both BfR and EFSA kept their conclusion that glyphosate is non-carcinogenic. We remind you that this has triggered a response, in an open letter (2) to the EU Commission by 94 well-respected scientists who criticised the BfR and EFSA's assessment as "scientifically unacceptable", "fundamentally flawed" and "misleading".

Although BfR went beyond their brief in explicitly noting the need for follow-up studies, this important point has yet to result in such studies being commissioned to create the additional data needed to be able to determine whether or not glyphosate is harmful to humans. ECHA should consider this when assessing glyphosate in the coming months.

While our concerns on the cancer risk posed by glyphosate are gravest, there are several other areas of risk that we ask you to consider in your review:

We ask you to carefully examine the evidence that points to glyphosate as an endocrine disruptor. In particular, we point you to the research paper "Potential toxic effects of glyphosate and its commercial formulations below regulatory limits" looking at low-dose toxicity through endocrine disruption and oxidative stress:

Source: Mesnage, Defarge, Spiroux de Vendômois, Séralini. "Potential toxic effects of glyphosate and its commercial formulations below regulatory limits." Food Chem Toxicol. 2015 Oct;84:133-53. doi: 10.1016/j.fct.2015.08.012. Epub 2015 Aug 14. <http://www.ncbi.nlm.nih.gov/pubmed/26282372>. (3)

We are particularly worried that this risk is already present at currently permitted levels of glyphosate in drinking water and at levels much lower than the allowed daily intake as outlined in the paper.

Furthermore, we ask you to look at the risk posed by the link between glyphosate and increased antimicrobial resistance. Both the World Health Organization and the US Centres for Disease Control have raised the alarm about the growing risk of disease from antibiotic-resistant pathogens. The European Commission estimates that 25,000 Europeans die every year from an infection due to antibiotic-resistant bacteria, and has produced an Action Plan (2011) on the issue (4). In its recent resolution on glyphosate, the European Parliament warned that "commercial formulations of glyphosate have been found to induce a changed response to antibiotics" in E. Coli and Salmonella, putting people at increased risk (5); and a study published in the the peer-reviewed journal of the American Society for Microbiology, mBio (6) found that higher doses of antibiotics will likely be needed to kill off bacteria if someone is exposed to herbicides and antibiotics at the same time.

According to Jack Heinemann, author of the mBio study, the current practice of testing herbicides in isolation "may underestimate [their] role in the emergence of antibiotic resistance".

In light of the public health crisis posed by the increased failure of the antibiotics people around the world rely on to respond to serious diseases, and

the ubiquity of glyphosate use, we call on you to take into account this link in your review.

Finally, we also ask you to take a look at the big picture. Given the widespread global use of glyphosate, it is of great importance to carry out the risk and hazard assessment with utmost care. However, several of the assumptions made in the initial risk assessment by BFR are false.
We would like to quote the following consensus statement on glyphosate:

"(1) [Glyphosate Based Herbicides, GBH]s, are the most heavily applied herbicide in the world and usage continues to rise; (2) Worldwide, GBHs often contaminate drinking water sources, precipitation, and air, especially in agricultural regions; (3) The half-life of glyphosate in water and soil is longer than previously recognized; (4) Glyphosate and its metabolites are widely present in the global soybean supply; (5) Human exposures to GBHs are rising; (6) Glyphosate is now authoritatively classified as a probable human carcinogen; (7) Regulatory estimates of tolerable daily intakes for glyphosate in the United States and European Union are based on outdated science."(7)

Source: John Peterson Myers, Michael N. Antoniou, Bruce Blumberg, Lynn Carroll, Theo Colborn, Lorne G. Everett, Michael Hansen, Philip J. Landrigan, Bruce P. Lanphear, Robin Mesnage, Laura N. Vandenberg, Frederick S. vom Saal, Wade V. Welshons and Charles M. Benbrook. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement Environmental Health 201615:19 DOI: 10.1186/s12940-016-0117-0. Myers et al. 2016
<https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0117-0>

We submit the original paper as an attachment for your consideration:

On the impact of glyphosate on our environment and particularly on biodiversity is extensively documented in the paper "The environmental impacts of glyphosate" (8) by Friends of the Earth.

Your agency has a vital role to play, and we trust in your commitment to work on the basis of the most current research and in the interest of taking action to control any unacceptable risk to humans and the environment. In short, the risk posed by glyphosate and the damage it has already done is unacceptable and must be stopped.

Footnotes:

1) Wood et al., 2009, ASB2012-11492; Nufarm / Kumar, 2001, ASB2012-11491; ADAMA / Sugimoto, 1997, ASB2012-11493; Arysta / Atkinson et al., 1993; TOX9552382; Cheminova / Knezevich and Hogan, 1983; TOX9552381; Monsanto

2) https://www.efsa.europa.eu/sites/default/files/Prof_Portier_letter.pdf

3) http://www.ncbi.nlm.nih.gov/pubmed/26282372

4) http://ec.europa.eu/dgs/health_food-safety/amr/action_eu/index_en.htm

5) http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P8-TA-2016-0119+0+DOC+XML+V0//EN

6) http://mbio.asm.org/content/6/2/e00009-15.abstract

7) https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0117-0

8) https://www.foeeurope.org/sites/default/files/press_releases/foee_5_environmental_impacts_glyphosate.pdf

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ATTACHMENTS:

1. Messages to decision-makers from Avaaz members across Europe voicing their concern about glyphosate

2. 12.000 citizen messages calling for a transparent glyphosate review at ECHA

3a. Study: Sublethal Exposure to Commercial Formulations of the Herbicides Dicamba, 2,4-Dichlorophenoxyacetic Acid, and Glyphosate Cause Changes in Antibiotic Susceptibility in Escherichia coli and Salmonella enterica serovar Typhimurium
Brigitta Kurenbacha, Delphine Marjoshia, Carlos F. Amábile-Cuevasb,Gayle C. Fergusonc, William Godsoed, Paddy Gibsona, Jack A. Heinemann -- http://mbio.asm.org/content/6/2/e00009-15.abstract

3b. Comment by Jack Heinemann

4. Study: Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement John Peterson Myers, Michael N. Antoniou, Bruce Blumberg, Lynn Carroll, Theo Colborn, Lorne G. Everett, Michael Hansen, Philip J. Landrigan, Bruce P. Lanphear, Robin Mesnage, Laura N. Vandenberg,Frederick S. vom Saal, Wade V. Welshons and Charles M. Benbrook.
https://ehjournal.biomedcentral.com/articles/10.1186/s12940-016-0117-0

5.Friends of the Earth: The Environmental Impacts of Glyphosate
https://www.foeeurope.org/sites/default/files/press_releases/foee_5_environmental_impacts_glyphosate.pdf

ECHA note - The following attachment was submitted with the comment above: *Avaaz ECHA submission attachments.zip*

Dossier Submitter's Response

This is a very extensive comment that compiles many of the arguments and claims which are used to discredit the current re-evaluation of glyphosate in the hope of banning glyphosate. However, these points are very general and

primarily concern risk assessment and risk management. Consequently, they are largely inconsequential with regards to the classification and labelling of glyphosate. Accordingly, this table is not the appropriate place to deal with them.
RAC's response
Noted. See response to comment no 4, 11 and 68.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	United Kingdom	Breast Cancer UK	BehalfOfAnOrganisation	153
Comment received				
Breast Cancer UK does not support the dossier's conclusion that there should be no hazard classification for carcinogenicity (see dossier Section 4.9.6, p93 and p98). We believe this conclusion is contrary to the evidence provided in the dossier and inconsistent with the conclusion of expert scientists including the WHO's IARC, which classified glyphosate as probably carcinogenic to humans (Group 2A), and Portier et al. (2016) who supported this conclusion (Portier et al. (2016) Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA) Journal of Epidemiology and Community Health 70: 741-745).				
Dossier Submitter's Response				
Noted. Even if the same data are looked at, there might be different views if a substance is carcinogenic or not. Why the DS did not propose classification and labelling for carcinogenicity has been sufficiently explained in the CLH dossier.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium	PAN Europe	BehalfOfAnOrganisation	154
Comment received				
Glyphosate has been detected repeatedly in human samples revealing that exposure is much wider than previously considered. The correct hazard classification of this substance is crucial to protect human, animal and environmental health. Glyphosate should be banned for being Category 1B Carcinogen and due to its potential to cause reproductive toxicity at low environmental levels.				
Dossier Submitter's Response				
Detection of glyphosate in human (urine) samples does not have an impact on classification and labelling. That correct hazard classification is needed and, indeed, Cat. 1B carcinogens should be banned is self-evident. However, as discussed in the CLH dossier, this classification is not appropriate for glyphosate.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	155
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	156
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Bulgaria		Individual	157
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by as much as 94 top scientists in an open letter. I really count on you to include all independent studies used in the IARC monograph in your assessment. Nevertheless, it is crucially important to review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists who should be free to make a comment on the matter. Please ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate. Thank you in advance and I really wish you to succeed with handling this assessment in favor of the well-being of man and nature!				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	158
Comment received				
We agree with the proposed classification and no classification for the other human health hazard classes.				
Dossier Submitter's Response				
Noted. Thank you for the support.				
RAC's response				
Noted. See response to comment no 4, 11, 228, 259 and 278.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	159
Comment received				
Prof. Dr. med. Eberhard Greiser Center for Social Policy Research & Epi.Consult, Musweiler		Bremen University - Socium		

Evaluation of Epidemiologic Studies/Publications as Classified in the EFSA Final Addendum to RAR (Glyphosate)

1. Epidemiologic Methods

The CLH report for gylphosate deals in several part with "human information". On page 80 some grave misunderstandings of epidemiologic methods become obvious.

The anonymous authors of the CLH report state (p. 80, first paragraph) that "it is difficult if not impossible to attribute health effects including cancer to gylphosate-containing products since humans are exposed to a great number of environmental chemicals. Therefore, the actual value of such data for classification is questionable and in any case limited."

In paragraph 3 the reservations against epidemiologic studies are embellished with further arguments:

"There are a lot of problems with confounders: in most studies, glyphosate is included together with several other pesticides/insecticides so that the specific effects of each individual substance are difficult if not impossible to determine with any certainty. Farmers who use one chemical substance may also use another. It is not clearly stated which formulation of glyphosate is used; that is, different brands may have been used which have slightly different chemical mixtures and co-formulants, which themselves may have carcinogenic effects. The exposure cannot be easily measured. For example, no measures from biomarkers from the blood are used. Exposure is measured through interviews or questionnaires. Here, the problem is in reliance on memory to accurately determine the amount of exposure to the chemicals. Furthermore, there may be a recall biases since individuals with cancer are more likely to think about possible reasons for their cancer than healthy individuals."

Obviously, there are two different problems:

A. Subsequent or simultaneous impact of different risk factors on health: This is a typical problem in epidemiology. It could be solved, if it would be possible to define subpopulations which are exposed to merely one specific risk factor or in consequence in a controlled manner to two or more risk factors. But, as humans are no guinea pigs, such populations do exist nearly nowhere.

Thus in epidemiology there are methods of analysis available which allow for simultaneous risk factors to be evaluated. The statistical procedure to do so is the multivariate logistic regression, where the impact of different risk factors on the risk for a specific disease is calculated. This method allows to separate risk factors with a major impact of risk from those with less or no risk at all. It is standard epidemiologic procedure to analyze data with one major risk factor in question (e.g. glyphosate exposure) and include as secondary risk factors e.g. the exposure to other pesticides, organic solvents, smoking, family history, age. These secondary risk factors are called confounders. This procedure also allows to analyse the impact of combined or subsequent exposure to different risk factor in including interaction terms.

If e.g. the question arises, if the disease risk after exposure with glyphosate changes with age, it would be advisable to construct an interaction term age*glyphosate.

B. Reliability of interview data

The anonymous authors of the CLH Report on glyphosate suspect that recollection could distort real occurrence of risk factors. This certainly is a problem of major concern for epidemiologists. But, recollection errors are to be

expected in all persons to be interviewed, both in cases and in controls. It might, however, be a problem, when due to the disease some cases are cerebrally impaired.
The suspicion, that cases would be more likely to remember risk factors than control persons, is highly unlikely. Because, one has to have in mind, that a questionnaire that is constructed and tested regarding standard epidemiologic procedures, would give no hint to the study participant, what the major scientific question could be. Imagine that a questionnaire contains specific questions on all occupations that a participant had held for lifetime, that further for any occupational period there would be questions regarding duration, occupational problems, chemicals, radiation, that further a multitude of questions on personal attitudes, leisure time activities, risk behaviour (e.g. smoking, drinking, drugs), that further all disease for life-time would be elicited. Which person would be able, at the end of several hundred questions, to guess what the researcher had in mind?
Case-control studies are the most potent epidemiological method to investigate risk factors for all kind of diseases. In the case of relatively rare diseases, case-control studies are the only method possible. For diseases with higher occurrence, e.g. cardiovascular diseases, cohort studies are indispensable, also. But one has to keep in mind, that a cohort study that could contribute enough cases to analyze the impact of glyphosate on malignant lymphoma, it must be by dimensions larger than the US Agricultural Health Study (AHS) with approximately 57.000 farmers enrolled. Not the total number of participants is crucial, but the number of cases, i.e. persons with the lymphomas in the AHS, where 92 cases of Non-Hodgkin's lymphoma and 32 cases of multiple myeloma were observed. In epidemiology not the total number of persons counts, but the number of persons with a specific disease and the number of persons who are exposed to specific risk factors.
Thus the AHS, which is so highly praised by the anonymous authors of the CLH report, contributes only one tenth of cases compared to the Swedish case-control study, published by Eriksson and co-authors in 2008, which contributed 910 cases.

2. Developmental Toxicity of Glyphosate-containing Herbicides
2.1 Glyphosate and spontaneous abortions
The paper of Arbuckle and co-authors describes a case-control study conducted within a Canadian cohort study, the Ontario Farm Family Health Study. The case-control study comprised questionnaire interviews with couples, where women had to be younger than 44 years of age. At least one part of the couple had to be working on a farm. The investigation intended to analyze possible effects of pesticides applied in the peri- or post-conceptional phase of gestations on the risk of spontaneous abortions.

The EFSA Final Addendum to the RAR 19-11-2015 (p. 695-696) classifies the study by Arbuckle et al. as "not reliable" giving as major deficiencies:
1. No information about exposure duration, used glyphosate products and application
rates. No information, if the subjects used more than one pesticide.

2. Three highly relevant confounding factors were not considered in the OFFHS questionnaire: history of previous spontaneous abortion(s), maternal age and smoking.

Comments to the above mentioned deficiencies:
1.1 Exposure duration: Arbuckle et al. (p.851): "We pooled pesticide exposure information from the farm operator...husband, and wife to construct a history of monthly agricultural and residential use." As it was the purpose of the study to identify potential risks of pesticide use to spontaneous abortions, it was of paramount importance to identify pesticide use in the time before and after conception. The use of total time of exposure to pesticides as a risk factor for abortions would have been inappropriate.

1.2 Used glyphosate products: Arbuckle et al. (p.851): "For each pesticide reported, we identified active ingredients and uses using a database of registered pesticide products in Canada". Thus all glyphosate products were identified automatically.

1.3 No information, if the subjects used more than one pesticide: As all pesticides were assessed, the resulting information contained data on multiple use of pesticides. Besides, figure 2 (Arbuckle et al., p 855) displayes odds ratios for different strata of use of different pecticide groups (triazines alone or in combination with phenoxy herbizides or thiocarbamates (see attached publication of Arbuckle et al.).

2.1 History of previous spontaneous abortion(s): The paper of Arbuckle et al. (p. 851) describes in detail the assessment of gestational histories: "The women in the study were asked to recall all their pregnancies, starting with their first. For spontaneous abortions, the woman was asked how many weeks pregnant she was (based on the last menstrual period) at the time of the abortion."

2.2 Maternal age: As for all couples it was ascertained, if the woman was 44 years of age or younger (Arbuckle et al., p.851) it is obvious that maternal age was assessed. Besides, figure 1 (Arbuckle et al., p. 855) provides odds ratios for risk increase stratified by age (<= 34 vs. >34 years of age).

2.3 Smoking: Smoking was assessed, as described on page 852 of Arbuckle et al.:
"We also created pregnancy-specific variables for all other time-related factors (parental age, smoking, farm activities, and alcohol and caffeine intake):"

Thus, it has to be concluded that all deficiencies described in the EFSA Final Addendum in fact don't exist.

The CLH report summarizes the results of the Arbuckle et al. study (p. 109), as follows: "In a study from Ontario (Canada), Arbuckle et al. reported a slight increase in the pre-conception glyphosate exposure odds ratio for spontaneous abortion of borderline signifcance (OR 0 1.4). Due to strong limitations in this study, no firm conclusion is possible."

As it has been shown above, these "strong limitations" in fact do not exist. As it is shown in the Arbuckle et al. paper that for spontaneous abortions occurring before the 12th week of pregnancy the OR indicates a very small increase of risk (10%), whereas for abortions between 12 and 19 weeks of

pregnancy the risk increase comes to 70%, there should be a major concern that a considerable risk for late abortions due to pre-conceptional exposure to glyphosate-containing herbicides could be true.

The anonymous authors of the CLH report further argue that the rate of abortions reported in the Arbuckle et al. paper came to 10% of all pregnancies, which is below the range of "the baseline rate in the general population of 12 to 25%" . There is no source given for the rate of abortions in the "general population", but one has to consider that

a) the population of the Ontario Farm Family Health study might be healthier than any "general population" and thus might have less spontaneous abortions;

b) in the Arbuckle et al. paper abortions were discarded when occurring during periods when the woman of a couple was not living on the farm;

c) abortions occurring past the 19th week of pregnancy were not assessed nor analyzed in the Ontario Farm Family Health Study.

It has to be assumed that the anonymous authors of the CLH report took e.g. the Abortion Surveillance Reports of the US CDC as source, where for the year of 2012
a rate of 210 per 1,000 live births was reported. This is equivalent to 17.4% of abortions of all pregnancies. However, the Abortion Surveillance Reports of the USA include in their statistics both spontaneous and induced abortions. In spontaneous abortions the medical intervention is curettage. In the year of 2012 3.952.841 live births were reported in the USA. The number of abortions with curettage for 2012 came to 420.908 equivalent to 9.62% of all pregnancies. Including the numbers of medically induced (i.e. induced by drugs inducing abortions) abortions the rate comes to 12.00% of all pregnancies.

For Canada no comparable data exist.

In conclusion it can be stated that all of the deficiencies of the Arbuckle et al. paper, claimed by the anonymous authors of the Glyphosate Task Force in fact do not exist.

2.2 ADHD Subsequent to Exposure of Glyphosate-containing Herbicides

In a paper authored by Garry and co-authors published the results of a study of birth defects and developmental anomalies among 1.070 pesticide applicators in the Red River Valley region of Minnesota, USA. Of the study population 855 were married or lived in a marriage-like relationship. Of these 802 women participated in a survey comprising details on reproductive health and on detailed pesticide use for a total of 1.532 live births, representing 70 congenital birth anomalies, 3 cases of childhood diabetes and 16 cases of autism/ADHD.

The EFSA Final Addendum to RAR classified this study as "not reliable" with

deficiencies described, as follows:

"Epidemiological study with some methodological /reporting deficiencies (selection of study subjects, no information about exposure duration, exposure concentration, pesticide use frequency). "

In quoting a review by Mink and coauthors it was states, that the "overall rate for the sample population (14/1532) was well below ADD/ADHD rates for the general population (7%)".

Mink et al. also noted: "Variables in statistical model analyses were not reported."

Williams and Co-authors made a remark regarding the prevalence of ADD/ADHD that was verbatim identical to that in the Mink et al. paper.

Comments to claimed deficiencies of Garry et a.:

1. Methodical/reporting deficiencies: The EFSA Final Addendum provided no specific details on methodical and/or reporting deficiencies.

2. Prevalence of ADD/ADHD in the Garry et al. paper much lower than in the general population:
In the Mink et al. paper there was no sentence referring to this claim.
In the Williams et al. paper a publication referring to a further publication which quoted data from the 2004 US National Health Interview Survey with specific results for children . Here the prevalence of ADHD for children of different age groups show a marked increase with increasing age: for age groups 3-4, 5-11, and 12-17 years the respective prevalence figures are 1.8, 6.5 and 10.2 %.

As in the Garry et al. paper no age data for ADHD are provided, it is unclear, which of the US National Interview Survey results could be used for comparison.

However, Garry and co-authors themselves discuss this problem and are quoting several publications, which provide a broad range of percentages (s. attached publication of Garry et al., p. 447).

3.Variables in statistical model analyses were not reported: Gary and co-authors report a vast variety of confounders that have been included in multivariate regression models (s. attached publication of Garry et al., p. 442). These confounders include among others mother's age, smoking status, alcohol consumption, season of conception, chronic diseases as diabetes, arterial hypertension, arthritis.

4. No information about exposure duration, exposure concentration, pesticide use frequency: This claim is unfounded, because for birth defects or developmental problems as ADHD the timing of exposure (shortly before or after conception) is the critical variable to be determined, not the lifetime exposure dose or sequence of use of different pesticides.

In the EFSA Final Addendum to RAR it is not defined, what kind of "reporting deficiencies" with regard to selection of study subjects could exist, as all procedures are well described and performed according to standard epidemiologic procedures..

In conclusion it has to be stated that all of the claimed deficiencies of the Garry and co-authors paper are in fact not existent or irrelevant.

3. Non-Hodgkin's Lymphoma and Exposure to Glyphosate-containing Herbicides

3.1 Hardell and co-authors published a paper which combined results from two previous case-control studies , , one investigating the risk of herbicides and other pesticides on hairy cell leukemia (Nordström et al., 1998), the second with identical risk factor evaluation on Non-Hodgkin's lymphoma. The pooling is justified, as the WHO defined hairy cell leukemia as one subgroup of Non-Hodgkin's lymphoma. In both studies an complex 18-page questionnaire was mailed to all participants with telephone follow-up by trained interviewers.

The anonymous authors of the Glyphosate Task Force classified the publication as "not reliable" claiming the following deficiencies:

"No information about exposure duration, exposure concentration, as well as medical
history, lifestyle factors (e.g. smoker, use of prescribed drugs etc). Study documen-tation is insufficient for assessment."

Comments: For both studies an extensive 18-page questionnaire was mailed to all participants with follow-up by telephone interviews by trained interviewers.The questionaire contained questions about life-long occupational history with specific questions regarding exposure to any chemical, especially pesticides, smoking history and history of previous diseases. This procedure is explained in detail in the 1999 publication of Hardell and Eriksson (s. attachment). In addition the author of this comment received from Prof. Eriksson the complete questionnaire, which proved the description of assessment procedures, as described in the 1999 paper.

In conclusion it has to be stated that none of the deficiencies exist,which were claimed by the anonymous authors of the Glyphosate Task Force.

3.2 De Roos and co-authors published a paper in which data from three previously conducted case-control studies , , to investigate possible farm-related risk factors, among them use of pesticides, for Non-Hodgkin's lymphoma in men.

The anonymous authors of the EFSA Final Addendum to RAR classify the De Roos et al. paper as "non reliable" claiming the following deficiencies:

"No useful information about exposure duration, exposure concentration, as well as medical history, lifestyle factors (e.g. smoker, use of prescribed drugs etc were reported. Specific lymphomas are not identified (NHL captures all

types of lymphoma other than Hodgkin's lymphoma). Documentation is insufficient to associate exposures with specific NHL diseases."

Comments: To evaluate the validity of these claims, it is necessary to take into account the differing ways, in which the assessment of exposures and other risk factors was achieved.

The respective parts are marked in the three primary publications (s. appendix),
in the Zahm et al. paper on pages 350 and 352, in the Hoar et al. paper on pages 1142 and 1145, in the Cantor at al. paper on page 2447.

The methods of assessment in all of these papers contradict the claims of deficiencies in the EFSA Final Addendum to RAR.

It is also claimed as a deficiency that "specific lymphomas are not identified". This claim is unsubstantiated as the De Roos et al. paper intended to identify different pesticides as risk factors for Non-Hodgkin's lymphoma, and not for the multitude of different sub-types of Non-Hodgkin's lymphoma.

In conclusion it has to be stated that the publication of De Roos et al., and also the three primary papers, on which the De Roos et al. paper is based, has none of the deficiencies that are claimed by the anonymous authors of the Glyphosate Task Force.

3.3 Eriksson and co-authors conducted a population-based case-control study to analyse the impact of pesticide odds ratio of 2.02 (95%-CI 1.10-3.71). exposure on the risk of Non-Hodgkin's lymphoma and its subgroups. The used 910 cases and 1016 controls, aged 18-74 years. The results showed an overall The anonymous authors of the EFSA Final Addendum to RAR classified the study as "not reliable".
"Multiple avenues for bias were introduced in study design, execution and data processing. No information about exposure duration, used glyphosate products and
application rates. Other factors (i.e. smoking habits,medication etc.) were assessed but not included in the evaluation."

Additionally they claimed
- that a response rate of 80% was insufficient,
- that information about use of glyphosate-containing herbicides by interviews might
be the cause for recall bias,
- that using the same hospitals for recruiting patients as for a previous study might
lead to assessment bias etc.

Comments:
1. For assessment of exposure to pesticides the same questionnaire was applied as
for previous studies (e.g. Hardell 1999) with identical procedures for follow-up by

telephone interviews. These procedures are the best in epidemiologic practice. In the questionnaire and in the subsequent telephone interviews a detailed assessment of different brands of pesticides, duration, intensity etc. was made.

2. Other variables as e.g. smoking were of course included in the analyses, as it is since decades common epidemiologic practice to include smoking in every case-control study on risk factors for cancer or cardiovascular diseases as a confounding factor. The authors wrote in their assessment of exposure that informations derived from "questions on e.g. smoking habits, medications, leisure time activities and proximity from home to certain industrial installations...are not included in this article". It certainly is a big difference between including variables as potential confounders into a multivariate logistic regression and reporting the results of including these confounding factors in an article. Usually the length of an article in international scientific medical journals is limited, thus results that are of no importance for the main questions can easily discarded. In addition Eriksson and co-authors with their wording indicated the possibility of a later publication reporting on these confounders.

3. A response rate of 80% in epidemiologic practice is hard to achieve in population-based case-control studies. In general a response rate of 70% is regarded as sufficient. Thus the claim that an 80% response rate could bring a bias of any kind is totally unfounded.

4. The use of interviews for ascertain the exposure to risk factors is general practice in epidemiology. To deduct a potential bias from this practice is not founded on any scientific basis.

5. To use for recruitment of patients such hospitals, which had cooperated for epidemiologic practice in the past, is good epidemiologic practice. There are no data available to support the claim that such recurrent use of a patient source for epidemiologic studies might induce any kind of bias.

In conclusion it has to be stated that all of the claims supporting the classification of the Eriksson and co-authors study as "not reliable" are without any scientific basis.

3.4 The publication of Cocco and co-authors reported the results of a case-

control study on pesticides as potential risk factors for the development of malignant lymphomas. They included 2348 incident lymphoma cases (from the international Interlymph Study) and 2462 were matched population-based controls or hospital controls. They derived increased odds ratios for chronic lymphocytic leukemia (CLL) for exposure to organic pesticides (OR 1.5; 95% CI 1.0-2.1) or organophosphates (OR 2.7; 95% CI 1.2-6.0).

In a short paragraph the anonymous authors of the EFSA Final Addendum to RAR
(p. 69) stated:

"Cocco et al. (2014, ASB2014-7523) investigated the role of occupational exposure to agrochemicals in the aetiology of lymphoma overall, B cell lymphoma and its most
prevalent subtypes. No increased CLL risk in relation to glyphosate was evidenced."

Comment: There is no basis in the publication of Cocco and co-authors for this claim, as odds ratios for glyphosate are presented exclusively in table 5 (p. 94). This table exclusively presents odds ratios for B cell lymphoma, not for CLL. The odds ratio for glyphosate as risk factor for B cell lymphoma is increased, but not statistically significant (OR 3.6; 95% CI 0.6-17.1). Thus, there is no odds ratio for glyphosate and CLL reported in the publication, and consequently it is impossible to state, if there is evidence linking glyphosate to CLL or not. The unsuspecting reader of the EFSA paragraph might assume, that there are no increases for any type of lymphomas caused by glyphosate.

4. Meta-Analyses

In the EFSA Final Addendum to RAR a paragraph (p.24) is devoted to meta-analyses.

"Meta-analysis is an accepted investigation tool to provide a statistical summary across a number of studies with the same research question and similar setting. RMS has reviewed the study of Schinasi and Leon (2014, ASB2014-4819) as it is described in the IARC monograph and a meta-risk ratio of 1.3 (95% CI 1.03 - 1.65) I2=0%, P for heterogeneity 0.589) for NHL and glyphosate (glyphosate-based
formulations, see discussion in section 2.5), as elicited by the IARC Working Group for glyphosate, could be reproduced by the RMS."

Thus, it can be concluded that the anonymous authors of the EFSA Final Addendum to RAR accept that a meta-analysis is a established scientific tool in epidemiology.

However, on page 69 of the EFSA Final Addendum to RAR the anonymous authors conclude claim regarding a meta-analysis, conducted by Schinasi and Leon:

"Schinasi and Leon (2014, ASB2014-4819) published the results of epidemiologic
research on the relationship between non-Hodgkin lymphoma (NHL) and occupational exposure to pesticides. Phenoxy herbicides, carbamate insecticides, organophosphorus insecticides and lindane were positively associated with NHL. However, no association between NHL an glyphosate was reported."

This, however, is in contrast to the Meta-Analysis conducted by Schinasi and Leon , as in table 5 (page 4513) the summary odds ratio for NHL is presented as 1.5 (CI 1.1-2.0) and for B cell lymphoma as 2.0 (CI 1.1-3.6). These odds ratios are equivalent for a strong association between NHL and glyphosate.

Comment: The claim, that in the meta-analysis of Schinasi and Leon no association between NHL and exposure to glyphosate-containing herbicides is reported, is obviously false.

Conclusions: The claims that epidemiologic studies on the impact of exposure to glyphosate-containing herbicides are flawed in such a way, that they are "not reliable", are obviously in all investigated papers without any scientific basis and thus are obviously false.

ECHA note - The following attachment was submitted with the comment above: *Appendix Greiser 18-7-2016.pdf*
Journal articles are not confidential as such, however, ECHA does not publish them on the website due to Intellectual Property Rights.

Dossier Submitter's Response

Thank you for this comment. Of course, we agree that epidemiological studies are a very valuable contribution in risk assessment of active substances. We agree also with your short description of well-known basic principles of epidemiology. On the other hand, the value for classification of such studies is limited in many cases which was shortly mentioned in the introduction of the chapter of the CLH proposal.

In the case of glyphosate, it should be noted that the substance is always used in combination with co-formulants which are often more toxic than the active substance glyphosate. This is particularly pertinent when considering previously published epidemiological studies where tallowamine was a co-formulant. In a range of studies the toxicity of tallowamine was clearly shown to be higher than glyphosate for different toxicological endpoints. In epidemiological studies the co-formulants in formulations are typically not considered to be relevant. However, this is not acceptable in the special case of glyphosate containing formulations. The published epidemiological studies are not sufficiently appropriate to differentiate between effects caused by glyphosate and effects caused by tallowamine and/or other co-formulants.

The additional comment on the study by Arbuckle et al. (2001) is partly based on a discussion of the EFSA RAR. However, the discussion of this paper was already performed and completed in 2015 when the draft of EFSA RAR was submitted to the public. Additionally it was criticised in comment 159 that in the CLH proposal the study by Arbuckle et al. (2001) was considered to have

"strong limitations". These limitations were described in the following sentences on page 109. In comment 159 the author states that these limitations are not valid. However, the submitted arguments (the population of the Ontario farm study might be healthier than any general population and abortions were discarded when occurring during periods when the woman of a couple was not living on the farm…) are speculative and not borne out by the facts. Furthermore, in comment 159 an additional extensive discussion of the EFSA RAR was submitted. However, as already mentioned above, the discussion of this paper was performed and completed in 2015 after submission of the EFSA draft report to the public. It is emphasised once more that the EFSA RAR contains an addendum on carcinogenicity in response on the IARC publication. All studies cited in the IARC review were extensively discussed there. Concerning the studies in humans (including studies mentioned in comment 159), there was considerable agreement between the assessments by IARC and the revised assessment in the EFSA RAR. Please take note of this addendum.
RAC's response
Noted. See response to comment no 11 and 259.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	United Kingdom	Sustainable Food Trust	BehalfOfAnOrganisation	160

Comment received
I will have to submit my entire comment in this general section as the issue of antimicrobial resistance is not listed below. I would like to draw your attention to a study by scientists in New Zealand (Kurenbach et al. 2015), attached, in relation to their findings which indicate that low level exposure to glyphosate induces phenotypic changes in the sensitivity of E. coli and Salmonella typhimurium to commonly used antibiotics, in some cases immediately triggering high levels of antimicrobial resistance, in other cases actually increasing the sensitivity of the bacteria to the antibiotics. The authors argue that both these changes have potential clinical importance. The development of resistance has obvious treatmenbt implications but the development of increased and unpredictable increases in sensitivity could also lead to overdosing in situations where empiracal prescribing is necessary in order to save a life or required due to technical or other impediments to sensitivity testing. While their research indicates that permitted levels of glyphosate in food would be too low to produce such changes in antimicrobial sensitivity they also point out that exposure to spray drift, something which may people encounter due to the widespread and frequent use of this herbicide, would be sufficient. They also draw attention to the impact on antimicrobial sensitivity in farm animals where residues of glyphosate in livestock are unmonitored and in honey bees which are often treated with antimicrobials to control bacterial infections, issues which may have indirect implications for human health. While there are some indications that the such adaptive resistance as observed in the study

could lead to acquired resistance this aspect clearly requires further research. With antimicrobial resistance increasingly recognised as a major concern for human health I feel it is important that consideration be given to the impact of glyphosate known (see Glyphosate's patent as an antimicrobial) and recently observed antimicrobial properties. Reference Brigitta Kurenbach, Delphine Marjoshi, Carlos F. Amábile-Cuevas, Gayle C. Ferguson, William Godsoe, Paddy Gibson and Jack A. Heinemann, 2015. Sub-lethal exposure to commercial formulations of the herbicides dicamba, 2,4-D and glyphosate cause changes in antibiotic susceptibility in Escherichia coli and Salmonella enterica serovar Typhimurium, mBio 6:1-9 ECHA note - The following attachment was submitted with the comment above: *mBio-2015-Kurenbach-.pdf* Journal articles are not confidential as such, however, ECHA does not publish them on the website due to Intellectual Property Rights.
Dossier Submitter's Response
Due to its unique mode of herbicidal action, some antibiotic activity of glyphosate may be assumed. In fact, there were effects of this compound on bacteria and some other micro-organisms, in particular when tested in isolation *in vitro*. Indeed, a U.S. patent covering antimicrobial use of glyphosate was granted even although the doses necessary to control certain infections in humans were very high. It has been also shown that the vulnerability of various bacteria species is different. These findings have been taken into consideration in the RAR (Volumes 1 and 3) and, thus, for risk assessment, but in the sections dealing with possible effects on animal health. The point of concern was the potential imbalance of the microbial communities in the digestive tract of ruminants. The DS even commissioned additional research activities to investigate a possible impact of glyphosate (i.e., a glyphosate-containing herbicide) on complex microbial communities in cattle at realistic dietary concentrations, but no adverse effects were detected (Riede *et al.*, 2016, see attached article). A possible impact of glyphosate on the susceptibility of clinically important pathogens to antibiotics is a different and relatively recent issue which was indeed not considered in the RAR. Based on the U.S. patent, no such effects are expected at realistic exposure however research activities are under way nonetheless. Effects of glyphosate on micro-organisms have not been considered in the CLH dossier since they are not covered by the health-related classifications of chemicals according to CLP. Such effects would be clearly more an issue for risk assessment than for classification and labelling.
RAC's response
Noted. See response to comment no 68.

Date	Country	Organisation	Type of Organisation	Comment number
06.07.2016	United Kingdom	Générations Futures	BehalfOfAnOrganisation	161

Comment received
The assessment undertaken by ECHA is very sensitive since the outcome of this regulatory assessment will have deep consequences. Since glyphosate is virtually present in every human urine sample tested so far, a precautionary approach has to be taken. The decision to classify glyphosate as a H373 toxicant – which may cause damage to organs through prolonged or repeated exposure – truly reflects the results of chronic and developmental toxicity studies. However, the rejection of the category 2 classification for carcinogenicity by ECHA deserves a clarification. We believe that the data available is sufficient to classify glyphosate as a suspected human carcinogen. Serious flaws in the scientific evaluation in the RAR incorrectly characterise the potential for a carcinogenic hazard from exposure to glyphosate. (Portier et al., 2015, Epidemiol Community Health doi:10.1136/jech-2015-207005). - ECHA rejects classification as a suspected human carcinogen mainly by referring to historical control data. The use of historical data can confound interpretations because differential diet contaminations artificially enhance background effects and hide significant effects. It is thus inappropriate to combine different controls from different experiments within the same laboratory because different batches of the same feed may not be always similarly contaminated over time. For instance, the incidence of mammary fibroadenomas among populations of Charles River Sprague-Dawley females ranged from 13 to 62%. This could not be considered as a natural variation since laboratory rat diets are contaminated by environmental pollutants (Mesnage et al., 2015, PLoS One. 2015 Jul 2;10(7):e0128429. doi: 10.1371/journal.pone.0128429). - Additionally, ECHA did not comment on human epidemiological studies to justify their rejection of the category 2 classification. As described by Portier et al., the finding of limited evidence by the IARC was for Non-Hodgkin lymphoma (NHL), based on high-quality case–control studies, which are particularly valuable for determining the carcinogenicity of an agent because their design facilitates exposure assessment and reduces the potential for certain biases. The Agricultural Health Study (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7–1.9) with no apparent exposure–response relationship in the results. Despite potential advantages of cohort versus case–control studies, the AHS had only 92 NHL cases in the unadjusted analysis as compared to 650 cases in a pooled case–control analysis from the USA. In addition, the median follow-up time in the AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency. Moreover, the AHS results could not be considered as conclusive because the environmental exposure to glyphosate was not measured. Evidence of glyphosate effects from epidemiological studies on farmers may be largely biased by the fact that environmental exposure is poorly characterized. In the study of Curwin et al., in 2007 (Ann Occup Hyg. 2007 Jan;51(1):53-65), urinary levels of glyphosate were measured among children, mothers, and fathers living in farm and non-farm households. The geometric mean of glyphosate concentration in urine of non-farm and farm children were respectively 2.5 and 1.9mg/L . In general, levels measured in case of occupational monitoring are in the same order compared to environmental monitoring. As glyphosate is poorly absorbed by skin or inhalation, glyphosate concentrations reported as occupational

exposures may be due to the background of environmental exposures. Thus, the AHS cannot be considered as conclusive. Overall, the rejection of the category 2 classification for carcinogenicity by ECHA deserves a clarification.
Dossier Submitter's Response
Many arguments for and against classification and labelling of glyphosate for carcinogenicity are in the table and will be weighed by the RAC. We refer you to the CLH report and arguments provided by the DS contained therein. With regard to the use of measured urinary concentrations, it should be emphasised that they point to a generally low exposure even of people in rural areas.
RAC's response
Noted. See response to comment no 11 and 278.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	162
Comment received				
You must consider studies on mousses which showed that glyphosat provoques cancer. It is very important that you consider comments of high level and independant scientists in this matter. You must stay transparent and impartial when examanating results of studies of various industries. It should be possible to the public consulting the results of these studies. Please respect our health and the health of our earth.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4 and 11.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	163
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is				

carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	164
Comment received				
You must evaluate the studies presented by industrials with great care , because of possible conflicts of interest. You also need to make it public so that they can be studied by other scientists, thank you !				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	165
Comment received				
I know that glyphosate generates a lot of profits, which generally generates a lot of pressure and counter-informations. Even if I am not myself a scientist in the area, I want every relevant elements to be taken into account and precautionary principle to be respected. I believe full transparency is the only way to achieve that.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action				

for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	166
Comment received				
To date, many independent (non-profit motivated) studies and associations of citizens are showing evidences of how toxic and dangerous glyphosate is for the Human being and the biosphere in general. It is scandalous that such universal poison is yet authorized. Corruption and fraud have to give way to democracy and common sense. Respectfully, [redacted]				
Dossier Submitter's Response				
Thank you for the comment. However, it is is a personal opinion which does not raise any points related to classification and labelling of glyphosate.				
RAC's response				
Noted. See response to comment no 68.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	167
Comment received				
Il en va de Notre VIE et de Notre SANTE. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate. Merci.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	168
Comment received				
In the European chemicals policy, the precautionary principle applies. Therefore CLP-classification generally is a hazard assessment not a risk assessment. In the attachment you will find additional facts according to the „human health hazard assessment" of the CLP-Report. These are facts that justify our proposal for a supplementary classification for human health. ECHA note - The following attachment was submitted with the comment above: *Internet-Konsultation ECHA.zip*				
Dossier Submitter's Response				
No new arguments or information have been submitted. The proposals reflect merely a different view on the same facts as expressed by the DS in its CLH dossier.				
RAC's response				
Noted. See response to comment no 4, 11 and 68.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	169
Comment received				
Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	170
Comment received				
Concernant le glyphosate. Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				

Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	171
Comment received				
Everybody knows by now that glyphosate represents a serious threat to the environment, our health and our children. Don't let your integrity be violated by pleasing Monsanto: the environment and our health are more important than poisoning the Earth for some money in your pocket.				
Dossier Submitter's Response				
Thank you for the comment. However, it is is a personal opinion which does not raise any points related to classification and labelling of glyphosate.				
RAC's response				
Noted. See response to comment no 68.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Ireland		Individual	172
Comment received				
I am concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. In your evaluation, can you include all independent studies used in the IARC monograph in your assessment. Can you review the studies submitted by industry with very strong caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Can you ensure that you take into account the six studies from registers of human cancer cases, and also the evidence on carcinogenicity in the mouse,				

when you decide how to classify glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	173
Comment received				
Glyphosat erzeugt Krebs				
Dossier Submitter's Response				
As explained in the CLH dossier, the DS has a different view.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	174
Comment received				
Glyphosat erzeugt Krebs				
Dossier Submitter's Response				
As explained in the CLH dossier, the DS has a different view.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	175
Comment received				
- Clearly elevated cancer incidence at 31.49 mg/kg d- in a 1981 industry study dismissed for using doses lower than industry used later (RMS agrees); a particularly insane argument when the effects of everyday (chronic) exposures are being investigated; p. 473.				

Dossier Submitter's Response
We assume that this comment relates to a slightly higher number of animals with islet cell carcinoma (i.e. 1/50 vs. 0/50 in the control, low and mid dose groups as shown in Table 27 of the CLH dossier) and to the increase in interstitial tumours of the testis (0/50, 3/50, 1/50, 6/50) in the study by Lankas (1981). If a certain type of cancer is elevated at a dose level of ca 31 mg/kg bw/day, at least reproducibility of this effect or, more likely, a much higher incidence would be expected at higher dose levels as included in subsequent studies to assign this finding to the test substance. This was not the case with glyphosate.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	176
Comment received				
Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als „wahrscheinlich krebserregend beim Menschen" (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als „vermutlich karzinogen, Kategorie 1B" einstufen. Zur Begründung: Gemäß der EU-Verordnung Verordnung 1272/2008 über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenität bei „zwei oder mehreren unabhängigen Studien an einer Spezies" aus, um eine Substanz als „vermutlich karzinogen beim Menschen" einzustufen. Im Fall von Glyphosat ist ein dosisabhängiger Anstieg von Krebstumoren bei Mäusen in mindestens fünf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos für Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf				
Dossier Submitter's Response				
The biological relevance of a higher number of mice with certain tumours is discussed in length in the CLH dossier. The DS is still convinced that classification for carcinogenicity is not needed.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
13.07.2016	France	International Agency for Research on Cancer (IARC)	BehalfOfAnOrganisation	177

Comment received
The IARC Monographs' programme will be readily available to provide clarifications requested by ECHA and or RAC regarding the completeness and interpretation of scientific data with regards to the carcinogenicity of glyphosate.
Dossier Submitter's Response
Noted.
RAC's response
Thank you for your offer to provide clarifications.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	178
Comment received				
Bellé, R., Le Bouffant, R., Morales, J., Cosson, B., Cormier, P., Mulner-Lorillon, O. (2007): Sea urchin embryo, DNA-damaged cell cycle checkpoint and the mechanisms initiating cancer development. J. Soc. Biol. 201, 317–327				
Dossier Submitter's Response				
This paper is known to the DS. Assessment for carcinogenicity is mainly based on long-term studies is rodents. Findings in sea urchin embryos are not sufficient to justify classification.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium	Greenpeace European Unit	BehalfOfAnOrganisation	179
Comment received				
Greenpeace believes that an EU classification of glyphosate in Category 1B is warranted, based on the strength of evidence ascertained in the IARC Monograph, as well as further evidence not considered by IARC. We ask the members of the Risk Assessment Committee to acknowledge the limited evidence of carcinogenicity in humans, as well as the strong and consistent evidence of carcinogenicity in animals, and to critically review the considerations brought forward by the Dossier Submitter to decrease the level of concern. ECHA note - The following attachment was submitted with the comment above: *Greenpeace_ECHA submission glyphosate_18072016.pdf*				
Dossier Submitter's Response				
Noted. The DS has clearly expressed its opinion in the CLH dossier.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	180

Comment received
For correct display of tables see public attachment. Whilst much effort has undeniably been made to analyze the huge mass of information, BECA would like to emphasize some points that may be worth further consideration: • In Kumar (2001, ASB2012-11491) study: BECA notes some inconsistencies between the CLH report and the Renewal Assessment Report (the number of animals affected and the statistical significance) (See table 1). Furthermore, a significant increase of incidence of malignant lymphoma was observed at the highest dose groups and a positive trend was detected in males. Table 1 : Total incidence of malignant lymphoma Males Females Doses (ppm) 0 100 1000 10000 0 100 1000 10000 Doses (mg/kg bw/d) 0 14.5 149.7 1453.8 0 15 151.2 1466.8 Number of animals affected (in the CLH report) 10/50 15/50 16/50 19/50* 18/50 20/50 19/50 25/50* Number of animals affected (in the Renewal assessment report) 1/28 3/30 3/28 6/23 9/34 10/34 6/30 13/30 * statistically significant increase • In Wood (2009, ASB2012-11492) study: A slight dose-dependent increase of malignant lymphoma in male was observed (See table 2). Moreover, the Renewal Assessment Report indicates that "the difference was not statistically significant but a possible effect might be suspected and should be clarified". The incidence was in the historical control data however this report mentions that "the quality and the regulatory value of the historical control data is very much compromised by the fact that the sexes were not considered separately". Table 2 : Total incidence of malignant lymphoma Doses (ppm) 0 500 1500 5000 Doses (mg/kg bw/d) 0 71.4 234.2 810 Number of animals affected 0/51 1/51 2/51 5/51* * statistically significant increase • In Sugimoto (1997, ASB2012-11493) study: BECA notes some inconsistencies between the CLH report and the Renewal Assessment Report (the number of animals affected) (See table 3). Furthermore, in the CLH report, in males, the trend test was significant (p-value = 0.0085) indicating a dose dependency Table 3 : Total incidence of malignant lymphoma Males Females Doses (ppm) 0 1600 8000 40000 0 1600 8000 40000 Doses (mg/kg bw/d) 0 165 838.1 4348 0 153.2 786.8 4116 Number of animals affected (in the CLH report) 2/50 2/50 0/50 6/50 6/50 4/50 8/50 7/50 Number of animals affected (in the Renewal assessment report) 0/26 0/34 1/27 5/29* 4/32 8/36 8/40 0/35* Number of animals affected (in the Renewal assessment report) : Revised results 0/26 0/34 0/27 2/29 4/32 0/36* 5/40 3/35

* statistically significant increase • In Atkinson (1993, TOX9552382) study: BECA notes a slight increase in the incidence of haemangiosarcoma in male mice at the highest dose of this study (4/50 at 1000 mg/kg bw/d vs 0/50 at 0, 100 and 300 mg/kg bw/d). Thus, BECA does not agree with the proposed NOAEL by the DS (1000 mg/kg bw/d).
Dossier Submitter's Response
With regard to malignant lymphoma, exactly the same incidence for the study by Kumar (2001) is given in the CLH dossier (Table 31) and in Vol. 1 of the RAR (Table 2.6.9). All animals in the study were taken into account. The lower numbers as cited in the comment are from Table B.6.5-46 in Vol. 3 and report the tumour incidences only in those animals which survived until scheduled termination. Only the incidence of malignant lymphoma in all animals studied was subject to statistical evaluation. As can be seen in the CLH report (Table 33), the increase in high dose males and females as compared to the controls was positive in the Z-test, but both Fisher's exact test and the trend test (Cochran Armitage) failed to reveal a statistically significant increase. In the study by Wood (2009), the trend test, in contrast, revealed a statistically significant increase in males whereas a pairwise comparison by Fisher's exact test and by the chi-square test did not. Again, the (rather unusual) Z-test (performed by DS) revealed a positive result (Table 34 of the CLH dossier). The "inconsistencies" as mentioned for the Sugimoto (1997) study for malignant lymphoma can also be readily explained. The lower numbers in the RAR as compared to the CLH dossier as given in the comment are apparently based on Table B.6.5-58 in Vol. 3 of the RAR but this data was found to be incorrect upon re-evaluation. This is clearly stated in the "RMS comments" at the bottom of section B.6.5.2 (3d new study) of Vol.3. Thus, it can be discarded. The correct incidences are given in Table B.6.5.60 (i.e., 0/26 – 0/34 – 0/27 – 2/29 in males and 4/32 – 0/36 – 5/40 – 3/35 in females). These numbers are correctly cited in the comment but, again, they reflect the findings at terminal sacrifice. The total incidence for the whole study is given in Table B.6.5-61 (2/50, 2/50, 0/50, 6/50 in males; 6/50, 4/50, 8/50, 7/50 in females). The same numbers of affected mice are given in Vol. 1 of the RAR (Table 2.6-9) and in the CLH dossier (Table 31). On balance, there are no inconsistencies. The relevance of the haemangiosarcoma is discussed at length in the CLH dossier and the addendum. Setting of the NOAEL is of no relevance for classification and labelling. The NOAEL for the study (1000 mg/kg bw/day) has been confirmed during the peer review process by EFSA and the MS. To conclude, this comment does not alter the current assessment of carcinogenicity in mice by the DS.
RAC's response
Noted. See response to comment no 11 and 210.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Sweden		Individual	181

Comment received
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Austria	GLOBAL 2000	BehalfOfAnOrganisation	182
Comment received				
Facing different results between the cancer assessment of the International Agency for the Research on Cancer (IARC) and the German Federal Institute for Risk Assessment (BfR), the Austrian environmental organization GLOBAL 2000 made some efforts to understand the underlying reasons for the obviously contradicting outcome. Our main findings were: 1) Serious doubts on the reliability and the scientific value of BfR's cancer assessment are raised by BfR's self-contradicting comments on the five regulatory long-term studies of carcinogenicity in mice: Using the example of the study of Wood et al, 2009 we demonstrate that BfR changed its evaluation of the study results step-by-step, from "no indications for carcinogenicity up to the highest dose level" in December 2013 (draft RAR), to "slight increase in the incidence of malignant lymphoma, but not statistically significant" in March 2015 (after IARC's classification) to "statistically significant increase of malignant lymphoma, which could be considered as treatment- dependent" in Aug 2015 (Addendum to the RAR). More details can be uploaded here as PDF: http://www.global2000.at/sites/global/files/Contradictions%20in%20the%20RAR.pdf				

2) A deeper analysis of the five long-term mice studies by the toxicologist Dr. Peter Clausing on behalf of GLOBAL 2000 finally revealed major flaws in BfR's and EFSA's cancer assessment: The authorities falsely interpreted regulatory mice carcinogenicity studies, by violating several relevant OECD guidelines and using inappropriate historical control data. More details can be uploaded here as PDF:
https://www.global2000.at/sites/global/files/Evidence%20in%20animal%20testing_PeterClausing.pdf

3) An Expert Statement, provided by the epidemiologist Prof. Eberhard Greiser on behalf of GLOBAL 2000 revealed that several epidemiological studies that demonstrated a correlation
between exposure to glyphosate-based herbicides and Non-Hodgkin's lymphoma have been systematically "classified" as unreliable in the notifiers dossier, claiming that relevant data (e.g. exposure to glyphosate, smoking behaviour, previous diseases) was lacking. Though these claims were false – which could easily have been noticed by the BfR and EFSA – these two institutions accepted these alleged errors as the basis to systematically discredit human evidence for the carcinogenicity of glyphosate as "not reliable". More details can be uploaded here as PDF:
https://www.global2000.at/sites/global/files/Human%20evidence_EberhardGreiser.pdf

4) Last but not least, an Expert Statement from Prof. Ivan Rusyn, a leading member of the IARC Working Group on glyphosate, compared the legal background and relevant guidelines for classification of carcinogenicity in the EU pesticide regulation with the IARC's internal rules. He concludes that "it does not appear that the BfR renewal assessment report on glyphosate (18 December 2013 version) followed these guidelines in evaluation of the human and animal carcinogenicity evidence for glyphosate". Rusyn concluded that the RAR "repeatedly downplays positive findings of cancerogenicity in animal studies based on dose considerations".
More details can be uploaded here as PDF: (please note that this PDF starts with the statement in German language. The English version can be found in the second half of this document):
https://www.global2000.at/sites/global/files/expert_statement_Bundestag_IvanRusyn.pdf

The attached statements from different scientist on different aspects of the BfR's and EFSA's cancer assessment have one thing in common: They show that the authorities adopted wrong assessments and false descriptions by industry without further scrutiny and used them to dismiss indications for carcinogenic effects of glyphosate in experimental animals and humans. Therefore, the above documents were submitted to the Offices of public Prosecutors in Vienna and Berlin.
GLOBAL 2000 considers the assessments performed by the BfR and the EFSA as a violation of their legal mandate. Therefore, GLOBAL 2000 and other NGOs have filed a criminal charge against these institutions, Monsanto Europa S.A. and Monsanto Agrar Deutschland GmbH.

ECHA note - The following attachment was submitted with the comment above: *Attachments.zip*
Dossier Submitter's Response
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 4, 11 and 68.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Chile		Individual	183
Comment received				
Since carcinogenicity induced by environmental substances includes epidemiological studies and experimental animals, the work on glyphosate is an important contribution to this concept. Human epidemiology studies through meta-analyses and tree plot indicated carcinogenicity induced by glyphosate. On the other hand, carcinogenicity studies in male mice showed male mouse renal tumors from the individual studies and pooled analysis of male mouse renal tumors. Studies were performed on renal tumors in male mice by poly-3 adjusted showing individual dose groups as well as clustered by similar doses. Studies also showed male mouse malignant lymphoma from the individual studies and pooled analysis of male mouse malignant lymphoma. Results on malignant lymphomas in male mice by poly-3 adjusted showed individual dose groups. Malignant lymphomas in male CD-1 mice poly-3 adjusted showing individual dose groups and clustered by similar doses were also found. Analysis of male mouse hemangiosarcomas from the individual studies and pooled analysis of male mouse hemangiosarcomas were studied. Hemangiomas in male CD-1 mice poly-3 adjusted and clustered by similar doses showed individual dose groups indicated positivity. It can be concluded that glyphosate is a carcinogenic substance.				
Dossier Submitter's Response				
The DS disagrees. Based on the explanations given in the CLH dossier but also in the addendum (according to the OECD framework), carcinogenicity of glyphosate is not likely. Poly-3 adjustment is usually not performed in the regulatory evaluation of pesticides in Europe. Even though it was developed decades ago, it did not make its way into the guidelines and guidances for carcinogenicity testing. See also our comprehensive response to the very extensive comment 197.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	184

Comment received
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	United Kingdom	Breast Cancer UK	BehalfOfAnOrganisation	185
Comment received				
The dossier presents evidence of three carcinogenicity studies in mice which show a statistically significant increase in incidence of malignant lymphoma (p.95). This is consistent with classification criteria for a carcinogen, as presented on p.95 of the dossier. Further mouse studies indicate a possible association with renal tumours (p.76) and haemangiosarcoma, (p.77), although the statistical significance of these associations is less certain. Epidemiological studies associated with non-Hodgkin's lymphoma and other cancers were also considered in the dossier report. The dossier states these revealed partly contradictory results (p.93) and suggests the findings based on the Agricultural Health Study (AHS) data (De Roos et al. 2005) are the most reliable, due to the size of their dataset. These show no association between glyphosate and cancer. Although based on the largest dataset of any epidemiological study, the AHS followed subjects for a relatively short period (average follow up of 6.7 years) and included only 92 cases of Non-Hodgkin's lymphoma. Although we agree to some extent that epidemiological studies alone can be of "limited value for detecting the carcinogenic potential of an active substance in a plant protection product, since humans are never exposed to a single compound alone" and "results are associated to different formulations containing glyphosate or mixtures of different active substances"(p93), they are nonetheless of some value, especially when combined with other data. The IARC finding of limited evidence for an				

association between glyphosate and non-Hodgkin's lymphoma, was based on high-quality case-control studies, including that of De Roos et al. (2003) [De Roos et al. (2003) Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occupational and Environmental Medicine 60:E11], which included 650 non-Hodgkin's lymphoma cases. We believe this study, with considerably more NHL cases, should be given greater consideration than the AHS study, which included only 92 cases. Since publication of the dossier, a study which presents evidence of an association between glyphosate and cutaneous melanoma has been published [see Fortes et al. (2016). Occupational Exposure to Pesticides With Occupational Sun Exposure Increases the Risk for Cutaneous Melanoma. Journal of Occupational and Environmental Medicine 58(4):370-375]. The study, which analysed data from two case-control studies in Brazil and Italy, presents evidence that occupational use of pesticides, especially glyphosate, is associated with a high risk of cutaneous melanoma, and that risk is exacerbated in the presence of sunlight. An association between glyphosate use and melanoma is in contrast to findings by Dennis et al. (2010) and De Roos et al. (2005), based on data from the Agricultural Health Study (see p85 and elsewhere in the dossier and for full references). Neither study examined whether or not glyphosate augmented the risk of melanoma among those exposed to occupational sunlight. This new data should be taken into consideration. Studies presented in the dossier demonstrate limited evidence of carcinogenicity in humans, together with limited evidence of carcinogenicity in experimental animals, which supports CLP classification of Category 1B or, at the very least, Category 2.
Dossier Submitter's Response
The epidemiological studies as well as the long-term studies in mice have been subject to detailed evaluation both in the RAR and in the CLH dossier. The animal findings were also addressed in the addendum according to the OECD framework. The overall conclusion was that glyphosate was not likely to be a human carcinogen. Others might come to different views. It is up to ECHA and its RAC to decide. The study by Fortes was just recently published and, accordingly, could not be included neither in the RAR nor in the CLH dossier. New information may be taken into account only up to a certain time point. Otherwise, a decision could be never made.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium	PAN Europe	BehalfOfAnOrganisation	186
Comment received				
According to the available data from scientific literature, glyphosate should be classified as category 1B carcinogen: presumed to have carcinogenic potential in humans due to sufficient evidence of carcinogenicity in animal experiments and limited evidence in humans. "Sufficient evidence in experimental animals" because an increased incidence of malignant neoplasms following glyphosate exposure was observed in 5 independent (regulatory) studies performed in				

mice, which is further supported by mechanistic data on cytotoxicity and genotoxcity. "Limited evidence in humans" because a positive association has been observed between exposure to glyphosate and non-Hodgkin's lymphoma (NHL) in 3 case studies from 3 different countries, and in one meta-analysis of 6 studies. Moreover, genotoxicity in the form of DNA damage (e.g. DNA strand breaks, DNA adducts), chromosomal damage (micronuclei formation and chromosomal aberrations) has been observed in human cells in vivo, in mammalian model systems in vivo and in vitro, and in numerous studies using non-mammalian organisms. Serious scientific errors have been detected in the analysis of regulatory studies by BfR, followed by EFSA and the present dossier that lead to a erroneous classification of glyphosate as non-carcinogen. These are: (1) neglecting the positive findings of an OECD-recommended statistical test for detecting dose-response effects in carcinogenicity studies (Cochran–Armitage trend test), (2) using inappropriate (different strain, >5 years old, different laboratory) historical control data to dismiss positive tumour findings following exposure to glyphosate in animal experiments, (3) inappropriately dismissing evidence from human studies from 3 different countries revealing a positive correlation between glyphosate exposure and NHL, (4) dismissing data on cytotoxicty and genotoxicty, which support the human and animal experiment observations. IARC reached the conclusion that glyphosate is "probably carcinogenic to humans", which is equivalent to "presumed carcinogens" in European CLH. IARC used only publicly available studies reported properly to perform the peer-review and therefore took into account only 2 out of the 5 studies in which BfR found that malignant tumours were statistically significant using the trend-test. Even with 2 studies IARC concludes that glyphosate is "probably carcinogenic", following the weight-of –evidence approach and considering mechanistic and human evidence. Please find attached the relevant documents.
Dossier Submitter's Response
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 11 and 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	187
Comment received				
Carcinogenicity Animal data The carcinogenic potential of glyphosate has been investigated in various				

studies in rats and mice, in which occasionally increases in certain tumour types were observed. The findings in the studies have been well described in the proposal for classification and labelling. Tumor incidences observed were generally low and within (historical) control levels, suggesting random variation but no substance related carcinogenicity. It cannot be excluded that at very high doses (>1000 mg/kg), oxidative stress and systemic toxicity may have mediated some of the observed tumors. Based on a thorough evaluation of the available data in the proposal it is concluded that the weight of evidence indicates no classification for carcinogenicity of glyphosate is needed according to the CLP criteria.
It was noted that the purity of the tested glyphosate in these studies varied between 94.61% and 99.7%. Given the high exposure levels of up to 4000 mg/kg bw/day in some studies, the actual exposure to impurities was up to 200 mg/kg bw/day. The observed differences in tumor incidence could potentially be due to differences in impurity. The DS is requested to assess whether the potential differences in tumour incidence between the various studies could be explained by differences in exposure to impurities.

Epidemiology
It is noted that the evaluation of epidemiological studies as discussed, including the 'Glyphosate Addendum 1 to RAR 2015', by the RMS and IARC are largely comparable/essentially similar. Except for one prospective study only case-control studies are available on the association between exposure to glyphosate containing herbicides and the risk of several types of cancer. Most case-control studies on multiple cancer types/sites did not find statistical significant associations. However, results are conflicting with respect to the risk of Non-Hodgkin lymphoma (NHL). Interpretation of the results is hampered by the low power of the individual case-control studies. Furthermore, case-control studies cannot definitely prove causal relationships, because of methodological limitations, such as recall bias. The only prospective study among >57,000 farmers with 92 NHL cases could not confirm an increased risk among appliers of glyphosate (de Roos, 2005). The prospective study did not report statistical significant associations with overall and other site specific cancers. It should be noted however, that 25% of the population in the study of de Roos (2005) was excluded because information on at least one of the 47 agents studied was lacking. This might have influenced the findings as has been shown for the risk of multiple myeloma (RR: 2.6 (0.7–9.4) in the fully adjusted model in the paper of de Roos and RR: 1.1 (0.5-2.4) in the re-analysis on the full cohort by Soharan (2015). This is not mentioned in the CHL report.

The meta-analysis of Schinasi and Leon showed an odds ratio of 1.5 (1.1-2.0). Table 45 of the CLH report states that there is agreement with the IARC conclusion, i.e. the estimate of the most adjusted models should be used (1.3 (1.03-1.65)). This is in contrast with the conclusion on page 83 of the CLH report stating that no association between NHL and glyphosate was observed.

Several analyses in the meta-analysis of Schinasi and Leon may be relevant, but are not mentioned in the CLH report.
- The association between glyphosate and NHL risk is stronger in the studies where NHL was diagnosed in the period 1975-1989 compared to more recent periods. One can only speculate about the reasons for this, but less exposure

to other compounds (that are no longer allowed) and better protection when applying glyphosate in more recent years may have played a role. - Studies that report a positive association between glyphosate exposure and NHL predominantly come from Sweden. Epidemiological associations that are robustly observed in various populations are more likely to be causal than associations that are heterogeneous between populations. As stated in the CHL report, the level of evidence from the epidemiological studies is indeed limited and therefore the conclusion that epidemiological data do not provide convincing evidence that glyphosate exposure in humans might be associated with cancer risk is justified according to CLP criteria. This evidence does therefore in itself not allow classification of glyphosate as carcinogenic.
Dossier Submitter's Response
It seems that the comments on epidemiology as well as on animal studies support, in principle, the opinion of the DS. A possible impact of impurities on tumours in mice at very high dose levels cannot be excluded but is still a hypothesis that would be difficult to verify. In the RAR, it was highlighted at least that striking differences in (non-neoplastic) high dose effects among the various subchronic and long-term studies were common. A different impurity profile might be a likely explanation.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Norway		MemberState	188
Comment received				
Due to the application of different statistical approaches selected for the evaluation, IARC and EFSA came to diverging conclusions. According to the OECD guidance document on the conduct and design of chronic toxicity and carcinogenicity studies, significance in a trend test is sufficient to reject the hypothesis that chance accounts for the result. In some studies on mice statistical significant positive trend and exceedance of the historical control data have been noted for some tumors.				
Dossier Submitter's Response				
This situation is clearly described in the CLH dossier in which a weight of evidence-approach according to the ECHA guidance documents for classification and labelling has been included. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	189

Comment received
Please include all studies and make them public to make sure none of them could be only representative of (very) profitable interests
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4 and 68.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	190
Comment received				
Je suis très préoccupé par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Belgium		Individual	191
Comment received				
Je suis très préoccupé(e) par le manque d'évaluation des risques de cancer , pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte. Vous devez inclure toutes les études mentionnées par la monographie du CIRC dans votre évaluation. Vous devez évaluer les études présentées par les industriels avec énormément de soin, à cause de possibles conflits d'intérêts. Vous devez également les rendre publiques afin qu'elles puissent être étudiées par d'autres scientifiques. Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				

Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Umweltinstitut München e. V.	BehalfOfAnOrganisation	192

Comment received

Einstufung durch die Internationale Agentur für Krebsforschung
Die Internationale Agentur für Krebsforschung (IARC) der Weltgesundheitsorganistation (WHO), prüfte den Wirkstoff Glyphosat anhand der ihr zur Verfügung stehenden (ausschließlich öffentlich zugänglichen Studien) und kam dabei zu dem Ergebnis, dass

-Glyphosat „wahrscheinlich krebserregend beim Menschen" ist (Kanzerogen Gruppe 2A) („probably carcinogenic to humans")
-ausreichend Beweise für eine karzinogene Wirkung von Glyphosat bei Versuchstieren vorliegen („sufficient evidence for the carcinogenicity of glyphosate in experimental animals")

Desweiteren konnte die IARC einen positiven Zusammenhang zwischen Glyphosat und dem Auftreten von Non-Hodgkin Lymphomen (bösartiger Lymphdrüsenkrebs, der in allen Organen des menschlichen Körpers auftreten kann) feststellen
(„A positive association has been observed for non-Hodgkin lymphoma").
Quelle
•IARC: Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology, 20 March 2015
http://monographs.iarc.fr/ENG/Monographs/vol1/mono112-09.pdf

Tierversuche an Mäusen

Laut der Verordnung über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen, CLP-Verordnung 1272/2008, Anhang I, 3.6.2.2.3 liegen ausreichend Nachweise aus Tierversuchen für eine Klassifizierung als „wahrscheinlich krebserregend für Menschen" (Kategorie 1B) vor, wenn ein ursächlicher Zusammenhang zwischen einem Stoff und der erhöhten Häufigkeit bösartiger Neoplasmen (Tumoren) oder einer Kombination von gutartigen und bösartigen Neoplasmen festgestellt wird,

a)bei zwei oder mehreren Arten von Tierspezies
oder
b)in zwei oder mehreren unabhängigen Studien zu einer Tierspezies, welche in

verschiedenen Zeiträumen oder in verschiedenen Laboratorien oder unter verschiedenen Protokollen durchgeführt wurden.

Dieser Nachweis wird bei leitlinienkonformer Auswertung durch wenigstens 5 verschiedene Langzeit-Fütterungsstudien an Mäusen erbracht. In allen Studien traten bösartige Tumoren in Nieren, Blutgefäßen oder Lymphdrüsen nach Verabreichung von Glyphosat auf. Der Anstieg an Krebstumoren ist dabei signifikant, was inzwischen auch vom BfR eingeräumt wurde.

Die Klassifizierung als ”vermutlich krebserregend für Menschen” (Kategorie 1B) hängt von der Beurteilung ab, ob “ausreichend Beweise” aus Tierversuchen bestehen um “eine karzinogene Wirkung bei Tieren nachzuweisen” (Verordnung über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen [CLP] 1272/2008, Anhang I; 3.6.2.1)

Da ein ursächlicher Zusammenhang zwischen Glyphosat und der Zunahme bösartiger Tumore feststellbar ist, darf das Pestizid nach der Verordnung über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen [CLP] 1272/2008, Anhang I; 3.6.2.2.3 und 3.6.2.1 in Europa nicht weiter zugelassen werden.

Quellen
•EPA (1983). Review of Knezevich A, Hogan G (1983). A chronic feeding study of glyphosate (Roundup Technical) in mice: Project No. 77–2061: Bdn-77-420. Final Report. MRID 00130406. Washington (DC): United States Environmental Protection Agency. http://www.epa.gov/ncct/toxrefdb/
•Sugimoto, 18-Month Oral Oncogenicity Study in Mice.Unpublished, designated ASB2012-11493 in BfR RAR, 1997.
•Unknown, Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice, designated ABS2012-11491 in BfR RAR, 2001.
•Unknown, Glyphosate Technical: Dietary Carcinogencity Study in the Mouse. Unpublished, designated ABS2012-11492 in BfR RAR, 2009.
•Atkinson et al. 1993. 104-week dietary cariciongencity study in mice.

Epidemiologische Studien zum Zusammenhang zwischen der Entstehung von Non-Hodgkin-Lymphomen und Glyphosat

Epidemiologische Studien weisen auf einen Zusammenhang von der Entstehung von Non-Hodgkin-Lymphomen und Glyphosat hin. Eine Zusammenfassung von 11 epidemiologischen Studien durch den Epidemiologen Prof. Dr. med. Eberhard Greiser ergibt, dass von den Personen, die eine vorhergegangene Exposition mit Glyphosat aufweisen und an Non-Hodgkin-Lymphomen erkrankt sind, 28,5% infolge der Glyphosat-Exposition erkrankt sind.

Die Ergebnisse der Studien wurden vom BfR im Renewal Assessment Report und in der EFSA Conclusion nicht berücksichtigt, da sie aufgrund von fälschlicherweise als fehlend erachteter Daten und Informationen als Nicht Zuverlässig verworfen wurden.
Sämtliche Epidemiologischen Studien die einen Zusammenhang zwischen der Entstehung von Non-Hodgkin-Lymphomen und Glyphosat nahelegen, sind im

Renewal Assessment Report des BfR und im EFSA Report bis auf eine Ausnahme als nicht zuverlässig (Klimisch-Code 3 = „not reliable") beurteilt worden. Die Begründungen für diese Beurteilung sind nicht haltbar, da das BfR nicht wie erforderlich epidemiologische Bewertungskriterien angewendet hat, sondern eine für Tierexperimente vorgeschlagene Methodik. Außerdem wurden Studien verworfen, weil wichtige Daten angeblich nicht erhoben wurden. Bei einer Überprüfung der Studien stellte sich heraus, dass alle vom BfR als fehlend monierten Informationen tatsächlich nach dem Stand der Wissenschaft vollständig erhoben worden waren. Vier relevante Studien sind im Renewal Assessment Report überhaupt nicht mit einbezogen worden.
Sämtliche dieser Studien müssen bei der Beurteilung durch die ECHA berücksichtigt werden.

Fälschlicherweise als nicht zuverlässig beurteilte Studien
•Hardell L, Eriksson M, Nordström M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: Pooled analysis of two Swedish case-control studies. Leukemia Lymphoma 2002; 43:1043-1049.
•Hardell L, Eriksson M. A case-control study of Non-Hodgkin Lymphoma and Exposure to Pesticides. Cancer 1999; 85:1353-1360.
•Nordström M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A.Occupational exposures, animal exposure and smoking as risk factors for hairy cell Leukaemia evaluated in a case-control study. Brit J Cancer 1998: 77:2048-2052.
•De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 2003; 60:e11.
•Zahm SH, Weisenburger DD, Babbitt PA et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorphenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990; 1:349-356.
•Hoar SK, Blair A, Holmes FF et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA1986; 256:1141-1147.
•Cantor KP, Blair A, Everett G et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in IIowa dna Minnesota. Cancer Res 1992; 52:2447-2455.
•Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer 2008; 123:1657-1663.
•De Roos AJ, Blair A, Rusiecki JA et al. Cancer incidence among glyphosate -exposed pesticide applicators in the Agricutural Health Study. Environ Health Perspect 2005; 113:49-54.

Nicht berücksichtigte Studien

•Brown LM, Burmeister LF, Everett GD et al. Pesticide exposure and multiple myeloma in Iowa men. Cancer Causes Control 1993; 4:153-156.
•Cantor KP, Blair A, Everett G et al. 1992; Cancer Res 1992; 52:2447-2455.
•Cocco P, Satta G, Dubois S et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med 2013; 70:91-98.
•Orsi L, Delabre L, Monnereau A et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009; 66:291-298

Dossier Submitter's Response
Thank you for your extensive comments and we refer you to the CLH dossier. The DS is still convinced that glyphosate should not be classified for carcinogenicity. It should be emphasised that the four epidemiological studies which have been claimed in the comment to be absent from the evaluation, have been taken into account both by the DS and by IARC (see Table 44 of the CLH dossier).
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	193
Comment received				
see above				
Dossier Submitter's Response				
No response possible.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France	ANSES, National Autority	BehalfOfAnOrganisation	194
Comment received				
The 9th of February, 2016, Anses issued an opinion available at : https://www.anses.fr/en/system/files/SUBCHIM2015sa0093EN.pdf				
Dossier Submitter's Response				
In its "Opinion on the glyphosate request No 2015.SA-0093" (09/02/2016), ANSES has expressed its view on the IARC monograph regarding carcinogenicity of glyphosate. In addition, the contradictory views of BfR/EFSA and IARC are described and partly explained by differences in the databases and in the different approaches for risk assessment in the EFSA conclusion and the hazard assessment of IARC. The French agency concluded that classification Carc. 1B was certainly not appropriate whereas no clear opinion on category 2 was expressed. On balance, evidence of carcinogenicity was regarded as "relatively limited". ANSES proposed a "rapid review" by ECHA, i.e., the process that is just going on. In addition, ANSES supported the proposal of the DS to address the genotoxicity of formulations. Regarding carcinogenicity of glyphosate, no new arguments have been put forward, thus a change in the classification and labelling is unnecessary.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	195

Comment received
IARC found glyphosate to fit in class 2B "probably causing cancer" in a study. Testing with laboratory animals linked the substance to cancer and tumors.
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. A more comprehensive answer is submitted in the response on comments number 4 and 21.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	196
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2016	Switzerland		Individual	197
Comment received				
Human Evidence On page 93 of the Report, the human evidence regarding glyphosate carcinogenicity is summarized as follows: "Epidemiological studies revealed partly contradictory results. However, in most studies, no association with an exposure to glyphosate could be established. In particular, the largest study, i.e., the AHS (see above), was negative. Taken together, the epidemiological data does not provide convincing evidence that glyphosate exposure in humans might be related to any cancer type. Epidemiological studies are of limited value for detecting the carcinogenic potential of an active substance in plant protection products since humans are never exposed to a single compound alone. Thus, the results of the studies are associated to different formulations containing glyphosate or				

mixtures of different active substances."

The first sentence claims the results are contradictory. This is only true if classify each study is classified as significant or non-significant. Examining the numerical findings presents a different picture. Table 1 lists the 8 studies (of sufficient quality to be utilized) that evaluated the relationship between non-Hodgkin lymphoma (NHL) and exposure to glyphosate. Simply looking to see if the studies tend to have a relative risk above or below 1 shows the studies to be consistently positive across the board with the exception of the AHS exposure-response analysis (that had problems with classifying the exposure) and the Orsi et al study (that had a relative risk of exactly 1). This is quite clearly illustrated using the tree plot in Figure 1.

The sentence 'Taken together, the epidemiological data does not provide convincing evidence that glyphosate exposure in humans might be related to any cancer type.' is difficult to accept given that the three meta-analyses, all including the AHS study, show a statistically significant association between use of glyphosate pesticides and NHL in humans (Table 2). Finally, the statement that "the results of the studies are associated to different formulations containing glyphosate or mixtures of different active substances." is not supported by actual data so this is speculation and not fact.

In "Guidance on the application of the CLP criteria – Version 4.1", Annex I: 3.6.2.2.3 states that "The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC) and read as follows: ... limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence." The meta-analyses indicate that a positive association has been observed so the only reason you would have for not classifying the human evidence as limited is that you believe the causal relationship is not credible or that the bias and/or confounding is so bad as to make these studies worthless. This is clearly not the case. It is likely that the decision is being skewed by placing too much emphasis on the AHS study; the meta-analysis is designed to avoid this problem.

Finally, this paragraph also implies that human epidemiology data will never be of importance in evaluating a pesticide because the pure compound is not used on humans. Such a statement is not scientifically sound and fails to use the science to address the safety of the public.

Mouse Carcinogenicity Data

Also on page 93 of the Report, the data on the carcinogenicity of glyphosate in mice is summarized.

"In the mouse, the incidences in malignant lymphoma, in renal tumours and haemangiosarcoma in male animals were considered in detail. Slightly higher incidences when compared with concurrent controls were confined to very high dose levels above the OECD-recommended limit dose of 1000 mg/kg bw/day and exceeding the MTD. In addition, the outcome of statistical tests was

contradictory. Mostly, but not always, trend tests revealed statistical significance but pairwise comparisons failed to detect a significant difference relative to the control group. The reported incidences of all three tumour types fell within their historical control range which were, however, of variable reliability. If the four studies in CD-1 mice are considered together, it becomes apparent that all tumours were observed also in the control groups and in some groups receiving lower doses in at least one concurrent study. Furthermore, the results were not consistent with regard to dose responses. To conclude, there is not enough evidence to consider the tumours in mice as treatment-related."

It is unusual to have four studies in the same species and strain for an evaluation. It is possible to make direct comparisons between the studies and even pool the data for a combined analysis. Table 3 quickly summarizes the findings from the four studies in CD-1 mice and the one study in Swiss mice. One thing that stands out in Table 3 is that the studies were conducted for either 18 months or 24 months. This is a critical difference that does not get much discussion in the Report.

Cancer increases in risk generally as a power of length of exposure (Portier, Hedges and Hoel, 1986). This relationship was used to develop a means to adjust the length of time an animal is on a study, enabling a scientist to determine risk at the end of two-years, the typical time used for animal bioassays (Bailer and Portier (1988) and Portier and Bailer (1988)). This is called the Poly-3 adjustment. The US National Toxicology Program uses the Poly-3 test to evaluate significance in their animal bioassays. Now you will note that three of the mouse studies were only conducted for 18 months. (Comparing 18 month studies with 24 month studies without making an adjustment for the differences in length of exposure is like comparing cancer rates in 40 year-olds exposed for 25 years to cancer rates in 65 year-olds exposed for 50 years and concluding they are not consistent with each other; the conclusion is meaningless because the correct evaluation was not done.) Thus, in order to compare all 5 studies, we must use the Poly-3 adjustment to extrapolate the 18 month studies to estimate what we think the cancer risk would have looked like at 24 months. The adjustment decreases the number of animals without tumors in all groups by (18/24)3.. The p-values for both the unadjusted trend test and the poly-3 adjusted trend test are given in Table 4 for male mouse renal tumors.

As an example of how the Poly-3 adjustments work, consider a comparison of the high-dose renal tumor response in the 1983 study (3/50=6%) to the high-dose response in the 1997 study (2/50=4%). In the 1997 study, 48 animals had no tumors at 18 months; the poly-3 adjustment reduces this to 20.25 leading to an incidence estimate of 2/22.25=9%. Because the Poly3 test effectively reduces the number of animals on study, even though the incidence estimate goes up, the p-value for the trend test could go down. Numerous evaluations of the validity of the poly-3 adjustment have been published in the peer-reviewed literature and it seems to work very well.

Now that the lengths of the studies have been adjusted, the next question to ask is whether this dose-response is consistent across all of the studies or whether there are anomalies. Combining all of the studies into one pooled

analysis (Table 5, Line 1) and performing a trend analysis on the pooled data yields highly significant findings (Table 5, Line 1). Excluding the Swiss Albino mouse study (2001) and only using the CD-1 mice also yields a significant trend (Table 5, Line 3). Repeating these analyses with the Poly-3 adjusted data does not alter the significant findings. Poly-3 adjusted dose-response for renal tumors in the entire set of mouse studies is shown in Figure 2. Here, each dose-response point from each study is plotted along with the 95% confidence bound around the response. It is somewhat hard to see that there is a pattern here that is consistent. To make it easier to see, I pooled all the controls into one group, pooled the animals given doses between 0<dose≤300 in a second group, and similarly for animals given doses between 300<dose≤1500 and dose>1500. These results are plotted against the mean dose in each set of pooled doses in Figure 3 (the horizontal blue lines show the range of the doses that were combined). The trend in the data is more evident in Figure 3 than in Figure 2. The pooled data sets were also analyzed by the unadjusted and poly-3 adjusted trend tests and shown to be significant (Table 5, Lines 2 and 4). Finally, as noted in the Report, it seems that all of the response is in doses above 1000 mg/kg/day. After removing all doses above 1000 mg/kg/day and repeating all of the analyses, the results of the analysis are shown in Table 5, Lines 5-8. Without the doses above 1000 mg/kg/day, the effect disappears.

Tables 6 and 7 repeat these analyses for malignant lymphomas and Figures 4, 5, and 6 show the resulting plots of the data. In Figure 4, it is easily seen that the Swiss mice had a very different background tumor rate compared to the CD-1 mice so for the remaining two Figures (5 and 6), only CD-1 mice are plotted. Because of the different backgrounds between the Swiss mice and the CD-1 mice, when they are all combined, the joint analysis is not significant (Table 7, lines 1 and 2). Removing the Swiss mouse study and only evaluating the CD-1 mice leads to highly significant trends in all analyses (Table 7, lines 3-8). A significant trend remains even after removing the doses>1000 (Table 7, lines 5-8) suggesting this is not a high-dose only effect. This is very clear when you examine Figure 7.

Tables 8 and 9 repeat these analyses for hemangiosarcomas and Figures 7 and 8 show the resulting plots of the data. The findings in the Swiss mouse were unclear in the reporting so these tables only contain analyses of the CD-1 mouse data. All analyses are highly significant (Table 9) and they remain significant if doses>1000 are excluded (Table 9, lines 3 and 4). So again, this is not a high dose-only effect.

With these analyses, certain things are clear. The statement "If the four studies in CD-1 mice are considered together, it becomes apparent that all tumours were observed also in the control groups and in some groups receiving lower doses in at least one concurrent study." is highly misleading. Combining all four studies in CD-1 mice leads to very strong statistical significance in the data. Also, "Furthermore, the results were not consistent with regard to dose responses." is also incorrect and not actually supported by the data. Finally, the statement "Slightly higher incidences when compared with concurrent controls were confined to very high dose levels above the OECD-recommended limit dose of 1000 mg/kg bw/day and exceeding the MTD." while partially correct is also very misleading. When doses above 1000

mg/kg/day are excluded, the pooled data from the four CD-1 mouse studies remain significant for both the malignant lymphomas and the hemangiosarcomas. Also, the OECD-recommended limit is not the MTD (maximum tolerated dose) and showing exceedance of an MTD requires more information than simply that the dose was large.

Given a careful, objective evaluation of these data, I strongly suggest you change your conclusion from the mouse studies from "To conclude, there is not enough evidence to consider the tumours in mice as treatment-related." to "To conclude, there is enough evidence to consider the tumours in mice as treatment-related."

Finally, a few comments on the reviews of the individual studies starting on page 67 of the Report.

Page 68 - "Obviously, the carcinogenicity study in Swiss albino mice by Kumar (2001, ASB2012-11491) revealed an increase in malignant lymphoma incidence over the control at the top dose level of around 1460 mg/kg bw/day in both sexes but the background (control) incidence was also quite high. In fact, at least in males, the number of affected animals in the control groups was markedly higher in this strain than in three studies in CD-1 mice. It must be emphasised that this tumour is quite common in ageing mice and that Swiss mice are frequently affected (for details, see below). In this study, malignant lymphoma accounted for 54.6% of the total number of tumours when all groups are considered together." Without actually using historical controls, an attempt is made here to downplay the significance of this finding by saying the concurrent control was high. And then it is not clear at all why the 54.6% figure is put into this paragraph. Is this study positive? Yes. Are there flaws in this study? No. Why does this Report then downplay this finding? Especially when you see similar findings in the other studies?

Page 68 -"In the most recent study in CD-1 mice by Wood et al. (2009, ASB2012-11490), there was a higher incidence of the same tumour type in high dose males (5/51 vs. 0/51 in the control group). Likewise, in the study by Sugimoto (1997, ASB2012-11493), there were a higher number of male mice affected at the exaggerated dose level of 40000 ppm (approx. 4350 mg/kg bw/day) than in the control group (6/50 vs. 2/50). In the study by Atkinson et al. (1993, TOX9552382), in contrast, there was no dose response and the incidence in the control group was similar to that at the top dose level." Regardless, this entire paragraph is attempting to compare control animals ranging over 16 years with differing terminal sacrifice times and from different laboratories. Such a comparison is inappropriate because of the known drift in strains over time and increasing tumor risk with age. The OECD guidelines make this very clear.

Page 69 – "The trend test also provided a p-value above the significance level of 0.05, most probably because of the high control incidence (see Table 33)." The p-value for trend is 0.0535122, technically above 0.05, but it is misleading when trying to compare across studies not to mention that this is almost significant.

Page 69 - "In contrast, re-analysis of the studies by Wood et al. (2009,

ASB2012-11490) and Sugimoto (1997, ASB2012-11493) showed statistically significant increases with dose for male CD-1 mice in the trend test (Table 34 and Table 35) but a rather low or even "zero" incidence in the control groups might be behind this finding." Where are the historical controls to support the speculation in the last part of this sentence? And of course the formal statistical analysis to go with it. Finally, as noted in the Report, OECD guidelines, IARC guidelines, NTP guidelines and others, the concurrent control is the best to use for evaluating a study.

Page 69 – "This result was confirmed by the chi-square test. Also for this comparison, the very low control incidence (0/51) should be taken into consideration." Again, where are the historical controls to support this statement?

Page 71 – "It may be concluded that the statistical significance of the suspected increase in malignant lymphoma in the various studies depends very much on the statistical method that is used for data analysis." This is usually the case; that is why the OECD guidelines make it clear that if either the trend test or the pairwise comparison is positive, the findings should be considered positive.

Page 71 – "When the trend test is applied, the studies by Wood et al. (2009, ASB2012-11490) and Sugimoto (1997, ASB2012-11493) provide evidence of an effect which was not the case when pairwise comparison was performed. In contrast, the increase in the study of Kumar (2001, ASB2012-11491) was not confirmed neither by the trend test nor by a different pairwise test than the Z-test that had been used first." From my Table 6, there are two significantly positive studies, two studies with a marginal p-value and one study that would be positive if not for the highest dose dropping down. As noted in the Report, there was a drop in weight gain in the 1993 which could explain the drop in tumors at the highest exposure group (animals with reduced caloric intake are less likely to get tumors).

Page 71 – "In the studies by Wood et al. (2009, ASB2012-11490) and by Atkinson et al. (1993, TOX9552382) in CD-1 mice, comparable top doses of 810 or 1000 mg/kg bw/day were administered and a similar incidence of malignant lymphoma was noted in high dose males (5/51 or 6/50, respectively). However, the control group incidences were clearly different (0/51 vs. 4/50) resulting in a positive trend test in the study by Wood et al. (2009, ASB2012-11490) only." The 1993 study was 24 months whereas the 2009 study was 18 months; it is not surprising the control tumor counts are higher in the 1993 study. What is surprising (and statistically significant) are the 6 tumors at the high dose in the 2009 study after only 18 months. And of course, this is another inappropriate comparison of control incidence over a 16 year timeframe. And finally, none of this is statistically significant.

Page 71 – "Thus, if all four studies in CD-1 mice are taken together, there is no consistent dose response." See my formal analysis of this question.

Page 71 – "Nonetheless, it seems well in line with information that was found in the literature providing confirmation that Swiss mice are prone to developing lymphoreticular tumours. According to older articles, control

incidences in male mice of Swiss or Swiss-derived strains may reach 18–27.5% and exceed 36% in females (Sher, 1974, Z22020; Roe and Tucker, 1974, ASB2015-2534; Tucker, 1979, Z83266). In a more recent publication, Tadesse-Heath et al. (2000, ASB2015-2535) even mentioned a nearly 50% lymphoma (mostly of B cell origin) incidence in a colony of CFW Swiss mice but also emphasised the contribution of widespread infections with murine oncogenic viruses to the high but remarkably variable incidence of tumours of the lymphoreticular system in this species." Why are there guidelines if they are not used? Again, an argument is being made about historical controls using data which does not match OECD guidance (even bringing in Swiss-derived strains). And, if there are had historical control values from the lab, giving all five numbers and some description of the studies (18 months or 24 months?) would seem to be in order.

Page 72 – "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." The entire discussion about infections is, at best, absurd if there is no evidence. Inclusion of this text is simply an attempt to discredit the study.

Page 72 – "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%." 12 studies with a mean of 6.33% and a range of 3.85 to 19.23 is an extremely skewed population. One study had 3.85% and one had 19.23 %; 12 x 6.33%=75.96 so the remaining 10 studies, in order to get an average of 6.33% would need to add up to 52.54 or 5.25% per study on average. Just from the math, it appears the 19.23% control is an outlier. Regardless, for sake of transparency, the actual rates should be given and assurances be given that they are all from studies of 18 months and not 24 months. And finally, a formal statistical analysis against the historical controls should be conducted. To illustrate; if the historical background is 6.33% and is based upon 50 animals in each control group and the controls are binomially distributed, then the probability of randomly seeing an outcome with a trend statistic equal to or larger than the one observed in this study is p=0.02. MATLAB code is provided that makes this calculation.

Page 72 – "Unfortunately, for the study of Wood et al. (2009, ASB2012-11492), the submitted historical control data was not particularly useful for the assessment." Stop with this statement; everything else written is an inappropriate use of historical control data and should be ignored.

Page 73 – "On balance, based on uncertainties with regard to partly contradictory study outcomes depending on the statistical method applied, inconsistent dose response in the individual studies, and a highly variable tumour incidence as suggested by historical control data, it is not likely that glyphosate has induced malignant lymphoma in mice. A possible role of oncogenic viruses should not be ignored. Moreover, human relevance of such an effect, if occurring only as a high-dose phenomenon as it was the case here, is considered equivocal." On balance, this entire paragraph is a wrong. The study outcomes are not contradictory (follow OECD guidance and it is

simple), does response is not inconsistent (see my analysis), tumor incidence is not highly variable when properly adjusted for time on study differences and the entire historical control discussion is either inappropriate or inadequately applied.

Page 74 -"Even though no historical control data from the performing laboratories was provided, a simple comparison of the control groups in the individual studies with glyphosate suggests that renal tumours may occur in untreated control males at a similar incidence than in the groups receiving very high doses." This is a misleading comment. First, no formal analysis of historical control data has been undertaken and, as we stated in our paper (Portier et al., 2016), your own guidelines provide guidance on how to obtain and use historical control data; this has not been done here. I am also surprised to see the statement that "no historical control data from the performing laboratories was provided" when in response to a letter sent to Commissioner Andriukaitis, the EFSA Executive Director, Professor Url, wrote "The Peer Review Report (EFSA, 2015b) confirms that EFSA conducted a specific check regarding the use of historical control data, requested additional information during the clock-stop procedure and only considered valid the historical control data from the performing laboratory in line with the international recommendations". Which is it? Does the Report rely on valid historical control data from the performing laboratories or not?

Page 75 - "Even if not fully comparable because of the strain differences, it should be remembered that the top dose incidence of 2/50 in this study was the same as seen in CD-1 mice in the study by Atkinson et al. (1993, TOX9552382) in the control and low dose groups." Why even include this sentence? They are not comparable.

Page 76 – "Even though there was no clear dose response, it may be assumed that glyphosate (acid) when administered at high doses might produce mucosal irritation." So, if I am reading this right, statistically significant positive cancer results are being dismissed based on non-statistically significant non-cancer results that have a questionable linkage to the cancer results. Does this seem reasonable? I guess not since this appears in the next papagraph "However, it is questionable if irritation would sufficiently explain tumour formation in the kidney.".

Page 76 – "The top dose finding of 2/50 in the study by Sugimoto (1997, ASB2012-11493) is at the upper edge of adenoma frequency. In the study by Knezevich and Hogan (1983, TOX9552381) which is not actually covered by the timeframe of the historical database, the adenoma incidence (2%) at the top dose level would be inside the historical range whereas a carcinoma incidence of 4% was above." Again, an improper use of historical controls. These are not appropriate for the 1983 study but are used anyway. For the 1997 study, only controls in mice sacrificed at 18 months should be used, mice sacrificed at 24 months will likely have greater incidence. This is quite evident when one looks at hemangiosarcomas in male mice in the Giknis and Clifford report (attached). Exactly half of the studies went 18 months, 24 went 2 years and the remaining two went 97 and 100 weeks. Hence this historical control dataset is inappropriate for this comparison. However, even if it were, the findings would still be significant. The paper gives a mean background

level for adenomas of 0.24% and for adenocarcinoma of 0.14% for a combined background of 0.38%. The probability of seeing a dose-response trend equal to or larger than what was seen in the 1997 study is 0.01, a significant finding. The p-value for the 1983 study would be even smaller.

Page 77 – "Even the incidences of affected animals at exaggerated doses exceeding the OECD-recommended limit of 1000 mg/kg bw/day and also the MTD were not statistically significantly increased when compared with the concurrent controls." As mentioned earlier in this document, if either test is positive, the findings should be considered positive so the second half of this sentence is inappropriate. How did "there is some evidence that the MTD was exceeded in both studies at the highest dose level" (Page 76) become absolute certainty about exceeding the MTD?

Page 77 – "Even the incidences at exaggerated doses are covered by the historical control range." As noted earlier, this finding is not supported.

Page 77 – "No pre-neoplastic kidney lesions have been observed in treated animals." Following this logic, the high dose animals got tumors by some unknown mechanism related to exceeding the MTD and that unknown mechanism did not damage the kidneys in any other animals enough to show preneoplastic effects. What is this mechanism and where is the evidence suggesting such a mechanism exists? And how does this statement "However, it is questionable if irritation would sufficiently explain tumour formation in the kidney." fit in to this theory?

Page 77 – "There is no plausible mechanism" Following the logic again, some unknown mechanism related to exceeding the MTD caused the tumors at the highest doses and because there is no mechanism, the results should be dismissed.

Page 78 – "According to Atkinson et al. (1993, TOX9552382), the historical control incidence in the performing laboratory ranged from 0/50 to 4/50 and, thus, would cover the incidence at the top dose level." Inadequate documentation of the historical control data makes it impossible to address this statement. The actual counts and ages at terminal sacrifice for the historical controls should be provided. As shown earlier, range is an inappropriate way to utilize historical controls. This is a clear example of a lack of transparency.

Page 78 – "Historical control data provided by Charles River indicate a very variable incidence of haemangiosarcoma. On different sites of the body, tumours of this type were seen in untreated control animals in 8 of 52 studies." In this case, Giknis and Clifford give the actual values for each of their control groups. For hemangiosarcomas, there were zero tumors in all 26 studies terminated at 18 months, and only 8 of the remaining 26 studies that went two years had hemangiosarcomas. Thus, the 18 month 1997 study is well outside the range of the historical controls.

Page 78 – "Furthermore, since Sugimoto (1997, ASB2012-11493) employed a more than four times higher top dose than Atkinson et al. (1993, TOX9552382), a markedly higher haemangiosarcoma incidence would have been expected if this tumour was in fact treatment-related." Again, this is a

comparison of an 18 month study to a 24 month study. The finding that the 24 month 1993 study has an 8% response at a dose of 1000 mg/kg/day while the 18 month 1997 study has a 4% response at a 4-fold higher dose is not unexpected.

ECHA note - The following attachment was submitted with the comment above: *SendToEcha.zip*

Dossier Submitter's Response

Thank you for your comments which will be considered in the final discussion of the CLH dossier.

Epidemiological studies

You commented that in the CLH proposal it was summarized: "Epidemiological studies revealed partly contradictory results. However, in most studies, no association with an exposure to glyphosate could be established." These sentences did not only summarize that there were no plausible associations demonstrated in the available studies between glyphosate and NHL but also that there was no association with all other types of cancers. In summary, the vast majority of all human studies demonstrated that there was no association between glyphosate and different types of human cancer.

In your comment number 197 you mentioned "the statement that the results of the studies are associated to different formulations containing glyphosate or mixtures of different active substances" is not supported by actual data so this is speculation and not fact. However, it is not possible to evaluate the effect of a single active substance such as glyphosate in epidemiological studies . In all of these studies there are additional confounding factors such as co-formlants as well as other pesticides. Therefore, it is of great importance to consider all these possible confounding factors very carefully.

The epidemiological evaluation by IARC is primarly based on results from 6 studies. Although one of these studies was a prospective cohort study, it was not ranked higher. One study was included in the meta-analysis even though its definition of NHL differs from the other studies. Even in the article, it was pointed out that further studies are needed.

A current review on carcinogenicity was submitted by the Environmental Protection Authority of New Zealand in August 2016. In this paper the evaluation of glyphosate by IARC is discussed and it is concluded that "the epidemiological support for the conclusion "limited evidence" in humans is not convincing. Furthermore, the NZ EPA concludes "glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification under HSNO as a carcinogen or mutagen". Concerning the epidemiological studies the authors concluded that depending on the statistical tests used in the three key studies only two studies show OR values indicating statistical significance at the 95% level. However, in the study by de Roos et al. (2003), this was only true using logistic regression, while in the study by Eriksson et al. (2008) only the univariate analysis showed statistical significance. Concerning the study by Eriksson et al. (2008) the review of the NZ EPA underlines that the highest OR was reported for an association between exposure to MCPA and NHL. When considering the latency period, >10 years exposure to glyphosate had an OR of 2.26 (95% Cl 1.16-4.4) in comparison to <10 years with an OR of 1.11 (95% Cl 0.24-5.08). It is concluded that the findings may be confounded by

exposure to MCPA or other phenoxy herbicides. There could be residual confounding from MCPA exposure if the participants under-reported earlier MCPA exposure.
The data of the AHS cohort study by DeRoos et al. (2005) showed no statistically significant difference for the trend to increased exposure with exposure bands at 0-20, 21-56 and 57-2,678 cumulative days of exposure, despite the higher exposure levels in comparison to the case-control studies. Furthermore, in the NZ EPA review it is considered to be particularly important to note that the lack of significant finding in a large cohort study (the AHS) where the potential for recall bias is greatly reduced and should therefore be given greater weight than the case control studies.

Mouse carcinogenicity data
You stated that in order to compare all 5 mouse carcinogenicity studies, we must use Poly-3 adjustment to extrapolate the 18 months studies to estimate the cancer incidence at 24 months.
In our view, only the data from the 4 studies in CD-1 mice should be looked at in a direct comparison, since their genetic background may be assumed to be similar. The study using Swiss Albino mice should be looked at separately. Since all mouse carcinogenicity studies were conducted before 2009, the OECD test guideline 451 (adopted: 12 May 1981) has to be considered which states that "generally, the termination of the study should be at 18 months for mice". Thus, adjustment for tumor response at 18 months would be more appropriate.

Regarding renal tumors, your analysis of the Poly-3 adjusted dose-response confirmed that the significant trend disappeared without the doses above 1000 mg/kg/day, which induced substantial toxicity incompatible with internationally accepted test guidelines.
Thus, there was no convincing association between exposure to glyphosate and kidney tumour induction in male mice at dose levels not exceeding the maximum tolerated dose, since the maximum tumour incidence in animals treated up to a dose level of 4348 mg/kg bw per day did not exceed the maximum tumour incidence which was observed in concurrent control group animals (2/50, i.e. 4%). For the slightly higher tumour incidence of 3/50 (6%) at the maximum dose level of 4841 mg/kg bw per day in one of the four studies in CD-1 mice, it cannot be excluded that this was an artefact of excessively high doses. Nevertheless, even at this excessive dose, the maximum kidney tumour incidence as found in a relevant historical control database (i.e., 6%) was not exceeded.

Regarding malignant lymphoma, there was no convincing association between exposure to glyphosate and malignant lymphoma induction in CD-1 mice, even at dose levels clearly exceeding the maximum tolerated dose (4841 mg/kg bw per day). In none of the four studies in CD-1 mice, the pairwise comparisons of control group and the treated groups revealed statistically significant differences. Furthermore, if the four studies in CD-1 mice are considered in combination, there is no evidence for a dose-response. All the group incidences were within reliable HCD ranges.

Regarding haemangiosarcoma, there was no statistically significant increase in haemangiosarcoma in any study when pairwise comparisons were applied. The

positive trend for this tumour in male CD-1 mice in two studies was due to the zero incidences for this tumour type in the control groups. Moreover, the highest incidence (4/50) was observed at 1000 mg/kg bw/day but in two studies including much higher dose levels of 4348 or 4841 mg/kg bw/day, the respective numbers of affected animals were 2 or even 0. However, one would expect a further increase in haemangiosarcoma incidence for a treatment-related effect. Also, the incidences were covered by the HCD ranges and there was no dose response when the four studies in CD-1 mice are taken into account.
A more comprehensive answer is submitted also in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.

RAC's response

Noted. See response to comment no. 11. For further details on the evaluation of the data for carcinogenicity, please see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Health and Environment Alliance	BehalfOfAnOrganisation	198

Comment received

16 July 2016

EU Classification of Glyphosate: meeting the criteria for Carcinogen Cat 1B
HEAL submission to ECHA public consultation on glyphosate

HEAL submits that the evidence on glyphosate qualify as
1. limited evidence of carcinogenicity for humans
and
2. sufficient evidence of carcinogenicity for animals
complemented by
3. mechanistic evidence for genotoxicity and oxidative stress
which together more than fulfil the minimum requirements for glyphosate to be classified as a Carcinogen Category 1B as per the criteria of the EU CLP regulation (EU 1272/2008).

In the EU CLP regulation, a substance is classified as Carcinogen category 1B when
• animal data show sufficient evidence to demonstrate carcinogenicity in animals
or
• there is limited evidence of carcinogenicity in humans plus limited evidence of carcinogenicity in animal studies.

The CLP Regulation specifies that when further factors are taken into consideration to either increase or decrease the level of concern for human

carcinogenicity, more complete information should be presented to decrease rather than increase the level of concern (CLP Annex I: 3.6.2.2.5.).

1. Limited evidence of carcinogenicity in humans.
The CLP regulation defines this as: a positive association observed between exposure to the agent and cancer where a causal interpretation is considered credible, but chance, bias or confounding could not be ruled out with reasonable confidence (CLP Annex I: 3.6.2.2.3).
The 3 meta-analyses demonstrate a positive significant association between glyphosate and Non Hodgkins Lymphoma. The issue of smoking as a confounder in these studies has been raised (in the EFSA opinion), but we think that the confounding is insufficient to de-credibilise the causal interpretation of the association for the following reasons:
First, the qualification of the evidence as LIMITED would allow for some potential confounding.
Moreover, because smoking is not associated with Non Hodgkins Lymphoma, smoking cannot be treated as a neglected confounder in the case control studies.
Also, no evidence has been given to suggest that higher exposure to glyphosate is associated with increased frequency of smoking, meaning that smoking cannot be regarded as a confounder on this basis.

2. Sufficient evidence of carcinogenicity in animals.
The CLP regulation defines this as a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. (CLP Annex I: 3.6.2.2.3)
We think the following evidence cannot be regarded as failing to meet the above definition:
• positive trends in renal tumors observed for 3 of 5 mouse studies
• positive trends for hemangiosarcomas in 2 of the 5 mouse studies
• significant increase of malignant lymphoma in 3 of the 5 mouse studies (confirming the reproducibility of this finding from studies performed in different laboratories and at different times).

The finding of an increased incidence of malignant lymphoma is further supported by the results of epidemiological studies indicating an association between glyphosate exposure and Non-Hodgkin lymphoma (see submission by Dr Peter Clausing, Attachment 2) and by mechanistic evidence, in particular genotoxicity and oxidative stress (submission by Dr Peter Clausing, Attachment 3).

The data also show a significant increase in the incidence of pancreatic islet cell adenomas in two studies in male Sprague-Dawley rats. In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased.

The data and arguments from the Dossier Submitter to disqualify the findings of the mouse carcinogenicity studies are incorrect or invalid (see Portier et al 2016; and submission by Dr Peter Clausing, Attachment 1).

The argument given by EFSA of high-dose toxicity to qualify the above findings is not verified or supported by the data presented. There is no increased incidence of kidney or bone marrow damage in the data. No data nor any statistical analysis of the historical controls is given that supports the EFSA argument that these data are in the range of the historical controls. The OECD guidelines clearly state that positive findings against the concurrent control should be viewed as positive. The OECD guidelines counter the argument that the trend test is inappropriate.

The Dossier Submitter missed stating that the incidences (of malignant lymphoma) reported in the Atkinson study were limited to the "histological examination of lymph nodes with macroscopic changes", which renders the data inappropriate to use as non significant and counter to the findings of a significantly increased incidence in malignant lymphoma.

1. + 2. Strength of Evidence
Taken together, points 1 and 2 above are above the minimum criteria necessary to assign a classification of Carcinogen 1B, because the evidence of carcinogenicity for animals is stronger than limited but actually sufficient (the minimum being limited evidence of carcinogenicity in humans plus limited evidence of carcinogenicity in animal studies).
3. Mechanistic evidence for genotoxicity and oxidative stress.
There is additional evidence on genotoxicity, mutagenicity and oxidative stress. See IARC Monograph and submission by Dr Peter Clausing, Attachment 3. Although HEAL believes the evidence in 1 & 2 is sufficient for a classification of C1B, the additional considerations of 3 should not be neglected, in order to ensure that the totality of evidence is weighed in an interrelated fashion.

Conclusion:
HEAL therefore submits that the Risk Assessment Committee, if it wishes to conclude that the classification and category of carcinogenicity 1B is not correct, would have to robustly elaborate
• why the totality of the evidence does NOT fulfil the minimum criteria for classification of C1B
• how and why the documentation of factors which the Rapporteur Member State has identified as decreasing the concern is NOT insufficient.
In the EU, the human biomonitoring data to date shows nearly ubiquitous exposure, and of particular concern, that the exposure between those who eat organically farmed food hardly differs from those who eat conventionally grown food, meaning that those who wish and choose to exercise a higher level of caution regarding their dietary exposure are not succeeding. The proper classification of glyphosate is therefore extremely important, to ensure that the measures to protect human health and the environment from carcinogens in the EU regulation of pesticides can work. We look to the Risk Assessment committee to provide the highest quality review and judgement of the

evidence.

References:

IARC Monograph 112
Portier, C. Armstrong, B.K., Baguley, B.C. et al. (2016): Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). J. Epidemiol. Community Health, doi:10.1136/jech-2015-207005.

Comments submitted under this consultation by [redacted]

[redacted]

Dossier Submitter's Response

The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.

RAC's response

Noted. See response to comment no 11 and 228.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	199

Comment received

Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als "wahrscheinlich krebserregend beim Menschen" (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf
Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als "vermutlich karzinogen, Kategorie 1B" einstufen. Zur Begr"ndung:
Gem"" der EU-Verordnung Verordnung 1272/2008 "ber die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenit"t bei "zwei oder mehreren unabh"ngigen Studien an einer Spezies" aus, um eine Substanz als "vermutlich karzinogen beim Menschen" einzustufen.
Im Fall von Glyphosat ist ein dosisabh"ngiger Anstieg von Krebstumoren bei M"usen in mindestens f"nf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf
Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos f"r Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf

ECHA note - The following attachment was submitted with the comment above: *info.txt*
Dossier Submitter's Response
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Fra mework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	200
Comment received				
e suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	201
Comment received				
Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als „wahrscheinlich krebserregend beim Menschen" (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als „vermutlich karzinogen, Kategorie 1B" einstufen. Zur Begründung: Gemäß der EU-Verordnung Verordnung 1272/2008 über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenität bei „zwei oder mehreren unabhängigen Studien an einer Spezies" aus, um eine Substanz als „vermutlich karzinogen beim Menschen" einzustufen.				

Im Fall von Glyphosat ist ein dosisabhängiger Anstieg von Krebstumoren bei Mäusen in mindestens fünf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos für Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf
Dossier Submitter's Response
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	202
Comment received				
Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als &#65533;wahrscheinlich krebserregend beim Menschen&#65533; (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als &#65533;vermutlich karzinogen, Kategorie 1B&#65533; einstufen. Zur Begr&#65533;ndung: Gem&#65533;&#65533; der EU-Verordnung Verordnung 1272/2008 &#65533;ber die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenit&#65533;t bei &#65533;zwei oder mehreren unabh&#65533;ngigen Studien an einer Spezies&#65533; aus, um eine Substanz als &#65533;vermutlich karzinogen beim Menschen&#65533; einzustufen. Im Fall von Glyphosat ist ein dosisabh&#65533;ngiger Anstieg von Krebstumoren bei M&#65533;usen in mindestens f&#65533;nf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos f&#65533;r Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf				
Dossier Submitter's Response				
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment				

according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	203
Comment received				
Je suis très préoccupé(e) par l'évaluation déficiente des données de carcinogénicité, pointée du doigt par des scientifiques de haut niveau dans une lettre ouverte.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	204
Comment received				
It creates carcinogenity ECHA note - The following attachment was submitted with the comment above: *info.txt*				
Dossier Submitter's Response				
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	205

Comment received
It creates carcinogenity
Dossier Submitter's Response
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	206
Comment received				
Glyphosat erzeugt Krebs				
Dossier Submitter's Response				
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to RAC to decide.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Romania		Individual	207
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action				

for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy	Food and Veterinary Toxicology section - Istituto Superiore di Sanità	BehalfOfAnOrganisation	208
Comment received				
There is no evidence indicating that Glyphosate mught be a directly-acting mutagen. Nevertheless, glyphosate may induce intracellular oxidative stress, thus it may induce oxidative DNA damage. This is suggested by the positive results obtained with assays exploring genomic recombination (Sister Chromatid Exchange assay) and DNA fragmentation (Comet assay): such assays canot be taken, per se, as a proof of genotoxicity, but are associated, also in epidemiological studies, with DNA damage mediated by oxidative stress. Oxidative DNA damage is a indirect, threshold mechanism which, nevetheless, deserves attention since it can be associated with tumour promotion in rapidly proliferating tissues, such as those of the immune system. Under this respect the increased incidence of malignant lymphoma in male mice exposed to Glyphosate may support some concern: - albeit the observed increases in incidence suggest a moderate potency, this effect is consistently observed in four studies and in two strains and different laboratios with different background incidence (Wood et al., 2009, Sugimoto, 1997, Atkinson et al., 1993, all in Cd-1 mice; Kumar, 2001, in Swiss mice). The over 30 year-old old study by Knezevich and Hogan (1983) should not be given undue weight and is superseded by the more up-to-date evidence. - the dose-responses and overall outcomes of the four studies are consistent with a high dose, tissue-specific tumor promotion occurring in cells with high, continuous turnover - Whereas the effect is not observed in rats, there is no evidence supporting that the rat is a better model than the mouse concerning Glyphosate tumorigenicity. Consequently, there are no data indicating to that the increase of malignant lymphomas in male mice is a species-specific effect of no relevance to humans. - In the lack of repeated toxicity studies in mice, the availabl chronic studies consistently support that Glyphosate affects immune cells with a sex-specific susceptibility in the mouse: again, there is currently no evidence that may indicate that this is a species-specific pattern of no human relevance. - The four mouse studies consistently indicate that the increase of malignant lymphomas is a top-dose effect. In two studies (Wood et al., 2009, LOAEL 810 mg/kg bw; Atkinson et al., 1993, LOAEL 1000 mg/kg bw) the increase is observed at dose levels equal or lower than the limit dose of 1000 mg/kg bw recommended by OECD. In the				

Kumar (2001) study, the LOAEL is slightly above the limit dose (1461 mg/kg bw, top dose), but the dose levels are widely spaced: the intermediate dose level (151 mg/kg bw representing the study NOAEL)is 1/10 of the top dose, making it difficult to estimate confidently a ose-response (e.g., a benchmark dose). - the hypothesized relationship of mouse lymphomas with viral infection appears as a mere hypothesis which is not supported by data. - Finally, as keenly pointed out by the CLH Report, human studies are contradictory and inconsistent; moreover, the assessment of exposure is weak, in most cases. Thus, the available human evidence appears to be of no avail either to support or disproof a possible carcinogenic hazard in humans. In general, when supported by consistent data and in the absence of evidence indicating a species-specific effect, a a tumour-promoting effect may be considered for a classification in Category 2, even though is not related to a direct genotoxic mode of action. Having in mind that classification is Hazard-based and that the glyphosate-related increase of malignant lymphomas in male mice can be observed at dose levels equal or below the limit dose of 1000 mg/kg, the case of Glyphosate tumorigenic hazard appears to deserve a detailed evaluation by ECHA. Based on the available evidence, the case should be carefully considered for possible classification in category 2 for carcinogenicity.
Dossier Submitter's Response
In this comment (similar to no. 104, see also our response there) the possible arguments for classification (Cat. 2 for carcinogenicity) are compiled once more. Clearly, they deserve careful consideration. In the CLH dossier and the addendum (including an evaluation according to the OECD framework), the DS has addressed all these concerns but came to the conclusion that classification would not be appropriate. Examination of the data may lead to different views. It is up to ECHA and its RAC to decide. We would like to highlight two points: (1) It was not argued that classification was not needed because a higher incidence of malignant lymphoma was observed only in mice and since this was a species-specific effect. Widespread infection of mouse colonies with oncogenic viruses was only mentioned to explain the extremely variable and sometimes very high background incidences. We have not claimed that any of the mouse studies would have been invalidated due to viral infection for which in fact no further evidence was obtained even though this argument was put forward by U.S. EPA with regard to the study by Kumar (2001). (2) There is currently no evidence to indicate that glyphosate is immunotoxic
RAC's response
Noted. See response to comment no 11 and 228.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	209

Comment received
I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest". I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Finland		MemberState	210
Comment received				
The Finnish CA appreciates a thorough analysis of rather abundant carcinogenicity data on glyphosate in the CLH report. Based on this data and weight of evidence approach, the DS draws a conclusion that no harmonized classification and labelling for carcinogenicity are warranted. Although it is diversely justified by the DS, the Finnish CA has some hesitance on the conclusion based especially on findings in mouse carcinogenicity studies. Based on the epidemiological data, the DS concluded that there is limited evidence of carcinogenicity of glyphosate in humans. The DS also concluded that several guideline compliant combined chronic toxicity/carcinogenicity studies (OECD 453) in rats do not support classification of glyphosate for carcinogenicity. These conclusions are agreed by the Finnish CA. In the CLH report, five mouse carcinogenicity studies (OECD 451) are presented. The data from these studies raises concern on the potential of glyphosate to cause cancer; i.e. malignant lymphoma, renal carcinoma, and haemangiosarcoma in mice. Most concern arises from studies by Kumar (2001) and Wood et al. (2009) suggesting that glyphosate exposure is associated with increased incidence of malignant lymphoma in mice. There are, however, uncertainties regarding the interpretation of the results from these mice studies as noted also by the DS. Uncertainties are related to the statistical				

method applied, inconsistent dose response, the most prominent tumour incidence only at high doses, and in some cases historical control (HC) data suggests a highly variable tumour incidence.

Based on these uncertainties, the DS concluded that it is not likely that glyphosate has induced malignant lymphoma in mice (page 73 in the CLH report). Also possible role of oncogenic viruses was discussed in the CLH report. Moreover, the DS noted that human relevance of such an effect, if occurring only as a high-dose phenomenon as it was in the case of malignant lymphoma in mice, is considered equivocal. The Finnish CA regards the studies by Kumar (2001) and Wood et al. (2009) pivotal to evaluate the concern of glyphosate-induced malignant lymphoma in mice. The highest doses causing increase in malignant lymphoma were 810 and 1460 mg/kg bw/d in male CD-1 (ICR) mice (Wood et al. 2009) and in male Swiss albino mice (Kumar 2001), respectively. Only the latter is above the recommended highest dose. In OECD Guideline 116 (2nd Edition), it is stated that a top dose not exceeding 1000 mg/kg bw/d may apply for the oral route of exposure. According to the ECHA Guidance on the Application of the CLP Criteria (version 4.1 – June 2015) tumours occurring only at excessive doses associated with severe toxicity generally have a more doubtful potential for carcinogenicity in humans. Excessive toxicity may affect the reliability of the study results when assessing carcinogenic effects. It is generally accepted that in carcinogenicity studies the highest dose should cause some signs of toxicity (such as slight depression of body weight gain) without substantially altering normal life span due to effects other than tumours (OECD Guidance Document 116, 2nd Edition). When considering the relevance or appropriateness of top doses higher than the recommended limit dose, it may also be necessary to take into account that glyphosate is rather poorly absorbed from gastro-intestinal tract, i.e. about 20% of the dose is evaluated to be absorbed.

In the study by Wood et al. (2009), no statistically significant adverse effects of any kind were observed, i.e. NOAEL being the highest dose of 810 mg/kg bw/d. This indicates that no such severe toxicity, which could compromise the results of this carcinogenicity study, was observed. In this study, glyphosate seems to increase dose-dependently incidence of malignant lymphoma in male Crl:CD-1 (ICR) mice. The DS has considered different statistical analysis methods. Pairwise comparison revealed that the increase was not statistically significant, not even at the highest dose of 810 mg/kg bw/d (5/51 vs. 0/51 in control group) even though close to it ($p < 0.056$ in Fisher's exact test or $p < 0.067$ in Chi-square test). Trend test, in turn, showed statistically significant effect ($p < 0.0037$). It has to be noted that in male control CD-1 (ICR) mice no malignant lymphoma was observed (0/51) whereas in about 22% of female controls (11/51) this malignancy was observed. No appropriate HC data from the study performing laboratory is available to further evaluate the spontaneous incidence of malignant lymphoma.

In the study by Kumar (2001), statistically significant ($p < 0.05$ in Z-test) increase in malignant lymphoma was observed in male and female Swiss albino mice at the highest dose level (1460 mg/kg bw/d). At this dose, the incidence was 38% (19/50) in male and 50% (25/50) in female mice. High incidence of malignant lymphomas was also observed in control mice; i.e. 20% (10/50) in male and 36% (18/50) in female mice, respectively. When the DS

considered another statistical pairwise comparison (Fisher's exact test), the increase was not statistically significant. In male mice, also cystic glands in stomach were observed. The DS regards this finding to have equivocal toxicological relevance. In this study, LOAEL and NOAEL were 1460 and 151 mg/kg bw/d, respectively. Although the highest dose exceeds the recommended limit of 1000 mg/kg bw/d, the Finnish CA is of an opinion that there is no severe toxicity reported compromising the carcinogenicity findings at this dose or lower doses. Despite the difference in outcome in statistical analysis with different methods, the Finnish CA finds the increase in the incidence of malignant lymphoma to be dose-dependent, at least in male Swiss albino mice. Trend test did not, however, indicate statistically significant effect.

In mice studies by Kumar (2001) and Wood et al. (2009), the observed association between glyphosate exposure and increased malignant lymphoma is at the borderline of statistical significance. Statistical significance depended on the method used for data analysis. It has to be emphasized that statistically significant effect is not necessarily biologically important but also that statistically non-significant effect does not necessarily mean that the effect is not biologically important. The observed effects appear to have a dose-response relationship, at least in male mice. Spontaneous appearance of malignant lymphoma seems to be a common phenomenon in mice, especially in Swiss albino mice. This raises a question whether the observed effects are also spontaneous in nature in exposed mice, and can be regarded as a chance event and not a consequence of exposure to glyphosate. According to the ECHA Guidance on the Application of the CLP Criteria (version 4.1 – June 2015), any statistically significant increase in tumour incidence, especially where there is a dose-response relationship, is generally taken as positive evidence of carcinogenic activity. However, in the case of glyphosate an increased incidence of malignant lymphoma lies at the borderline of biological and/or statistical significance and malignant lymphoma seems to appear also spontaneously in mice. Therefore, comparison with HC data is strongly encouraged as also the DS has done.

Reliable HC data from performing laboratory in CD-1 (ICR) mice for study by Wood et al. (2009) is not available. HC data (250 mice/sex in 5 studies during years 1996-1999) from laboratory performing carcinogenicity studies used in study by Kumar (2001) indicates an incidence of malignant lymphoma within a range of 6 – 30% (mean 18.4%) in male and 14 – 58% (mean 41.6%) in female Swiss albino mice. In the study by Kumar (2001), the incidence of lymphomas observed in control mice (i.e. 20% in males and 36% in females) was approximately at the level of mean value in the HC data. The comparison of malignant lymphoma incidence at the highest dose to HC data shows that the incidence both in male (38%; 19/50) and female (50%; 25/50) is above the mean value. Only in male mice, the incidence (38%) is outside the HC range (6 – 30%). When evaluating especially the latter observation together with the finding of dose-response relationship and also statistical significance at the highest dose (but only in Z-test) in male mice, the Finnish CA is prone to consider that the increased incidence of malignant lymphoma in male Swiss albino mice may be due to glyphosate exposure.

The DS concludes that harmonized classification and labelling for carcinogenicity are not warranted for glyphosate. According to the CLP criteria,

substance can be placed in Category 2 "Suspected human carcinogen" if there is limited evidence of carcinogenicity in animal studies suggesting a carcinogenic effect. According to the Guidance on the Application of the CLP Criteria (version 4.1 – June 2015), the evidence of carcinogenicity in experimental animals can be regarded as limited if e.g. the evidence of carcinogenicity is restricted to a single experiment or there are unresolved questions regarding the interpretation of the studies. Although findings in rat studies were mainly negative, OECD Guideline 451 compliant mice studies raise especially a concern that glyphosate increases the incidence of malignant lymphoma. Despite the DS has thoroughly analyzed the carcinogenicity data, taken into account various uncertainties regarding the interpretation of the data and used weight of evidence approach, the opinion of Finnish CA is that based on the available data the concern on carcinogenicity of glyphosate cannot be unequivocally excluded.

Dossier Submitter's Response

Thank you for these comments which describe very well the uncertainties and inconsistencies when drawing conclusions on the human relevance of malignant lymphoma observed in mice studies (i.e., the increase in the incidence of this quite common tumour at very high dose levels). As explained by the DS in the CLH dossier and the addendum, the uncertainties and inconsistencies in the various studies do not justify classification and labelling. We are sure that the arguments put forward by the Finnish CA will be seriously taken into account by the RAC. However, it should be taken into account that a true exceedance of historical control data was confined to male Swiss mice at a dose level above the usual OECD limit. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.

RAC's response

Noted. See response to comment no 11.

As regards the malignant lymphoma reported in mice, an increased incidence of was reported in three carcinogenicity studies in CD-1 mice and one study in Swiss albino mice.

When pairwise comparison with Fisher's exact test was used, the increases in lymphomas did not reach statistical significance in any of the studies. In two of the studies in CD-1 mice (Sugimoto, 1997; Wood et al., 2009), a statistically significant trend for malignant lymphoma was observed in male animals when using the Cochran-Armitage trend test.
In mice, lymphoma is a common spontaneously occurring neoplasm.
No significant increases in malignant lymphomas were found in the study by Knezevich and Hogan (1983). In this study, malignant lymphoma was not used as a separate histopathological entity. However, the term "lymphoreticular neoplasms" is considered to include the group of malignant lymphomas and the findings were reported to be non-significant in the RAR.
The tumour incidence of 12% at the high dose of 4348 mg/kg bw/d in the study by Sugimoto (1997) was within the relevant HCD range for Crj:CD-1 male mice

obtained from the laboratory in which the study was performed (mean 6.3%; range of 3.96% - 19.2%, the majority of the studies had a control incidence ≤ 6%, 9 studies initiated between 1993 to 1998; Kitazawa, 2013, ASB2014-9146). In the study by Sugimoto (1997), treatment related increases in pre-neoplastic lymp node pathology in the form of mesenteric lymph node hyperplasia was not reported.

The 10% incidence in the study by Wood et al. (2009) was borderline significant in the pairwise Fisher's exact test. However, the incidence of lymphomas in controls is very low. There are limited HCD from the laboratory to support the interpretation of the biological relevance of the glyphosate effect. The only information provided to RAC regarding control data from the same laboratory as Wood et al., 2009 was from a study performed in 2008 with a incidence of malignant lymphoma in the control group at 12% (in males and females). Further, control incidences for malignant lymphomas in male CD-1 mice from a control database of the Harlan Laboratories between 2000 – 2010 had a mean of 7.5% with a range of 0 – 32% (Letter from Eric Wood, 2010). The data provided is for 24 month and not 18 month studies and appears to be from different test facilities. The incidence of malignant lymphomas has a strong age component and thus the range given is not considered representative for the 18 month study by Wood (2009). RAC has also included control incidences for Crl:CD-1 mice obtained from Charles River Laboratories (mean incidence in males of 2.7% and a range of 0-14% for the 18 month studies; Giknis and Clifford, 2005, with studies initiated between 1987 - 2000, ASB2007-5200). In the RAR a second report from Giknis and Clifford (2010) is mentioned describing control tumour incidences in CD-1 mice in studies initiated in the period between 2002-2006 (mean 2.5%; range 0-6.7% in males of 8 studies of 18 month duration). It should be noted that these control data are from different laboratories and should thus be used with caution. It appears from the available control data that the incidences of malignant lymphomas in Charles River CD-1 mice are relatively variable and the incidences reported in the study by Wood (2009) is considered to be within or slightly above reported control values. No treatment related increases in non-neoplastic lesions such as lymph node hyperplasia was not reported in this study.

There was no significant increase in malignant lymphomas in the study by Atkinson (1993). It should be noted that only those lymph nodes were investigated histologically which showed macroscopic changes. This may lead to an underestimation of the actual tumour numbers. In this study no treatment related increases non-neoplastic lymp node pathology in the form of mesenteric lymph node hyperplasia was found in the animals examined. No HCD from the test facility was identified. RAC has used control incidences for CD-1 mice obtained from Charles River Laboratories (mean incidence in males of 5.3 % and a range of 0-21.7 % for the 24 month studies; Giknis and Clifford, 2005, with studies initiated between 1987-2000, ASB2007-5200). It should be noted that the substrain of CD-1 mice used in the study by Atkinson (1993) is not known and the data shoud be used with caution.

In Swiss albino mice (Kumar et al., 2001) the incidence of malignant lymphoma in male and female mice at the top dose was 38% and 50%, respectively. However, the high background incidence in this strain must be taken into consideration. The HCD, according to information in the study report (no additional information given on the basis of these HCD), was in males a mean of 18.4% with a range of 6-30% and in females a mean of 41.6 with a range of

14–58%. Thus, the incidences of malignant lymphomas were above the upper range of the HCD for the male mice.
No significant increases in malignant lymphomas was found in the mouse studies when assessed by the pairwise Fisher's exact test. However, in two of the five studies, a significant positive trend of malignant lymphoma incidences in males was reported. In two studies, increases were observed that were not significant. In the fifth and oldest of the studies, the term malignant lymphoma was not used, but there was no significant increase in lymphoreticular neoplasms reported in this study in response to glyphosate exposure. Thus, the lymphoma incidences in male mice show a slight, but clearly variable increase. Further, no increase in treatment related non-neoplastic lymp nodes were reported, thus supporting a spontaneous nature of the tumours. The biological and human relevance of the findings is uncertain for the following reasons:
i) the maximum incidences were regarded to be within the historical control range for the CD-1 mice, although adequate HCD were not available for all studies;
ii) the increases in malignant lymphoma incidences appeared to be confined to the high dose groups in the CD-1 mice;
iii) the incidence of malignant lymphomas are known to increase with the age of the animals. However, significant associations between exposure and induction of malignant lymphomas were not observed in the 24 month studies. Furthermore, there was no reduction in overall survival in the exposed groups;
iv) no parallel increases were observed in female CD-1 mice. It is known that female CD-1 mice are usually more prone to develop spontaneous malignant lymphoma than male mice (Son and Gopinath, 2004, ASB2015-2533). The lymphoma incidences were generally higher in females than in males, but no glyphosate related increases were seen in female CD-1 mice.

For further details on the evaluation of the data for carcinogenicity, see the RAC opinion.

Date	Country	Organisation	Type of Organisation	Comment number
02.06.2016	Denmark		Individual	211
Comment received				
It creates carcinogenity.				
Dossier Submitter's Response				
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Sweden		MemberState	212
Comment received				
The SE CA considers that the available data presented in the CLH-report warrant classification of glyphosate as Carc. 2 according to the CLP criteria based on limited evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals for the following reasons: - A positive association has been observed between exposure to glyphosate and the frequency of non-Hodgkin lymphoma (NHL) in case-control studies from Canada, USA and Sweden. In contrast, the Agricultural Health study (AHS) cohort did not show an increased risk of NHL. A limitation of the AHS-study is that the follow up-time was rather short which impacts the ability of the study to detect an association. For that reason, although AHS is a large well-conducted study, the lack of an association between exposure of glyphosate and risks for NHL do not outweigh the results of the case-control studies. We consider that there is limited evidence of carcinogenicity in humans mainly based on the positive association of NHL in case-control-studies. - There is limited evidence of carcinogenicity in male mice in five (out five) experimental studies carried out at different times and in different laboratories with some consistency in tumour profile, with supporting data from two (out of nine) rat studies. - There was a positive trend in the incidence of malignant lymphoma in CD-1 male mice in two chronic dietary studies. - NHL is a form of malignant lymphoma and thus there is a potential concordance between the malignant lymphoma in mice and the human NHL findings, which raises a noteworthy concern. Increase in malignant lymphoma was not detected in rat. - There was a positive trend in the incidence of renal tubule carcinoma in male mice in two feeding studies of CD-1 mice and in one feeding study in Swiss albino mice. Renal tubule adenoma is a rare tumour in CD-1 mice according to IARC WG, and based on historical control data from Charles River Laboratories of 52 studies (between 1987 and 2000) where adenoma were seen in only five studies. - There was a positive trend in the incidence of haemangiosarcoma in CD-1 male mice in two chronic dietary studies. - There was a positive trend in the incidence of pancreatic islet-cell adenoma in male SD-rats in two studies. - There is no confounding effects of excessive toxicity at the tested doses in the available chronic/carcinogenicity studies where tumours are reported, however, the administered doses are in the majority of studies considered as high, and are at or above the generally recommended limit dose (1000 mg/kg bw/day) in OECD TG 453. It should be noted that the toxicokinetic data from rat indicate a low oral uptake of glyphosate after repeated administration, only approx. 10% at low dose administration (10 mg/kg bw/day) meaning that the internal doses in the chronic/carcinogenicity studies likely are several times lower than the administered dose. There is no data on oral absorption after repeated exposure of high doses, however oral absorption appears to be similar in rat after single administration of both high and low doses. There are no studies of toxicokinetics in mouse.				

- Glyphosate is genotoxic in somatic cells and thus has a mode of action that is relevant for humans (please refer to discussion in the Mutagenicity section)
- Glyphosate is an organophosphate pesticide with structural similarity to the organophosphate pesticides malathion, diazinon, tetrachlorovinphos and parathion that IARC has classified in Group 2A or 2B (probably/possibly carcinogenic to humans).

To summarize, considering the overall picture the existing data give rise to a concern for carcinogenicity. Glyphosate appears to induce a multi-site response in chronic/carcinogenicity studies with various tumours in different studies, both malignant and benign, in predominantly male mouse and in rat at rather low incidences, but with statistically significant positive trends. There is a positive association with an increased risk of NHL in epidemiological studies that may suggest a carcinogenic potential in humans, and there is evidence of mutagenic activity in vivo of glyphosate that indicates a relevant mode of action for humans.

Below follows some comments on the available studies and various tumour types.

Mouse studies
In total five long-term studies in mouse are available and considered valid in the CLH report.
Tumours were found in all five available studies:
- Malignant lymphoma (Wood et al., 2009; Sugimoto 1997)
- Renal tumours (Kumar, 2001 and Sugimoto, 1997, Knezevich and Hogan, 1983)
- Haemangiosarcoma (Atkinson et al., 1993; Sugimoto, 1997)

Three studies (Wood et al, 2009; Kumar, 2001; Sugimoto, 1997) are in compliance with OECD TG 451 (18 months), two studies (Knezevich and Hogan, 1983; Atkinson et al., 1993) are in compliance with OECD TG 453 (24 months). The study by Kumar (2001) was performed in Swiss albino mouse, the four other studies were performed in CD-1 mouse.
The study by Kumar (2001) was dismissed by EPA due to occurrence of viral infections, however no such data in the study report to support this statement.

Malignant lymphoma in mouse
Lymphoma findings in 3/5 mouse studies at high dose (where trend-tests or pair-wise comparisons were significant) are the most consistent among the observed malignancies in the mouse, although no dose-response is observed.
A positive trend for malignant lymphoma observed in CD-1 male mice in Wood (2009) with incidences of 5/51 in high dose (1081 mg/kg) and 0/51 in control group. There were no reliable historical control data for this study.
A positive trend for malignant lymphoma observed in CD-1 male in Sugimoto (1997) with incidences at 6/50 (12%) at high dose (4350 mg/kg) and 2/50 (4%) in control group. The incidence in high dose group was within historical control data range, but above historical control data mean. The reported historical control data by the performing laboratory ranged from 3.85% to 19.23%, and mean value was 6.33%.
In the study by Kumar (2001) there was an increase in malignant lymphoma in Swiss albino mice at high dose 1460 mg/kg bw/d with incidences in males at

19/50 (38%) in high dose versus 10/50 (20%) in control group, and in females 25/50 (50%) at high dose versus 18/50 (36%) in control. The incidence at high dose was outside the historical control data range for males 3/50-15/50 (6-30%); but within HC range 7/50-29/50 (14-58%) and above mean 20.8/50 (41.6%) for females. According to the original study report there was a statistically significant increase in high dose both in males and females as compared to control (in females this was based on percentage and not on total number of affected mice). There was no positive trend test.
In CD-1 males in Knezevich and Hogan (1983) there was an increase of lymphoreticular neoplasia (malignant lymphoblastic tumours) 5/59 at 157 mg/kg bw/day (low dose) and 4/50 at 814 mg/kg bw/day (intermediate dose), not statistically significant different from control (2/48). Incidence at high dose (4841 mg/kg bw/day) was 2/49. No historical control data were available.
There was an increase in malignant lymphoma in male CD-mice in Atkinson (1993) with incidences of 6/50 at 1000 mg/kg bw/d (high dose) and 4/50 in control group. No statistical significant difference in pairwise comparison and no positive trend. There was also a high incidence in the female control group and at high dose (14/50 and 13/50). No reliable historical control data were available.

Renal tubule tumours in mouse
A positive trend for renal (tubular) carcinoma, and for adenoma and carcinoma combined in CD-1 male mice in Knezevich and Hogan (1983). One adenoma (1/49) were observed in control, one adenoma and two carcinomas (in total 3/50) were observed in high dose (4841 mg/kg bw/day) and one carcinoma (1/50) was observed at mid dose (815 mg/kg bw/day). No historical control data available from the performing lab.
A positive trend for renal tubular adenoma in CD-1 male mice in Sugimoto (1997) with incidences of 2/50 in high dose group (4348 mg/kg bw/day) and 0/50 in control group. No historical control data available from the performing lab.
A positive trend for renal tubular adenoma in Swiss albino male mice in Kumar (2001) with incidences of 2/50 at high dose (1460 mg/kg bw/day), 1/50 mid dose, and 0/50 in control. No historical control data available from the performing lab.
In Atkinson (1993), the incidence of renal tubule tumours was 2/50 both in control and low dose (100 mg/kg bw/d) males, including one carcinoma in each of these two dose groups. No tumours in the two other dose groups (300 mg/kg bw/d and 1000 mg/kg bw/d) were reported. No historical control data available from the performing lab.
In Wood (2009) there were no renal tumours in any dose groups. No historical control data available from the performing lab.

Haemangiosarcoma in mouse
A positive trend for haemangiosarcoma was observed in CD-1 male mice in Atkinson et al (1993). Incidences were 0/50 in control and 4/50 at 1000 mg/kg (high dose). Historical control data ranged from 0/50 to 4/50, thus incidence was at the upper limit of historical control data.
A positive trend for haemangiosarcoma was observed in CD-1 male mice in Sugimoto (1997) with incidences of 0/50 in control and 2/50 at 4348 mg/kg bw/day (no tumours at any other dose). No appropriate historical control data from the performing lab was available.

Rat studies
Nine unpublished long-term feeding studies with active substance, six of these were in compliance with OECD TG 453.
Two more (published) studies with a glyphosate salt and a formulation (Chruscielska et al 2000 and Seralini et al 2012) were of low reliability and not taken into account.

Tumours were found in two out of nine available studies:
- Pancreatic islet cell tumours (Stout and Ruecker, 1990; Lankas, 1981)
- Liver tumours (Stout and Ruecker, 1990)
- Thyroid C-cell tumours (Stout and Ruecker, 1990)
- Interstitial cell tumours of the testes (Lankas, 1981)

The study of Stout and Ruecker, 1990 was in compliance with OECD TG 453, and the study by Lankas, 1981 was in general in accordance with TG 453. The two studies were performed in Sprague Dawley rats. These two studies were also assessed as positive by IARC:
Five out of six of the negative studies were in compliance with OECD TG 453 and the doses tested in these studies were above the highest doses tested in the positive studies. Three out of the six negative studies were performed in Wistar rat, one in Charles-River albino rat, and two in SD rat.

Islet cell tumours of the pancreas in rat
A statistically significant increase in pancreatic islet cell adenoma in male SD-rats at low dose (89 mg/kg bw/day) compared to control in Stout and Ruecker (1990). There was also an increase at high dose (940 mg/kg bw/day), but the difference was not statistically significant as compared to control. The incidence was however outside the historical control data range. There was no positive trend, no progression to carcinoma or no dose-response observed. EPA did additional analyses excluding animals that died or were killed before week 54-55. In this analysis incidences for adenoma were 2%, 18% (s.s), 10%, 15% (s.s), in control, 89 mg/kg bw/d, 362 mg/kg bw/d, 940 mg/kg bw/day dose groups. Incidences in all three exposed groups were outside the HCD range.

A statistically significant increase in pancreatic islet cell adenoma in Lankas (1981) and for adenomas and carcinomas combined at 3 mg/kg bw/day (low dose) in male SD-rats. There was a positive trend for carcinomas in male animals with incidences of 0/50, 0/49, 0/50 and 1/50 in control, 3 mg/kg bw/d, 10.3 mg/kg bw/d, 31.5 mg/kg bw/d dose groups respectively. No positive trend for adenomas.

Liver tumours in rat
A positive trend for hepatocellular adenoma in males in Stout and Ruecker (1990) in SD-rats with an observed dose response relationship and incidences of 2/44, 2/45, 3/49, 7/48 in control, 89 mg/kg bw/d, 362 mg/kg bw/d, 940 mg/kg bw /d dose groups respectively. There was no positive trend for carcinoma, or when adenoma and carcinoma were combined. Incidences for carcinoma were 3/44, 2/45, 1/49, 2/48 in control, 89 mg/kg bw/d, 362 mg/kg bw/d, 940 mg/kg bw /d dose groups respectively.

C-cell adenoma of the thyroid in rat
A positive trend for C-cell adenoma of the thyroid in female SD-rat in Stout and Ruecker (1990) with incidences of 2/57, 2/60, 6/59, 6/55 in control, 113, 457, 1183 mg/kg bw/day dose groups respectively. Incidences for carcinoma was 0/60, 0/60, 1/60, 0/60.

Interstitial cell tumours of the testis in rat
A statistically significant increase in interstitial cell tumours of the testis in SD-rats in Lankas (1981) in high dose group as compared to the control group. Incidences were 0/50, 3/50, 1/50, 6/50 in control, 3, 10.3, and 31.5 mg/kg bw/day respectively. Thus, no clear dose-response. The incidence at high dose was above the historical control range.

Dossier Submitter's Response

Thank you for this comprehensive comment! However, the DS maintains its position that glyphosate should not be classified with respect to carcinogenicity.
The epidemiological evidence for a carcinogenic effect of glyphosate in humans is much too weak to justify classification. The main deficit of nearly all studies is the insufficient information on previous exposure (duration and dose).
Taking a weight of evidence approach, there is no doubt that glyphosate (i.e., the active substance) is devoid of a mutagenic potential. (It cannot be excluded that some of the formulations might exhibit genotoxic properties but the decision now concerns glyphosate only.)
The few tumour findings in rats were not reproducible in other studies and were not dose-related.
With regard to higher numbers of affected mice at high dose levels, see please the addendum which has been prepared by the DS according to the OECD framework. In this addendum, the framework is applied to all three tumour types of concern.

RAC's response

Noted. See response to comment no 11, 210 and 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Brazil		Individual	213

Comment received

Epidemiological studies are not consistent in their results (diferent tumor outcomes)and deal with to ill-defined exposures to glyphosate-based formulations (GBF) and not to the a.i. Animal studies do not report tumor sites consistently considering rodent species and gender, the statistics are disputable and, more important from the scientific state-of-art view, there in not a putative mode of action proposed under well established rules such as those issued and/or adopted by entities like the IPCS, USEPA and the ILSI/HESI: the so-called IPCS framework for mode of action and human relevance. Causality, as could be provided by weight of evidence and the Bradford-Hill viewpoints, has not been established for glyphosate and the reported tumors. Therefore, based on human data and on rodent data, and considering that glyphosate carcinogenic potential has not been evaluated according to the state-of-art, no labelling for human carcinogenicity is warranted.

Dossier Submitter's Response
This comment seems to support the opinion of the DS that no classification of glyphosate for carcinogenicity is necessary. However, we would like to stress that glyphosate has been tested and evaluated for carcinogenicity according to internationally accepted guidelines and, thus, according to current practice.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	214
Comment received				
I am extremely concerned about the flawed evaluation of carcinogenicity data pointed out by top scientists in an open letter. Include all independent studies used in the IARC monograph in your assessment. Review the studies submitted by industry with extreme caution because of their potential conflict of interest, and make sure they become publicly available for scrutiny by other scientists. Ensure you take into account studies from mice that show that glyphosate is carcinogenic and the six studies from registers of human cancer cases, when you decide how to classify glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Germany	Pesticide Action Network germany	BehalfOfAnOrganisation	215
Comment received				
The conclusion that no hazard classification for carcinogenicity is warranted (Section 4.9.6., page 98 of the Dossier) is CONTRARY TO THE EVIDENCE provided in the Dossier itself and its supporting documents (the RAR and its Addendum). Addressing the errors and distortions described below will necessarily lead to a revision of the conclusions drawn in Section 4.9.4 (Summary and Discussion of Carcinogenicity, Dossier p.93) and Section 4.9.6 (Conclusions on classification and labelling, Dossier p.98) resulting in a				

Category 1B classification. Most importantly, males of all five mouse carcinogenicity studies considered by the authorities of acceptable quality show a statistically significant increase in the incidence of one or several tumour types. Notably, three of these five mouse studies exhibited a significant increase in the same type of cancer (malignant lymphoma), underscoring the reproducibility of this finding in studies performed in different laboratories and at different times. This clearly exceeds the criteria for classification as a carcinogen as given in CLP Regulation, documented on page 95 of the Dossier. Also, the fourth study which reported incidences of malignant lymphoma, but was lacking statistical significance is invalid in this regard, because of severe deficiencies in the histopathological assessment of type of tumour (see Attachment 1). Importantly, the finding of an increased incidence of malignant lymphoma is further supported by the results of epidemiological studies indicating an association between glyphosate exposure and Non-Hodgkin lymphoma (see Attachment 2) and by mechanistic evidence, in particular genotoxicity and oxidative stress (Attachment 3). It is important to note, that the Dossier Submitter (DS) used incorrect data and false arguments in an attempt to invalidate the findings of the mouse carcinogenicity studies (Attachment 1). PROPER EVALUATION of the evidence provided in CLH Report, the RAR and its Addendum INEVITABLY LEADS TO the conclusion that glyphosate is carcinogenic in experimental animals, warranting a CATEGORY 1B carcinogenicity labelling of glyphosate. ECHA note - The following attachment was submitted with the comment above: *Attachments 1-3.pdf*
Dossier Submitter's Response
We would like to strongly reject the accusation that we have used incorrect data and false arguments. Moreover, the comment does not provide any new information with respect to the classification, rather it once more confirms that the same data may be interpreted differently to draw different conclusions. All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen.
RAC's response
Noted. See response to comment no 4 and 11.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	216
Comment received				
The GTF agrees with the CLH report (pages 59-98) that the weight of evidence based on both epidemiological data and long-term studies in rats and mice clearly demonstrate that no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria. The International Agency for Research on Cancer (IARC) classified glyphosate as "probably carcinogenic to humans" in Category 2A, which is inconsistent				

with the Rapporteur's (Germany) RAR, the additional detailed review of Monograph 112 by the BfR in Addendum 1 to the RAR, the Member States opinions and EFSA's conclusions.
Since IARC published its opinion, several comprehensive reviews of glyphosate by the Canadian PMRA (2015), United States Environmental Protection Agency Cancer Assessment Review Committee (US EPA CARC, 2015) and Food and Agriculture Organization of the United Nations and World Health Organization Joint Meeting on Pesticide Residues (JMPR, 2016) concluded that glyphosate is unlikely to be carcinogenic in humans. Most recently, the Food Safety Commission (FSC) of Japan (Japanese FSC, 2016) reviewed data from five different glyphosate registrants which included 10 chronic/carcinogenicity rodent studies, two of which had not been reviewed by regulators elsewhere, and concluded that glyphosate is not carcinogenic. Unlike IARC reviews, these evaluations were in most cases conducted over multiple years (other than the recent expedited WHO/FAO JMPR review) with full access to multiple sets of detailed toxicology sets of data requirements from glyphosate registrants, as well as all the publically available scientific literature considered by IARC.
Glyphosate has been rigorously and extensively tested for carcinogenicity by administration to mice (five studies) and rats (nine studies). The subset of the four of these fourteen chronic rodent studies leveraged in the IARC evaluation are discussed within the appended report to these public comments.
The IARC evaluation of glyphosate claimed limited evidence of an association between non-Hodgkin lymphoma (NHL) and glyphosate use. The last decade has not yielded newly published raw epidemiology data on NHL and glyphosate use. However, several reanalysis of old studies have been undertaken and these are discussed within the appended report. Most notably, Chang and Delzell (2016) conducted a systematic review and meta-analysis that rigorously examined the possible relationship between glyphosate exposure and risk of lymphohematopoietic cancer (LHC) including NHL, Hodgkin lymphoma (HL), multiple myeloma (MM) and leukemia. As part of their comprehensive review, these authors critiqued a meta-analysis of glyphosate conducted by IARC researchers (Schinasi and Leon, 2014), and concluded that the IARC scientists "did not assess study quality and did not specifically address the potential impact of study limitations on the findings for glyphosate, nor did they discuss whether the apparent association between glyphosate and NHL risk is likely to be causal".
The IARC review also considered oxidative stress a relevant cancer mode of action based on published literature. The CLH report evaluated the same publications of in vitro and in vivo studies where oxidative stress is reported, concluding that the literature was contradictory and non-conclusive. The appended comments address the literature in greater detail.
The GTF supports the CLH report position that there is no sound scientific basis for a carcinogenicity classification of glyphosate.

Dossier Submitter's Response

Even though some support for the evaluation of carcinogenicity in the CLH dossier is expressed, this comment seems to be primarily a criticism of the IARC evaluation and the approach taken by IARC. The DS has no response to this matter. We are sure that the background documents will be also taken into consideration by ECHA and its RAC.

RAC's response
Noted. See response to comment no 4 and 11.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Sweden		Individual	217
Comment received				
According to Avaaz and other organizations glyphosate can cause cancer according investigations of about 94 scientists. It goes into the groundwater and makes it toxic, like the vegetables on which it is used.				
Dossier Submitter's Response				
Apparently, second-hand information is relied on in this comment that does not provide a substantial contribution. The claim glyphosate would make the groundwater and crops toxic is not backed by any scientific evidence.				
RAC's response				
Noted. See response to comment no 11 and 68.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium		Individual	218
Comment received				
Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Switzerland		Individual	219
Comment received				
Attached are my comments on the evaluation of carcinogenicity in the CLH Report for Glyphosate (the Report), EC Number 213-997-4, prepared by the Federal Institute for Occupational Safety and Health (BAuA). In my				

comments, you will see that I disagree with the conclusions on the human epidemiological data and that I find serious flaws in the evaluation of the animal carcinogenicity data. I have also prepared a pooled analysis of the animal carcinogenicity data that clearly indicates the hemangiosarcomas and malignant lymphomas show statistically significant trends even when excluding doses above 1000 mg/kg/day.

I am also including several supplemental files with this submission including all cited papers, the computer code I used to produce the pooled analysis, and the computer code I used to calculate statistical significance for testing the observed data sets against the historical controls. I have also included a manuscript by Ghisi et al. (2016) that does a meta-analysis on the ability of glyphosate to induce micronuclei.

What I found most disturbing with this submission is that, despite our previous concerns about the EFSA conclusions on carcinogenicity, the review continues to disregard guidance set forth by ECHA, OECD, IARC and others on how to evaluate carcinogenicity data, especially regarding the use of the limited evidence category for the human data, the appropriate use of historical controls and the proper use of findings of a positive trend in an animal cancer study.

In my opinion, having reviewed a large number of compounds for carcinogenicity and having read both the Report and the ECHA Guidelines, glyphosate should be classified into Group 1b.

ECHA note - The following attachment was submitted with the comment above: *SendToEcha.zip*

Dossier Submitter's Response

This comment once more shows that the same data may be interpreted differently to draw different conclusions. Indeed, the interpretation of guidelines and guidance documents by various scientists may differ. All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen.

RAC's response

Noted. See response to comment no 11, 197 and 228.

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	220

Comment received

Carc. IB, H350
more details see: attachment

Dossier Submitter's Response
There is no new information but this comment reflects the fact that different views on the same studies/data are possible. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2016	Germany		Individual	221
Comment received				
Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als „wahrscheinlich krebserregend beim Menschen" (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als „vermutlich karzinogen, Kategorie 1B" einstufen. Zur Begründung: Gemäß der EU-Verordnung Verordnung 1272/2008 über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenität bei „zwei oder mehreren unabhängigen Studien an einer Spezies" aus, um eine Substanz als „vermutlich karzinogen beim Menschen" einzustufen. Im Fall von Glyphosat ist ein dosisabhängiger Anstieg von Krebstumoren bei Mäusen in mindestens fünf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos für Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf				
Dossier Submitter's Response				
Same comment as 199 and 201. The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Spain		MemberState	222
Comment received				

Cancer in experimental animals

We agree with the dossier submitter that with such a large quantity of animal data regarding carcinogenicity, the criteria of the CLP-Regulation may not be applicable directly to the available information of glyphosate. Instead, the large volume of animal data for glyphosate should be evaluated using a weight of evidence approach. It should be avoided to base any conclusion only on the statistical significance of an increased tumour incidence identified in a single study, without consideration of biological significance of the finding.

In most cases tumours incidence were not statistically significant, only observed in a single sex, not consistent with regard to dose response, within the range of historical controls and with a highly spontaneous background incidence of a given tumour type in the strain used. Confounding effect of excessive toxicity cannot be excluded and could be the cause of the increased incidence of tumours at the highest dose in life time studies in some of the rodent studies.

It is worth pointing out that in mouse, the low incidence of malignant renal tumours appeared only in studies of longer duration (2 years). Therefore, it cannot be ruled out that older animals (24 months old instead of 18 months old) in combination with exaggerated doses used, exceeding the OECD-recommended limit of 1000 mg/kg bw/day and in some cases exceeding the MTD (dose levels of > 4000 mg/kg bw per day), is what gave rise to the progression of lesions to malignancy (adenomas to carcinomas).

Consistency and reproducibility are very important factors to take into account in making a decision. Clearly, there is lack of consistency among animal studies. Based on data from studies considered acceptable for classification and labelling purpose, five carcinogenicity studies in mice and six chronic toxicity and carcinogenicity studies in rats, the overall weight of evidence indicates that there is no unequivocal evidence of carcinogenicity in animals.

Studies of cancer in humans

Epidemiological studies revealed partly contradictory results. However, in most studies, no association with an exposure to glyphosate could be established. It is noteworthy that the most powerful study, the AHS (Agricultural Health Study), the prospective cohort-study, which in epidemiological terms is best suited to study the relationship, showed no association witn cancer incidence. This study should be given a higher weight in the overall assessment of the possible association between glyphosate use and NHL (non-Hodgkin lymphoma).

Besides that, it has to be highlighted the limitations of the epidemiological studies: multiple exposure, low power, very few studies show marginally increased ORs (not always statistically significant), quality criteria not always detailed, internal validity not assess due to limitations in the reporting of the study. Problem with the classification of cancers, Non-Hokgkin´s Lymphomas (NHLs) have not consistently defined over time. No measures from biomarkers from the blood are used (exposure measured through interviews or questionnaires), the number of cases involved and no knowledge of glyphosate

or the type of glyphosate formulate used. A differentiation between the effects of glyphosate and the co-formulants is not possible. We agree with the dossier submitter that epidemiological studies are of limited value for detecting the carcinogenic potential of an active substance in plant protection products since humans are never exposed to a single compound alone and the results of the studies are associated to different formulations containing glyphosate or mixtures of different substances. Therefore, it is difficult to use the results of epidemiological studies to demonstrate a carcinogenicity potential of glyphosate, given the very weak, inconsistent (across studies) and in most cases non-statistically significant associations reported. Conclusions on classification and labelling regarding carcinogenicity We agree with the dossier submitter that, based on the epidemiological data as well as on data from long-term studies in rats and mice and taking a weight of evidence approach, no hazard classification for carcinogenicity is warranted for glyphosate according to the CLP criteria.
Dossier Submitter's Response
Thank you for the support!
RAC's response
Noted. See response to comment no 11.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Austria	GLOBAL 2000	BehalfOfAnOrganisation	223
Comment received				
Facing different results between the cancer assessment of the International Agency for the Research on Cancer (IARC) and the German Federal Institute for Risk Assessment (BfR), the Austrian environmental organisation GLOBAL 2000 made some efforts to understand the underlying reasons for the obviously contradicting outcome. Our main findings were: 1) Serious doubts on the reliablitiy and the scientific value of BfR's cancer assessement are raised by BfR's self-contradicting comments on the five regulatory long-term studies of carcinogenicity in mice: Using the example of the study of Wood et al, 2009 we demonstrate that BfR changed its evaluation of the study results step-by-step, from "no indications for carcinogenicity up to the highest dose level" in December 2013 (draft RAR), to "slight increase in the incidence of malignant lymphoma, but not statistically significant" in March 2015 (after IARC's classification) to "statistically significant increase of malignant lymphoma, which could be considered as treatment- dependent" in Aug 2015 (Addendum to the RAR). More details are provided in the attached file: "Contradictions in the RAR"				

2) A deeper analysis of the five long-term mice studies by the toxicologist Dr. Peter Clausing on behalf of GLOBAL 2000 finally revealed major flaws in BfR's and EFSA's cancer assessment: The authorities falsely interpreted regulatory mice carcinogenicity studies, by violating several relevant OECD guidelines and using inappropriate historical control data. More details are provided in the attached file: "Evidence in Animal Testing_PeterClausing".

3) An Expert Statement, provided by the epidemiologist Prof. Eberhard Greiser on behalf of GLOBAL 2000 revealed that several epidemiological studies that demonstrated a correlation
between exposure to glyphosate-based herbicides and Non-Hodgkin's lymphoma have been systematically "classified" as unreliable in the notifiers dossier, claiming that relevant data (e.g. exposure to glyphosate, smoking behaviour, previous diseases) was lacking. Though these claims were false – which could easily have been noticed by the BfR and EFSA – these two institutions accepted these alleged errors as the basis to systematically discredit human evidence for the carcinogenicity of glyphosate as "not reliable".
More details are provided in the attached file: "Human Evidence_EberhardGreiser".

4) Last but not least, an Expert Statement from Prof. Ivan Rusyn, a leading member of the IARC Working Group on glyphosate, compared the legal background and relevant guidelines for classification of carcinogenicity in the EU pesticide regulation with the IARC's internal rules. He concludes that "it does not appear that the BfR renewal assessment report on glyphosate (18 December 2013 version) followed these guidelines in evaluation of the human and animal carcinogenicity evidence for glyphosate". Rusyn concluded that the RAR "repeatedly downplays positive findings of cancerogenicity in animal studies based on dose considerations".
More details are provided in the attached file: "Expert Statement Bundestag_IvanRusyn" Please note that this PDF starts with the statement in German language. The English version can be found in the second half of this document.

The attached statements from different scientist on different aspects of the BfR's and EFSA's cancer assessment have one thing in common: They show that the authorities adopted wrong assessments and false descriptions by industry without further scrutiny and used them to dismiss indications for carcinogenic effects of glyphosate in experimental animals and humans. Therefore, these documents were submitted to the Offices of public Prosecutors in Vienna and Berlin.
Diese Dokumente wurden daher auch an die Staatsanwaltschaften von Wien und Berlin. GLOBAL 2000 considers the assessments performed by the BfR and the EFSA as a violation of their legal mandate. Therefore, GLOBAL 2000 and other NGOs have filed a criminal charge against these institutions, Monsanto Europa S.A. and Monsanto Agrar Deutschland GmbH.

Dossier Submitter's Response

This comment was, to a large extent at least, copy-pasted from no. 182. See our response to that comment, please.

RAC's response
Noted. See response to comment no 4, 11 and 68.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	224
Comment received				
Die Internationale Krebsforschungsagentur (IARC) der Weltgesundheitsorganisation (WHO) stuft Glyphosat als „wahrscheinlich krebserregend beim Menschen" (Katerogie 2A) ein. Vgl.: http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf Dieser Bewertung sollte auch die ECHA folgen und Glyphosat als „vermutlich karzinogen, Kategorie 1B" einstufen. Zur Begründung: Gemäß der EU-Verordnung Verordnung 1272/2008 über die Einstufung, Kennzeichnung und Verpackung von Stoffen und Gemischen reicht der Nachweis von Karzinogenität bei „zwei oder mehreren unabhängigen Studien an einer Spezies" aus, um eine Substanz als „vermutlich karzinogen beim Menschen" einzustufen. Im Fall von Glyphosat ist ein dosisabhängiger Anstieg von Krebstumoren bei Mäusen in mindestens fünf Studien dokumentiert. Vgl.: https://www.global2000.at/sites/global/files/Analyse%20Dr.%20Peter%20Clausnig.pdf Epidemiologische Studien liefern zudem Hinweise auf einen Anstieg des Risikos für Non-Hodgkin-Lymphome beim Menschen durch Glyphosat-Exposition. Vgl.: http://www.umweltinstitut.org/fileadmin/Mediapool/Downloads/01_Themen/05_Landwirtschaft/Pestizide/Gutachten_Prof._Greiser_Glyphosat_Studien.pdf				
Dossier Submitter's Response				
Same comment as 199, 201, or 221. See our responses there.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
06.06.2016	Germany		Individual	225
Comment received				
It creates carcinogenity				
Dossier Submitter's Response				
The assessment of carcinogenicity by the DS is clearly reported in the CLH dossier. A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document. The same data may be interpreted by others in a different way. It is up to ECHA and its RAC to decide.				
RAC's response				
Noted. See response to comment no 11.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	France		Individual	226
Comment received				
How many people are required to die of cancer, before a substance is designated carcinogenic and its use is banned?				
Dossier Submitter's Response				
This comment is not specifically related to the classification of glyphosate and cannot be addressed here.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	227
Comment received				
see above				
Dossier Submitter's Response				
There is no information in this comment.				
RAC's response				
Noted				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Austria	GLOBAL 2000	BehalfOfAnOrganisation	228
Comment received				
The Dossier submitter (DS) concluded: „No hazard classification of glyphosate for mutagenicity is warranted according to CLP criteria" (Dossier, p. 59). More specifically the DS concluded that "because of the negative results in the majority of the in vitro and in vivo mutagenicity tests including nearly all guideline-compliant standard assays and since positive findings were mainly confined to indicator tests, categories 1B and 2 also do not apply". For the reasons given below, this conclusion is wrong. The proper application of a weight of evidence approach inevitably leads to a conclusion that supports the IARC assessment of "strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic" (IARC 2016, p. 78). The hazard classification of glyphosate for mutagenicity needs to be re-considered, and the existing evidence for genotoxicity must be regarded as supportive of the exisiting evidence for carcinogenicity. The conclusion by the DS that the majority of in vitro and in vivo tests was negative is wrong. Here, it is contested for two important reasons. FIRSTLY, out of the 40 negative tests conducted or commissioned by industry, 16 were based on the Ames test, i.e. conducted in bacteria. However, since many years it is known that glyphosate possesses antibiotic properties. Its mode of action is the inhibition of the EPSP synthase an enzyme which is present in plants as well as bacteria. In the Ames test mutagenicity is assessed by the growth of nutrient (histidine) deficient strain Salmonella typhimurium. The principle of the test is to identify reverse mutations by the test substance				

(i.e. glyphosate) by the growth of bacteria after making them histidine-producing due to reverse mutation. But it can be expected that the antibacterial action of glyphosate will prevent the growth of back-mutated Salmonella, thereby producing systematically false negative results. To avoid such a falsification the Ames test is considered not suitable for testing antibiotics (Luijten et al. 2016). Therefore, the DS has a strong bias when he uses 16 Ames tests as part of argument that "negative results in the majority of the in vitro and in vivo mutagenicity tests" exist and at the same time dismisses the many positive findings in eukaryotic "non-standard" test systems (plant, insect, worm, fish etc.). In the Addendum to the RAR which claims to compare the findings of the assessments of the RAR and the IARC monograph, 13 publications demonstrating genotoxic effects of glyphosate and glyphosate-based formulations were not even mentioned (for the 13 publications cf. Attachment "List of references").
SECONDLY, it needs to be taken into consideration that negative results from micronucleus assays do not necessarily mean that there is no genotoxic effect. As Koller et al. (2012) point out: "Thus, false negative results were obtained in bone marrow MN studies with representatives of certain classes of potent DNA-reactive carcinogens such as heterocyclic aromatic amines and nitrosamines (Hayashi et al. 1989). Therefore, the lack of a positive result with G and R in these experiments does not prove that the test compounds are safe in regard to their genotoxic properties."

In summary, strong evidence exists that identifies genotoxic action of glyphosate as a mechanism of carcinogenicity. Moreover, the hazard classification assessment on mutagenicity made by the DS is severely biased and needs to be revisited to ensure a proper weight of evidence approach.

References:
Hayashi, M.; Sutou, S.; Shimada, H.; Sato, S.; Sasaki, Y.F.; Wakata, A. (1989): Difference between intraperitoneal and oral gavage application in the micronucleus test. The 3rd collaborative study by CSGMT/JEMS.MMS. Collaborative study group for the micronucleus test/mammalian mutagenesis study group of the environmental mutagen society of Japan. Mutat. Res. 223: 329–344.

Koller, V.L.; Fürhacker, M.; Nersesyan, A.; Mišik, M.; Eisenbauer, M.; Knasmueller, S. (2012): Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells. Archives of Toxicology 86: 805-813.

Luijten, M.; Olthof, E.D.; Hakkert, B.C.; Rorije, E.; van der Laan, J.-W; Woutersen, R.A.; van Benthem, J. (2016): An integrative test strategy for cancer hazard identification, Critical Reviews in Toxicology, DOI: 10.3109/10408444.2016.1171294

ECHA note - The following attachment was submitted with the comment above: *List of References.pdf*

Dossier Submitter's Response

In principle, criticism of the evaluation by the DS in this comment is based on two considerations. On the one hand, the antibiotic properties of glyphosate due to its mode of action are used to dismiss the negative results in the numerous Ames tests. However, if a test substance exhibits an antibiotic effect, one would expect cytotoxicity preventing testing in concentrations up to 5000 µg/plate or at least reduced background growth of bacteria. Indeed, such finding have been reported in a few of the Ames tests with glyphosate (usually in concentrations from 2500 µg/plate onwards) but, in most studies, this was not the case. (For detailed information on the individual studies, see section B.6.4.1 in Volume 3 of the RAR.) Thus, they can be fully relied on for testing of genotoxicity in bacteria. On the other hand, it is suggested that the results of the micronucleus tests might be "false negative". This claim is not substantiated for glyphosate. Likewise, no evidence has been provided why the investigations in "non-standard" systems should be given higher relevance. If this is intended, the organisation providing this comment should make efforts to revise the data requirements and to develop further OECD guidelines. For the time being, there is no other way than to rely on existing guidelines and on studies which were performed according to them. It cannot be expected that glyphosate should be tested according to other principles than all the other pesticides.
RAC's response
The database available for evaluation of germ cell mutagenicity is extensive and includes studies covering bacterial and mammalian cell *in vitro* mutagenicity assays as well as *in vivo* mammalian mutagenicity assays and some human data. The database includes studies of sufficient reliability and relevance to allow a robust evaluation following the criteria of CLP. Mutagenicity data related to exposures to AMPA and GBH are not considered in this analysis by RAC (the purpose is to provide a harmonised classification of glyphosate itself), the exception being the inclusion of human biomonitoring data. Genotoxicity data from non-mammalian species are not included in the assessment, because the relevance of the findings to humans of such studies conducted using non-standard protocols is lower than in the many studies available which were conducted using standard protocols and standard animal models. Classification of a substance as a germ cell mutagen in Category 1A is based on positive evidence from human epidemiological studies according to the CLP criteria. A limited number of biomonitoring 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. Some of these studies showed an apparently positive relationship between exposure to glyphosate and the levels of the markers being studied. However, all these studies were compromised by the lack of clear information about exposure to glyphosate itself and glyphosate based formulations, and the extent to which other substances or lifestyle factors could have contributed to the findings. In some cases, the low numbers of subjects involved was also a factor. Although not completely negative, these studies do not provide sufficiently robust evidence of glyphosate genotoxicity to justify classification for this endpoint. Classification of glyphosate as Muta. 1A is not justified.

According to the CLP criteria, classification of a mutagen in Category 1B is largely based on positive result(s) from *in vivo* heritable germ cell mutagenicity tests in mammals; or from *in vivo* somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations in germ cells. There was no evidence for mutagenic activity in germ cells of mice or rats at oral doses up to 2000 and 5000 mg/kg, respectively, in the dominant lethal tests presented. However, given that glyphosate has a wide distribution in the body, exposure of germ cells is likely, therefore results from the somatic mutagenicity studies are relevant also for the evaluation of germ cell mutagenicity. The bacterial mutation assays and mammalian cell gene mutation tests gave consistently negative results. Furthermore, a total of 7 oral and 7 i.p. bone marrow micronucleus tests and two chromosomal aberration test in rodents were reported. All oral tests and three of the i.p. tests were conducted according to OECD TG 474 or 475 and performed according to GLP. 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 may well have been within the anticipated control level. Thus, the evidence from these two positive studies does not override the overall conclusion from the numerous other *in vivo* mutagenicity studies, that glyphosate does not induce somatic cell mutations. The mammalian *in vivo* database is considered sufficient and an overall evaluation indicates that glyphosate does not warrant classification as Muta 1B. Classification in Category 2 is largely based on positive evidence obtained from somatic cell mutagenicity tests in mammals or other *in vivo* somatic cell genotoxicity tests which are supported by positive results from *in vitro* mutagenicity assays. Glyphosate is only metabolised to a very limited degree and is not a DNA reactive substance. Bacterial and mammalian gene mutation assays were all negative. Thus, the genotoxicity observed for glyphosate in some studies is likely caused by indirect mechanisms. Glyphosate appears to induce transient DNA strand breaks as observed in the *in vitro* and *in vivo* comet assays. However, as glyphosate does not induce gene mutations and the bone marrow mutagenicity endpoint is 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 concludes that there is not sufficient evidence to warrant classification of glyphosate for germ cell mutagenicity.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	229
Comment received				
The GTF agrees with the CLH report that the substantial data on genotoxicity fails to demonstrate evidence for classification (CLH report, page 59). This extensive genotoxicity database with studies conducted by multiple glyphosate				

registrants for regulatory purposes, as well as studies available in the open literature, are consistent with reviews by regulatory authorities, scientific bodies and independent experts who have concluded that glyphosate and glyphosate formulations (GBFs) are not genotoxic to humans; Australian PVMA, Canadian PMRA, RMS Germany - RAR, EFSA Conclusion, US EPA CARC, JMPR and the FSC of Japan. Comprehensive peer reviewed expert publications evaluating both well conducted studies and the literature have consistently noted that genotoxicity is unwarranted (Williams et al., 2000; Kier and Kirkland, 2013; and Kier, 2015). The IARC opinion suggesting strong evidence of genotoxicity is attributable to an insufficient review of the all the data, wherein the majority of available published study results were not considered. A considerable volume of published detailed primary study data (Kier, 2013, including appended data tables for over 50 in vitro and in vivo GLP genotoxicity studies) were provided to IARC in advance of the Meeting 112, as required, but these were not considered. A recent expert evaluation of the IARC review of glyphosate notes "the absence of evidence indicating that glyphosate or GBFs induced lesions characteristic of genotoxic carcinogens, in well-validated test systems with robust experimental protocols, invalidates conclusions that glyphosate or GBFs might act via a genotoxic mode of action". The weight of evidence from epidemiology studies, validated test systems and in vivo studies via relevant routes of exposure, all demonstrate a lack of genotoxicity hazard and warrant no mutagenicity hazard classification under CLP regulation.
Dossier Submitter's Response
Noted.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	230
Comment received				
Please include all studies and make them public to make sure none of them could be only representative of (very) profitable interests.				
Dossier Submitter's Response				
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	231

Comment received
Glyphosat ist als mutagen einzustufen. Begr&#65533;ndung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege (&#65533;strong evidence&#65533;) daf&#65533;r gefunden, dass der Stoff &#65533;(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht&#65533;. Der Deutsche &#65533;rztetag stellt ferner dazu fest: &#65533;F&#65533;r gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unsch&#65533;dlicher Schwellenwert,&#65533; und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verl&#65533;ngern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/
Dossier Submitter's Response
In the CLH dossier, the available studies have been taken into consideration. Taking a weight of evidence approach, glyphosate (active substance) is not considered genotoxic. Accordingly, speculations on a threshold or its absence and resulting consequencies are not relevant.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	232
Comment received				
Epidemiologische Studie in Paraguay zum Kontakt mit Glyphosat zeigt einen Zusammenhang mit Geburtsfehlern und Fehlbildungen. Benitez-Leite, S., Macchi, M. A., Acosta, M. (2009): Malformaciones congénitas asociadas a agrotóxicos. Arch. Pediatr. Drug 80, 237-247.				
Dossier Submitter's Response				
This paper is known to the DS. Glyphosate was not mentioned there and, accordingly, the article was not referred to in the CLH dossier. In addition, not all malformations mentioned there may be considered as such in a narrow sense since many of them were rather variations. Their numbers and percentages are not that much different from what is to be expected in Europe. On balance, the article is not suitable to prove a higher risk of birth defects to agrochemicals and certainly not to glyphosate.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	233
Comment received				
Concurrent neg. controls discarded in favor of less accurate historic controls biased to false negative: - This even occurred despite the glyphosate dose in two studies that found micronuclei in vivo being 20-fold apart(!), p. 357; 359. Despite such ignoring				

of concurrent controls, the - - RMS without shame for its other approvals of historic controls properly ignores a genotox finding for not having a neg. control (p. 399)! - While dismissing a low dose genotox finding, RMS reveals its dose range was chosen due to UNNAMED earlier finding of low dose toxicity; p. 399.
Dossier Submitter's Response
This comment clearly relates to the RAR (section B.6.4.5) but not to the CLH dossier. The reasons for dismissing certain findings were clearly stated in the RAR.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	234
Comment received				
Human cells and chromosomes are negatively affected by the substance.				
Dossier Submitter's Response				
No further information is given to support this claim.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany	Pesticide Action Network	BehalfOfAnOrganisation	235
Comment received				
The Dossier Submitter (DS) concluded that "because of the negative results in the majority of the in vitro and in vivo mutagenicity tests including nearly all guideline-compliant standard assays and since positive findings were mainly confined to indicator tests, categories 1B and 2 also do not apply" (CLH-Report p.59). This includes 17 negative Ames tests as listed in Table 21 of the CLH-Report. The DS failed to acknowledge that bacterial test systems are scientifically flawed for the assessment of compounds with antibiotic properties. Glyphosate has been patented as a broad spectrum antibiotic (US patent number 7771736) and then again as an "antimicrobial agent" (US patent number 20040077608 A1). The Ames test is not suitable for testing antibiotics (cf. Luijten et al. 2016). Taking this into account, the alleged number of negative results "proving" lack of genotoxicity of glyphosate is significantly reduced. The CLH-Report (p. 57) points out that epidemiological data for genotoxicity of glyphosate is available, but cautions: "It must be taken into account that the study participants had been always exposed to plant protection products containing glyphosate but never to the active substance itself." This is commonplace and applies to almost all epidemiological data for pesticides. Nevertheless this information is particularly valuable, because these are human data. In case of glyphosate these findings should be evaluated (weight				

of evidence approach) together with the results of in vitro tests for mutagenicity, clastogenicity or DNA damage/repair with glyphosate acid in mammalian cells as summarized in Table 22 of the CLH-Report (p. 47/48). Of the 18 tests listed in this table 7 were performed with cells of animal origin, 11 with cells of human origin. It is remarkable that 6 of the 7 tests performed with cells of animal origin were negative. In contrast the majority (i.e. 7 of the 11 tests) with cells of human origin were positive. This, taken together with the results of the epidemiological studies and the scientific discredit of the Ames test for assessing mutagenic effects of glyphosate, are strong indications that a proper evaluation would lead to a same conclusion as was drawn by the IARC in its monograph, i.e. that "there is strong evidence that exposure to glyphosate and glyphosate-based formulations is genotoxic" (IARC 2015, p. 78). References: IARC (2015): IARC monograph No. 112. Glyphosate. http://monographs.iarc.fr/ENG/Monographs/vol112/index.php Luijten, M.; Olthof, E.D.; Hakkert, B.C.; Rorije, E.; van der Laan, J.-W; Woutersen, R.A.; van Benthem, J. (2016): An integrative test strategy for cancer hazard identification, Critical Reviews in Toxicology, DOI: 10.3109/10408444.2016.1171294
Dossier Submitter's Response
The antibiotic properties of glyphosate due to its mode of action are used to dismiss the negative results in the numerous Ames tests. However, if a test substance exhibits an antibiotic effect, one would expect cytotoxicity preventing testing in concentrations up to 5000 µg/plate or at least reduced background growth of bacteria. Indeed, such finding have been reported in a few of the Ames tests with glyphosate (usually in concentrations from 2500 µg/plate onwards) but, in most studies, this was not the case. (For detailed information on the individual studies, see section B.6.4.1 in Volume 3 of the RAR.) Thus, they can be fully relied on for testing of genotoxicity in bacteria. The epidemiological studies do not provide convincing evidence of genotoxicity. With regard to Table 22 (since this one is mentioned in the comment), it must be emphasised that the positive results were predominantely seen in so-called indicator tests (Comet assay, SCE) or in less used test systems such as bovine lymphocytes but not in regulatory standard tests. Even if there might be some concern about possible clastogenic effects or DNA damage *in vitro*, these findings were contravened and far outweighed by the many negative *in vivo* studies. The situation that a pesticide is "positive *in vitro*, negative *in vivo*" is not unusual.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
07.07.2016	Austria		Individual	236
Comment received				
The classification of glyphosate as "non-mutagenic" is scientifically not justified and is in contrast to the conclusions which were made by the IARC experts				

(vol. 112, "Evaluation of five organophosphate insecticides and herbicides", 2015).
The conclusions of the BfR/EFSA are based more or less solely on results of chromosomal aberration and micronucleus assays (MN) with one specific type of target tissue (bone marrow). It is known that bone marrow MN and CA studies are insensitive to highly dangerous groups of genotoxic carcinogens such as nitrosamine and aromatic amines. The fact that it was found that glyphosate reaches in small amount the bones cannot be taken as a convincing indication that the test is reliable in regard to the prediction of the effects of this compound as it is unknown if potential genotoxic metabolites (which are not known at present) reach the target cell. A large number of bone marrow data experiments were conducted by the producers are evaluated and were partly published. Almost all of them yielded negative results indicating that glyphosate is indeed not genotoxic in this specific test. However, positive results were obtained in mammalians in comet assays and adduct measurements. The authorities criticised that these results maybe irrelevant as only high doses were tested and no dose response relationships were studied. However, this is only speculative assumption and meaningful studies should be conducted, to find out if this hypothesis is justified or not. The observations which were made so far are in my opinion by no means irrelevant! Notably, positive results were seen in these experiments in tissues other than the bone marrow! Furthermore, strong evidence for genotoxic properties of glyphosate comes from more than twenty individual studies with non-mammalian vertebrates. These findings are partly listed in the IARC monograph (vol. 112, "Evaluation of five organophosphate insecticides and herbicides", 2015), additionally seven newer studies appeared in last years. The findings of all these experiments were completely ignored by the BfR/EFSA which is a serious mistake in the light of the similarity of the metabolic activation/detoxification pathways of xenobiotics in fish, amphibians and mammals (including humans). Also other pathways such as DNA repair mechanisms are highly similar. Almost all highly relevant classes of genotoxic carcinogens cause DNA damage and cancer in non-mammalian vertebrate species as well.
Notably, also positive results of plant bioassays were completely ignored by the authorities. The sensitivity of these tests is relatively high but, unfortunately, their specificity is quite low (Ennever, Andreano et al. 1988). This indicates that a positive result should be taken seriously.
Finally, there is also some evidence for genotoxic activity of glyphosate in vitro. In lymphocytes, findings in chromosomal aberration studies and other tests are controversial. Clear positive results were obtained in certain experiments with other indicator cells. One published study with HepG2 and one with a buccal cell line yielded positive results in terms of MN and comet induction. The study with the buccal derived cells was realized by Koller et al. (2012) in my laboratory and clearly positive findings were obtained with very low concentrations which are identical to those which can be expected in sprayers and in workers in factories. Furthermore, a positive result was obtained in an additional newer study (available in abstract form only) by Kasuba et al. (2016) with HepG2 cells (Kasuba. V et al, ICOETOX, Portugal, June 2016). Notably, these cells have contrast to blood cells active phase I and phase II enzymes and reflect the activation of certain genotoxins were better than lymphocytes and other stable cancer cell lines which are currently used (Knasmüller, Schwab et al. 1999).
Results of human studies with exposed individuals are difficult to interpret. In

most of them co-exposure with other pesticide enharden firm conclusion. However, at least two studies were conducted with defined glyphosate exposure. One yielded a moderately positive result, in the other are clearer effect was seen in exposed individuals, however the exposure was not well quantified in this latter investigation.
Taken together, the findings show convincingly that there is limited evidence for genotoxic activity of the compound. The assumption that it is harmless comes from only relatively unreliable in vivo assays with bone marrow cells and the conclusion that the compound can be classified at present as not mutagenic, is simply a mistake. Further experiments are warranted which allow to draw clear conclusions:
(i) Clarification, if glyphosate indeed causes positive effects in comet assays in different organs other than the bone marrow in vivo
(ii) Additional experiments should be conducted to elucidate its potency in blood and liver cells. Such experimental model are available and should be used.
(iii) Further attempts should be made to clarify the modes of action by which the coumpond may leads to DNA damage (such as adduct formation and oxidative damage which were found it in some studies.)
(iv) Experiments if glyphosate exposure causes genetic damage in exposed humans are of particular interest. It should be very easy to conduct such investigations with workers who are employed in industries that produce the herbicide.
I am (Siegfried Knasmüller) plan to publish the critical commentary concerning to the ongoing controversy between scientists and regulators in September or in October this year in Mutation Research Section Genetic Toxicology for which I am serving at present as chief editor.

Refernce:
Ennever, F. K., G. Andreano and H. S. Rosenkranz (1988). "The ability of plant genotoxicity assays to predict carcinogenicity." Mutation Research/Genetic Toxicology 205(1-4): 99-105.
Knasmüller, S., C. E. Schwab, S. J. Land, C. Y. Wang, R. Sanyal, M. Kundi, W. Parzefall and F. Darroudi (1999). "Genotoxic effects of heterocyclic aromatic amines in human derived hepatoma (HepG2) cells." Mutagenesis 14(6): 533-540.
Koller, V. J., M. Fürhacker, A. Nersesyan, M. Mišík, M. Eisenbauer and S. Knasmueller (2012). "Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells." Archives of toxicology 86(5): 805-813.

Dossier Submitter's Response

Firstly, glyphosate is neither a nitrosamine nor an aromatic amine. Secondly, concern about "potential genotoxic metabolites" is not justified since glyphosate is not metabolised in mammals (except of a very small amount that is transformed into AMPA, most likely by gut bacteria).
With regard to the more general parts of this comment, it must be emphasised that genotoxicity of pesticides is investigated according to legally binding data requirements by means of studies which have to be conducted in compliance with OECD test guidelines under GLP conditions. Normally, their results are relied on. The assessment of glyphosate should follow these same principles. If

there is real concern about the sensitivity of the current test methods, efforts should be made to replace them with better tests. The DS is of the opinion that there is sufficient data available to draw a final conclusion on glyphosate.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Austria	GLOBAL 2000	BehalfOfAnOrganisation	237
Comment received				
The Dossier submitter (DS) concluded: „No hazard classification of glyphosate for mutagenicity is warranted according to CLP criteria" (Dossier, p. 59). More specifically the DS concluded that "because of the negative results in the majority of the in vitro and in vivo mutagenicity tests including nearly all guideline-compliant standard assays and since positive findings were mainly confined to indicator tests, categories 1B and 2 also do not apply". For the reasons given below, this conclusion is wrong. The proper application of a weight of evidence approach inevitably leads to a conclusion that supports the IARC assessment of "strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic" (IARC 2016, p. 78). The hazard classification of glyphosate for mutagenicity needs to be re-considered, and the existing evidence for genotoxicity must be regarded as supportive of the exisiting evidence for carcinogenicity. The conclusion by the DS that the majority of in vitro and in vivo tests was negative is wrong. Here, it is contested for two important reasons. FIRSTLY, out of the 40 negative tests conducted or commissioned by industry, 16 were based on the Ames test, i.e. conducted in bacteria. However, since many years it is known that glyphosate possesses antibiotic properties, even a patent had been filed describing these properties (US Patent Number 7771736). Its mode of action is the inhibition of the EPSP synthase an enzyme which is present in plants as well as bacteria. In the Ames test mutagenicity is assessed by the growth of nutrient (histidine) deficient strain Salmonella typhimurium. The principle of the test is to identify reverse mutations by the test substance (i.e. glyphosate) by the growth of bacteria after making them histidine-producing due to reverse mutation. But it can be expected that the antibacterial action of glyphosate will prevent the growth of back-mutated Salmonella, thereby producing systematically false negative results. To avoid such a falsification the Ames test is considered not suitable for testing antibiotics (Luijten et al. 2016). Therefore, the DS has a strong bias when he uses 16 Ames tests as part of argument that "negative results in the majority of the in vitro and in vivo mutagenicity tests" exist and at the same time dismisses the many positive findings in eukaryotic "non-standard" test systems (insect, plant, worm, fish etc.). In the Addendum to the RAR which claims to compare the findings of the assessments of the RAR and the IARC monograph, 13 publications demonstrating genotoxic effects of glyphosate and glyphosate-based formulations were not even mentioned (for the 13 publications cf. Attachment "List of references"). SECONDLY, it needs to be taken into consideration that negative results from micronucleus assays do not necessarily mean that there is no genotoxic effect. As Koller et al. (2012) point out: "Thus, false negative results were obtained in				

bone marrow MN studies with representatives of certain classes of potent DNA-reactive carcinogens such as heterocyclic aromatic amines and nitrosamines (Hayashi et al. 1989). Therefore, the lack of a positive result with G and R in these experiments does not prove that the test compounds are safe in regard to their genotoxic properties."

In summary, strong evidence exists that identifies genotoxic action of glyphosate as a mechanism of carcinogenicity. Moreover, the hazard classification assessment on mutagenicity made by the DS is severely biased and needs to be revisited to ensure a proper weight of evidence approach.

References:
Hayashi, M.; Sutou, S.; Shimada, H.; Sato, S.; Sasaki, Y.F.; Wakata, A. (1989): Difference between intraperitoneal and oral gavage application in the micronucleus test. The 3rd collaborative study by CSGMT/JEMS.MMS. Collaborative study group for the micronucleus test/mammalian mutagenesis study group of the environmental mutagen society of Japan. Mutat. Res. 223: 329–344.

Koller, V.L.; Fürhacker, M.; Nersesyan, A.; Mišik, M.; Eisenbauer, M.; Knasmueller, S. (2012): Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells. Archives of Toxicology 86: 805-813.

Luijten, M.; Olthof, E.D.; Hakkert, B.C.; Rorije, E.; van der Laan, J.-W; Woutersen, R.A.; van Benthem, J. (2016): An integrative test strategy for cancer hazard identification, Critical Reviews in Toxicology, DOI: 10.3109/10408444.2016.1171294

Dossier Submitter's Response

This comment compiles arguments which we have addressed in our responses to comments 228, 235 and 236. Please refer to our responses there.

RAC's response

Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium	PAN Europe	BehalfOfAnOrganisation	238

Comment received

Glyphosate was first patented as an antibiotic compound which explains why the Ames test has come negative in all 16 industry assays reported in p. 45. Once these tests are taken out and peer-reviewed scientific studies are considered, the evidence (DNA damage) show that glyphosate is genotoxic.

Dossier Submitter's Response

Antibiotic activity would not automatically cause a negative Ames test but a reduced background growth or cytotoxicity. Even if only Ames tests are relied on in which concentrations up to 5000 µg/plate could be used (still the majority), there is a sufficient number to exclude a genotoxic potential in bacteria. DNA damage was mainly shown in so-called indicator tests in non-

standard test systems. Assessment of pesticides for genotoxicity is based on an internationally agreed selection of methods which, in the vast majority, were negative in case of glyphosate.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
10.06.2016	Germany		Individual	239
Comment received				
Glyphosat ist als mutagen einzustufen. Begründung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege („strong evidence") dafür gefunden, dass der Stoff „(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht". Der Deutsche Ärztetag stellt ferner dazu fest: „Für gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unschädlicher Schwellenwert," und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verlängern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/				
Dossier Submitter's Response				
You are refered to the response to comment 231. In the CLH dossier, the available studies have been taken into consideration. Taking a weight of evidence approach, glyphosate (active substance) is not considered genotoxic. Accordingly, speculations on a threshold or its absence and resulting consequencies are not relevant.				
RAC's response				
Noted. See response to comment no 228.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	240
Comment received				
The report describes in an excellent way the tests performed to conclude on the genotoxic potency of glyphosate. The considerations made during the evaluation of all the tests are well documented which makes the conclusion of no classification for germ cell mutagenicity evident. We agree with the statement on page 43 not to use studies with formulations as for positive results it remains unclear whether the effects are due to glyphosate or the other ingredients. The use of non-standard systems is often hampered by the lack of validation making the value of the result unclear. The same may apply to some indicator tests and in addition, they are overruled by more apical endpoints. Although these studies are often very useful to determine the mechanism behind observed effects in the absence of more apical effects their benefit is limited. We prefer to use a strategy based on the three genotoxic endpoints, gene mutations, structural chromosome aberrations and numerical chromosome aberrations. Tests that measure primary DNA damage (indicator tests) are exclusively used as additional, supportive evidence; a conclusion will				

never be made on these indicator tests. This opinion is based on reports, predominantly performed by CRO's commissioned by industry (producer), done under GLP conditions according to OECD test guidelines. In addition, the CLP criteria are based on results in mammalian species. These reports are the best there is and cover all three genotoxic endpoints. In conclusion, we agree with the argumentation of the DS in this opinion, the conclusions reached on the tests used for this evaluation and with the proposal for no classification for germ cell mutagenicity.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Norway		MemberState	241
Comment received				
Several studies, including the comet assay, mentioned in the IARC evaluation, show that glyphosate technical have a DNA damaging potential. The regulatory studies show negative results. However, these do not include a comet assay. In our opinion, a regulatory comet assay should have been conducted to clarify the reported DNA damaging potential of technical glyphosate.				
Dossier Submitter's Response				
Such a test might be useful for clarification since, according to the CLP guidance, it would provide supporting information. However, even a positive *in vivo* Comet assay would be probably not sufficient to contravene the many negative *in vivo* studies (mainly micronucleus assays). Moreover, the Comet assay is not part of the European data requirements so far. We think that there is enough information available to conclude on the genotoxicity of glyphosate.				
RAC's response				
Noted. See response to comment no 228.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	242
Comment received				
Glyphosat ist als mutagen einzustufen. Begründung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege („strong evidence") dafür gefunden, dass der Stoff „(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht". Der Deutsche Ärztetag stellt ferner dazu fest: „Für gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unschädlicher Schwellenwert," und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verlängern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-				

detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/
Dossier Submitter's Response
You are refered to the response to comment 231. In the CLH dossier, the available studies have been taken into consideration. Taking a weight of evidence approach, glyphosate (active substance) is not considered genotoxic. Accordingly, speculations on a threshold or its absence and resulting consequencies are not relevant.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	243
Comment received				
Glyphosat ist als mutagen einzustufen. Begründung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege („strong evidence") dafür gefunden, dass der Stoff „(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht". Der Deutsche Ärztetag stellt ferner dazu fest: „Für gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unschädlicher Schwellenwert," und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verlängern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/				
Dossier Submitter's Response				
You are refered to the response to comment 231.				
RAC's response				
Noted. See response to comment no 228.				

Date	Country	Organisation	Type of Organisation	Comment number
07.06.2016	Germany		Individual	244
Comment received				
Glyphosat ist als mutagen einzustufen. Begr&#65533;ndung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege (&#65533;strong evidence&#65533;) daf&#65533;r gefunden, dass der Stoff &#65533;(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht&#65533;. Der Deutsche &#65533;rztetag stellt ferner dazu fest: &#65533;F&#65533;r gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unsch&#65533;dlicher Schwellenwert,&#65533; und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verl&#65533;ngern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/				

Dossier Submitter's Response
You are refered to the response to comment 231.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	245
Comment received				
Glyphosat ist als mutagen einzustufen. Begründung: Die IARC hat im Rahmen ihrer Bewertung von Glyphosat starke Belege („strong evidence") dafür gefunden, dass der Stoff „(...) DNA- und chromosomale Defekte in menschlichen Zellen verursacht". Der Deutsche Ärztetag stellt ferner dazu fest: „Für gentoxische Effekte besteht nach derzeitiger wissenschaftlicher Meinung kein unschädlicher Schwellenwert," und fordert deshalb die Zulassung von Glyphosat als Pestizid-Wirkstoff nicht zu verlängern. Vgl.: http://www.bundesaerztekammer.de/presse/pressemitteilungen/news-detail/aerzte-fordern-widerruf-der-glyphosat-zulassung/				
Dossier Submitter's Response				
See our response to previous comment 242.				
RAC's response				
Noted. See response to comment no 228.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	246
Comment received				
I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest". I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.				
Dossier Submitter's Response				
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become				

publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Spain		MemberState	247
Comment received				
When the weight of evidence is considered, it can be concluded that glyphosate is not mutagenic. A classification for mutagenicity is not warranted according to the CLP criteria.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted. See response to comment no 228.				

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Umweltinstitut München e. V.	BehalfOfAnOrganisation	248
Comment received				
Mutagenität Die Internationale Agentur für Krebsforschung (IARC) der Weltgesundheitsorganistation (WHO), prüfte den Wirkstoff Glyphosat anhand der ihr zur Verfügung stehenden (ausschließlich öffentlich zugänglichen Studien) und kam zu dem Ergebnis, dass -starke Beweise für eine gentoxische Wirkung durch eine Exposition mit Glyphosat („strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic") -starke Beweise für die Auslösung von oxidativem Stress durch eine Exposition mit Glyphosat, AMPA und auf Glyphosat basierenden Formulierungen („strong evidence exists that glyphosate, AMPA, and glyphosate-based formulations can induce oxidative stress") vorliegen. Durch die genotoxische Wirkung werden Schädigungen des Erbguts verursacht, die krebserzeugende Prozesse auslösen können. Oxidativer Stress stört die Reparatur- und Entgiftungsfunktion der Zellen, was unter anderem zu DNA-Schäden führen kann. Quelle •IARC (2015): Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncology, 20 March 2015, http://dx.doi.org/10.1016/S1470-2045(15)70134-8 http://monographs.iarc.fr/ENG/Monographs/vol12/mono112-09.pdf				
Dossier Submitter's Response				
The DS is aware of the IARC´s opinion and has addressed it in the CLH dossier.				

RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	249
Comment received				
It is scientifically invalid TO APPLY EVIDENCE FOR ONE HYPOTHESIS TO ANOTHER! But you do this repeatedly when evaluating DNA and chromosome damage (mutagenicity & clastogenicity), saying the preponderance of negative findings for the former invalidates the positive findings for the latter (e.g. the intro and the conclusions on M classification in the draft CLH report, pp. 43 & 59). THIS HAS TO CHANGE; IT ALMOST GIVES THE APPEARANCE OF OUTRIGHT SCIENTIFIC FRAUD. You must re-evaluate the total evidence for clastogenicity from the ground, on up; leaving out irrelevant findings in bacteria which do not even have chromosones!) and any other DNA mutation findings, positive or negative. Even after IARC's intervention caused Germany to reassess all the missed literature in the DAR, I don't know of the almost half of the 20 or so published positive findings of genotoxicity (e.g. #122: vitro genotoxicity @ 1/10,000 dilution: population body levels). While I have not compared your and any missed genotoxicity findings to the guidelines for classifying as category 1 or 2; in general the mandatory re-assessment of clastogenicity will work to upgrade technical glyphosate towards a classification. Any positive in vivo findings, including in somatic cells towrs cat. 1B, cannot be dismissed except by many, and related, negative findings. Last I repeat: if other pesticides have had their FORMULATION findings considered in their C&L (by RAC or others in EU), you are obliged to treat glyphosate similarly				
Dossier Submitter's Response				
We have expressed our view on genotoxicity in sufficient depth in the CLH dossier and explained why classification is not appropriate. For pesticides, classification is not based on data obtained with formulations but with the active substance, however, we agreed that there is a need for testing formulations also.				
RAC's response				
Noted. See response to comment no 4, 68 and 228.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	250

Comment received
Muta 2, 341 more details see: attachment
Dossier Submitter's Response
There is no new information but this comment reflects the fact that different views on the same studies/data are possible. It is up to ECHA and its RAC to decide.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	Sweden		MemberState	251
Comment received				
The SE CA considers that existing evidence could be discussed as meeting the criteria for Muta. 2 for glyphosate based on the following: - Statistically significant increase of DNA damage (as measured by Comet assay) was reported in the liver and blood cells of Balb C mice administered glyphosate via drinking water for 14 days. There was a clear dose-response in the liver (at 40 mg/kg bw/day and 400 mg/kg bw/day). - DNA damage in the liver was also found in mouse in vivo studies of DNA strand breaks and also DNA adducts after i.p. administration, thus showing a consistency with the results from Comet assay. - Comet assays in vitro in human fibroblast GM 39, human fibrosarcoma HT1080, Hep-2 cells, human lymphocytes, buccal carcinoma TR146 were positive. However, as study summaries were not available and the statement of the DS concluding that the reliability of the interpretation of the results were questionable due to presence of high rate of early apoptotic/necrotic cells could not be confirmed, these results are considered to be of limited value. - The positive findings of DNA damage in vivo is supported by results from micronucleus studies in vitro. Thus, the Comet assay in vivo confirms the genotoxic potential observed in vitro. - In contrast, mouse micronucleus tests (OECD TG 474) via oral administration were negative in seven studies (six in mouse and one in rat). Only one study showed a statistically significant increase in micronucleus formation in high dose female mice (Suresh 1993). It is noted that none of the studies show effect (reduction) in the proportion of immature erythrocytes among total erythrocytes in the bone marrow and therefore it may be questioned whether the substance is reaching the bone marrow in sufficient amount to detect a mutagenic effect. However, ADME data shows that the substance is found at detectable levels in bone marrow. - Furthermore, two mouse micronucleus tests (OECD TG 474) after i.p. administration were positive, whereas five studies were negative. - Two chromosomal aberration tests (OECD TG 475), one in mouse after oral administration and one in rat after i.p. administration, were negative. - Since the chromosomal aberration studies and micronucleus tests detects effects in bone marrow these mainly negative results do not contradict the in vivo findings in liver of DNA damage in Comet assays and studies of DNA strand breaks and DNA adducts in vivo in the liver. - Two dominant lethal test in rat and mouse, respectively, were negative.				

However, this method is considered to be a rather insensitive method with not enough power to detect potential germ cell mutagenicity. Therefore, the results from this test cannot overrule the mutagenic findings in somatic cells, justifying classification of glyphosate in category 2. - Toxicokinetics data show that glyphosate is found at detectable levels in reproductive organs. To summarize, there are consistent findings of DNA-damage in vivo in the liver, which is not overruled by studies in bone marrow which are equivocal but mainly negative.
Dossier Submitter's Response
It is clear that genotoxicity will be thoroughly evaluated by ECHA and its RAC. The partly contradictory data are correctly mentioned in this comment. The DS concluded that glyphosate was not genotoxic, taking a weight of evidence approach. If there would have been DNA damage of sufficient extent in the liver, one would expect some more pronounced liver toxicity including tumours in the long-term studies. This was not the case.
RAC's response
Noted. See response to comment no 228.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	252
Comment received				
see above				
Dossier Submitter's Response				
No response possible.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	253
Comment received				
The GTF agrees with the CLH report that the substantial data on developmental and reproductive toxicity (DART) fails to demonstrate any basis for classification (CLH report, page 114). This position is consistent with recent detailed evaluations by regulatory authorities (Canadian PMRA, US EPA, RMS Germany - RAR, EFSA and the Japanese FSC) and the published literature. Detailed review publications which note a lack of glyphosate related reproductive effects in DART studies (Williams, 2000; Williams et al., 2012; Kimmel et al, 2013) are discussed in the appended report. Expert critique of published DART literature by Williams et al. (2000) identified technical deficiencies and provides context for a thorough weight of evidence evaluation which aligns with the CLH report. Glyphosate registrants in the United States were subject to US EPA Tier 1 Test Orders under the Endocrine Disruptor Screening Program (EDSP). The results				

across the battery of studies demonstrated an unequivocal conclusion that glyphosate does not have potential to interact with the endocrine pathways. There were no endocrine mediated effects due to glyphosate exposures noted across the eleven Tier 1 EDSP studies. Based on the results from the EDSP Tier 1 studies, the US EPA weight of evidence evaluation concluded that Tier 2 studies for glyphosate are not recommended.
Dossier Submitter's Response
Noted. However, this comment does not provide any new information.
RAC's response
Noted. See response to comment no 259.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	254
Comment received				
Please include all studies and make them public to make sure none of them could be only representative of (very) profitable interests.				
Dossier Submitter's Response				
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.				
RAC's response				
Noted. See response to comment no 4.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	255
Comment received				
Antoniou, M., Ezz El-Din Mostafa Habib, M., Howard, C. V., Jennings, R.C., Leifert, C., Onofre Nodari, R., Robinson, C. Fagan, J. (2011): Roundup and birth defects: Is the pub-lic being kept in the dark? Earth Open Source				
Dossier Submitter's Response				
This paper is known to the DS. We do not agree with the conclusions of the authors. All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	256

Comment received
- At least four confirmations of found toxicities (p. 501-2, 578-9, 647 (reprotox), 651 (teratogen)), some at low dose, dismissed by industry (sometimes at RMS urging) by claiming that industry's personal database of «historical negative controls» suffer exactly the maladies found, even though the experiment's own negative control animals did not. - Organs analysis simply not performed at the low & mid dose (3 & 10 mg/kg d-) in a low dose industry study (pg. num. lost, but was in reprotox section). This may save money, but it also can disappear a lot of low dose toxicity. - Male reproductive organ damage in F1, not repeated at 10x & 100x the dose, so dismissed even though lower dose is more relevant to most exposures; p. 573-4. - Similarly, heart defects found at 20 mg/kg d- and higher, but not at highest dose, so industry & RMS dismiss it as not a dose/response (p. 651), though it confirms other results. ---
Dossier Submitter's Response
It seems that this comment (as others from the same source) is rather related to the RAR than to the CLH dossier under review. Unfortunately, its meaning is difficult to understand. If we understood it right, it is mainly about dose response and "low dose effects". The DS is still of the opinion that developmental findings in a study should demonstrate a dose-response or occur only at the top dose level to become allocated to the test substance. This principle has been followed in the evaluation of glyphosate, too.
RAC's response
Noted. See response to comment no 259.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Netherlands		Individual	257
Comment received				
The bees are threatened with extinction. When they all die, we all will.				
Dossier Submitter's Response				
Thank you for comment. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on direct effects of substances on the aquatic environment. There is no hazard class in the CLP regulation to classify glyphosate for indirect effects on biodiversity or bees.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	258
Comment received				
Indirect effects of damage in micronuclei to reproductivity should be further eamined.				
Dossier Submitter's Response				

The vast majority of micronucleus assays were negative, even at very high dose levels. There is no need for further research on that issue.
RAC's response
Noted. See response to comment no 228.

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	259
Comment received				
Repr. 2, H361, but there is a strong tendency to Repr. 1B, H360 more details see: attachment				
Dossier Submitter's Response				
There is no new information but this comment reflects the fact that different views on the same studies/data are possible. It is up to RAC to decide.				
RAC's response				
Fertility: RAC concludes that the six 2-generation reproductive toxicity studies and the study by Dai *et al.*, (2016) did not provide any evidence of effects of glyphosate exposure on fertility or on the male and female reproductive organs. Further, no effects on sexual maturation was reported in the studies where this parameter was assessed. The effects seen were of equivocal relevance and were confined to high dose levels (>1000 mg/kg bw/d) in the presence of parental toxicity. RAC concluded that a classification for fertility is not considered justified. Developmental toxicity: The six studies studies with rats with doses up to 3500 mg/kg bw/d showed insufficient evidence of developmental toxicity following *in utero* exposure to glyphosate including reduced ossification and skeletal malformations at maternally toxic doses, with LOAEL for developmental effects ≥ 1000 mg/kg bw/d. In the seven developmental toxicity studies in rabbits, limited evidence of cardiovascular malformations, skeletal malformations post-implantation loss and embryo-foetal death were reported following *in utero* exposure to glyphosate. These effects were reported at low incidences and in some of the studies without a clear dose-response. Further, these effects were not consistently reported in the seven developmental toxicity studies in rabbits, and for cardiac malformations more than one of these malformations were seen in the same foetus. Skeletal malformations evident as craniofacial malformation was reported in one study. However, it is noted that no similar malformations were recorded in the other acceptable studies at dose levels up to and including 500 mg/kg. The effects were reported in the presence of severe maternal toxicity including death of the does and GI tract intolerance to glyphosate exposureIt should be kept in mind that some of the deaths were related to mis-gavage and				

therefore not substance related. Further, 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. Overall, RAC concluded that no classification for developmental toxicity is justified. For further information on the evaluation of reproductive toxicity, please refer to the opinion by RAC.

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	United Kingdom		Individual	260
Comment received				
Glyphosate should be classed a reproductive toxin in category 1B as there is sufficient evidence in animals from the industry studies on pure glyphosate (see the attached paper, Antoniou et al 2012). ECHA note - The following attachment was submitted with the comment above: *antoniou2012_terat.pdf* Journal articles are not confidential as such, however, ECHA does not publish them on the website due to Intellectual Property Rights.				
Dossier Submitter's Response				
This paper is known to the DS. We do not agree with the conclusions of the authors.We have tried to improve reporting of the developmental effects in the RAR nonetheless.				
RAC's response				
Noted. See response to comment no 259.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Belgium	PAN Europe	BehalfOfAnOrganisation	261
Comment received				
Regulatory reproductive toxicity studies rarely use low environmental levels of exposure. In the dossier, some low dose effects have been dismissed in certain developmental experiments with scientifically unfounded reasoning e.g. dilated hearts at 20 mg/Kg (rabbit experiment, Suresh et al., 1993) and embryonic deaths at 50 mg/kg (rabbit experiment, Brooker et al., 1991). Especially in the 2nd experiment (1993) it says that the concurrent control had remarkably low number of deaths (5.7%) and therefore the results shouldn't be considered valid. A control group with a low number of deaths certainly must mean that the experiment went well and the results are valid. Scientific literature shows that glyphosate and glyphosate-based products have effects on the reproduction of experimental animals at very low and environmentally relevant concentrations that cannot be ignored. Furthermore, the reported effects on their endocrine system could explain the observed reproductive effects. Please find attached a review of the literature with the				

specific references. ECHA note - The following attachment was submitted with the comment above: *for ECHA.zip*
Dossier Submitter's Response
Currently there is no evidence that glyphosate has an endocrine disrupting effect. There is no reason to assume low dose effects would not occur at higher dose levels or that there is an absence of a dose response. Even in well-conducted studies, a certain percentage of fetal deaths is normal.
RAC's response
Noted. See response to comment no 259.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	262
Comment received				
We agree with no classification for effects on fertility or development. However, a conclusion regarding effects on or via lactation is missing although the available data do not warrant such a classification.				
Dossier Submitter's Response				
Thank you for the comment and your general support. In fact, we did not consider a need for such a conclusion since there were no findings in the multi-generation studies which might have suggested adverse lactational effects on the pups. In addition, elimination of glyphosate via the milk was not measured in rats but was found extremely low in dairy cows and could not be shown by validated methods in lactating women.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
28.06.2016	Norway		MemberState	263
Comment received				
The developmental toxicity study in the rabbit (Brooker et al., 1991 TOX9552391) shows a treatment-related increase in a variety of malformations of the heart and great vessels (interventricular septal defects, retroesophageal right subclavian artery and other malformations) at 450 mg/kg/day. An increase, above the historical control data, in the retroesophageal right subclavian artery, was also seen at 150 mg/kg/day. The increase in the occurrence of this malformation did not follow a clear dose-response. However, a possible dose-response relationship for this effect may have been masked by the limited number of fetuses at the highest dose level. A treatment-related increase in the post-implantation loss was seen at 450 mg/kg/day. This parameter was also statistically significant increased at 50 and 150 mg/kg/day, but without a clear dose-response.				

The developmental toxicity was observed in the presence of maternal toxicity. One death occurred at 450 mg/kg/day. However, the maternal toxicity observed in the remaining dams consisted of a slight reduction in the body weight gain associated with a reduction in food consumption. An increase in the occurrence of soft/liquid faeces was also observed, but gross-examination at necropsy did not identify any treatment-related findings. Based on the increase in the occurrence of the cardiovascular malformations and in the post- implantation loss in this study, glyphosate should be considered for a classification as a developmental toxicant. This is in accordance with the 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, 2013): Annex I: 3.7.2.4.2 `Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies.
Dossier Submitter's Response
For glyphosate, all available developmental studies (here: in rabbits) should be taken into account. Based on the overall picture, we don't think that classification for developmental toxicity is appropriate. This is explained in length in the CLH dossier. If only the Brooker (1991) study which is referred to in the comment was available, the outcome of the evaluation might have been different.
RAC's response
Noted. See response to comment no 259.

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Germany		Individual	264
Comment received				
The developmental toxicity study in the rabbit (Brooker et al., 1991 TOX9552391) shows a treatment-related increase in a variety of malformations of the heart and great vessels (interventricular septal defects, retroesophageal right subclavian artery and other malformations) at 450 mg/kg/day. An increase, above the historical control data, in the retroesophageal right subclavian artery, was also seen at 150 mg/kg/day. The increase in the occurrence of this malformation did not follow a clear dose-response. However, a possible dose-response relationship for this effect may				

have been masked by the limited number of fetuses at the highest dose level. A treatment-related increase in the post-implantation loss was seen at 450 mg/kg/day. This parameter was also statistically significant increased at 50 and 150 mg/kg/day, but without a clear dose-response. The developmental toxicity was observed in the presence of maternal toxicity. One death occurred at 450 mg/kg/day. However, the maternal toxicity observed in the remaining dams consisted of a slight reduction in the body weight gain associated with a reduction in food consumption. An increase in the occurrence of soft/liquid faeces was also observed, but gross-examination at necropsy did not identify any treatment-related findings. Based on the increase in the occurrence of the cardiovascular malformations and in the post- implantation loss in this study, glyphosate should be considered for a classification as a developmental toxicant. This is in accordance with the 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, 2013): Annex I: 3.7.2.4.2` Based on pragmatic observation, maternal toxicity may, depending on severity, influence development via non-specific secondary mechanisms, producing effects such as depressed foetal weight, retarded ossification, and possibly resorptions and certain malformations in some strains of certain species. However, the limited number of studies which have investigated the relationship between developmental effects and general maternal toxicity have failed to demonstrate a consistent, reproducible relationship across species. Developmental effects which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be unequivocally demonstrated on a case-by-case basis that the developmental effects are secondary to maternal toxicity. Moreover, classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality, significant post-natal functional deficiencies

Dossier Submitter's Response

For glyphosate, all available developmental studies (here: in rabbits) should be taken into account. Based on the overall picture, we don't think that classification for developmental toxicity is appropriate. This is explained in length in the CLH dossier. If only the Brooker (1991) study which is referred to in the comment was available, the outcome of the evaluation might have been different.

RAC's response

Noted. See response to comment no 259.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	265

Comment received

I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest".
I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and

recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.
Dossier Submitter's Response
All studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
14.07.2016	Germany	Umweltinstitut München e. V.	BehalfOfAnOrganisation	266
Comment received				
Reproduktionstoxizität Für den Zusammenhang zwischen der Störung der menschlichen Fortpflanzung und Glyphosat liegen Nachweise durch die Ergebnisse Epidemiologischer Studien vor. Diese Studien wurden im Renewal Assessment Report des BfR und in der EFSA Conclusion als „nicht zuverlässig" beurteilt. Begründung dafür waren unter anderem fehlende Daten, die in den Studien tatsächlich aber differenziert erhoben worden waren. In den Studien konnten zum Teil signifikante Zusammenhänge zwischen der Exposition mit Glyphosat und Fehlgeburten festgestellt werden. In die Bewertung durch die ECHA mit einzubeziehende, fälschlicherweise als nicht zuverlässig beurteilte Studien •Savitz DA, Arbuckle T, Kaczor D et al. Male pesticide exposure and pregnancy outcome. Am J Epidemiol 1997; 146:1025-1036. •Arbuckle TE, Lin Z, Mery LS. An exploratory analysis of the effect of pesticide exposure on the risk of spontaneous abortion in an Ontario farm population. Environ Health Perspect 2001; 109:851-857. •Garry VF, Harkins ME Eriksson LL et al. Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Perspect 2002; 110 (suppl. 3):441-449.				
Dossier Submitter's Response				
Please refer to our response to comment no. 159.				
RAC's response				
Noted. See response to comment no 259.				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	267
Comment received				
Dai P, Hu P, et al. 2016 (Acta Histochemica) is a new, male reprotoxicity in rats oral dosing of technical glyphosate for a semi-chronic (5 week) experiment. Though a bit small it is not underpowered (good significance statistics); its methods are adequately described, and it covers the same broad (if unrealistic) dose range as you favorite methods--in short effectively an OECD TG methodology. It clearly (in D/R manner) finds testicular, sperm and male sex hormone deficits at the high dose, 500 mg/kg d- which is industry's alleged most reliable study NOAEL (i.e for the ADI). That no reprotox effects occurred at the two lower doses, or in other reprotox endpoints, strongly supports the causitive nature of the effects. All three findings support a n effect by glyphosate ultimately on sperm production--serious, indeed. This new study--not suffering from the scientific deficiency of industry's financial need to find no effects--clearly puts glyphosate into the Reprotox category 1B classification (and makes DE/EFSA's ADI invalid--in fact the a LOAEL ~10 mg/kg d- in one of Monsanto's rabbit study was ignored in selecting 500 mg/kg d- as the NOEAL!). - Germany has ignored throughout five of seven published findings of technical glyphosate endocrine disruption (and a couple of the handful or reprotox findings published by academe). RAR missed or not, these note these low dose reprotox & ED findings (keyed to the M&D report): - Thongprakaisang et al.'13, 10(- 12)M (pptrillion) E2 mediatd prolifertn @ < popultn. burden. - #93: Teratogen to chickens & frogs, 1:5000 dilution of product of glyph alone.				
Dossier Submitter's Response				
No effects on male fertility have been found in a number of well-conducted multi-generation studies. Effects on cells or on tadpoles and chickens in the egg (using artificial administration routes) cannot contravene or outweigh the developmental studies in rodents.				
RAC's response				
Noted. See response to comment no 259.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	268
Comment received				
BE CA would like to emphasize some effects and inconsistencies in the provided documents : ☐- In Takahashi (1997, ASB2012-11495) study, the NOAEL for reproductive toxicity is 30 000 ppm in the CLH report, however, in the Renewal Assessment Report, the RMS chose to reduce the NOAEL to 6000 ppm based on the decrease of the gestation index (95.8, 95.8, 87.5 and 79.2 for controls, 1200,				

6000 and 30 000 ppm, respectively). Considering that the gestation index is already slightly decreased at 6000 ppm, BE CA suggests to select the NOAEL at the lowest dose (1200 ppm).

☐- In Suresh (1993, TOX9300009) study, the dose level of 10 ppm mentioned in the CLH report is not presented in the Renewal Assessment Report. Furthermore, BE CA would like to emphasize an inconsistency in the Renewal Assessment Report: at necropsy, a higher incidence of emaciated pups was observed at the mid dose level in F1 and at the high dose in F1 and F2 pups. However, the reported body weight of these pups was inconsistent with the previous information (for F1 pups, on Day21, the mean BW of mid dose group was higher than in controls).

☐- In a Monsanto study (1981, TOX9552385), which was mentioned in the Renewal Assessment Report but not in the CLH dossier, in the reproductive parameters, the mating index of the F2 generation was lower than controls in each treated-groups for each mating intervals. In F1 generation, the lowest pregnancy rate was seen in the highest dose group. Furthermore, concerning the viability index, it was significantly lower during the day 4-21 interval in each treated-groups, compared to the control. Information is lacking to interpret these changes, indeed, it is not clear which generation is affected.

☐- In Brooker et al. (1992, TOX9552389) study, the total litter size in the highest dose group (10000ppm) was lower than control across all four matings and remained lower than control group at day 4 in three of the four matings. Thus, BE CA does not agree with the proposed NOAEL for reproductive toxicity (10 000 ppm) and suggests the mid dose level (3000 ppm) as the NOAEL.

☐- In Suresh (1991, TOX9551105) study, very little information is available in the CLH report, however, the mentioned developmental NOAEL (< 1000 mg/kg bw/d) is lower than the maternal toxicity NOAEL (1000 mg/kg bw/d) considering the reduction of ossification in pups.

☐- In Coles and Doleman (1996, ASB2012-11499) study, an increase in post-implantation loss was observed in the mid and high dose level groups (3.7, 3.6, 11.5* and 12.1% at 0, 50, 200 and 400 mg/kg bw/d, respectively).

☐- In Tasker and Rodwell (1980, TOX9552392) study, significant inconsistencies were noted between the CLH report and the Renewal Assessment Report: species, duration of exposure, doses, …

☐- In Brooker et al. (1991, TOX9552391) study, post-implantation loss rate was significantly increased at the highest dose and out of the historical control range. Moreover, BE CA is not convinced by the reasoning on the severity of interventricular septal defect given in the Renewal Assessment Report: there was an increase of the incidence of the malformation in the highest dose (450 mg/kg bw/d) slightly outside the historical control data. Furthermore, the Renewal Assessment Report mentioned that this modification was observed in conjunction with clear signs of maternal toxicity, however, BE CA does not agree (the reduced food consumption, the BW and clinical signs data were not significantly affected).

☐- In Suresh et al. (1993, TOX9551106) study, in the Renewal Assessment Report, BE CA does not agree with the RMS comment on the dilated heart effect: it is mentioned that the absolute number of affected fetuses and litters were quite small and did not show a marked difference between the treated-groups. However, the provided data showed an important modification (% of fetuses with dilated heart was 0, 5.1, 5.2 and 17.9 and the % of litter incidence was 0, 23.1, 16.7 and 40.0 at 0, 20, 100 and 500 mg/kg bw/d, respectively). ☐- Several studies were only mentioned in the summary tables of the CLH report, thus, it is not easy to verify and interpret the indicated NOAELs: Reyna (1990, TOX9552387), Antal (1985), Brooker et al. (1991, TOX9552393), Suresh (1991, TOX9551105), Anonym (1981, TOX9650160), Tasker et al. (1980, TOX9552390). Furthermore, some published papers noted potential reproductive effects: -☐ Romano et al. (2011), "Glyphosate impairs male offspring reproductive development by disrupting gonatropin expression", Arch. Toxicol. 86, 663-673: the authors observed change in sexual behavior, significant increases in the testosterone and estradiol concentrations, in LH mRNA expression and in total and daily sperm production at 50 mg with glyphosate-based commercial formulation of Roundup Transorb. ☐- Dai et al. (2016), "Effect of glyphosate on reproductive organs in male rat", Acta Histochemica (article in press): the authors noted significant decrease of the total sperm count at 500 mg/kg bw, a trend to decrease in testosterone, progesterone and estradiol concentrations in a dose-dependent manner, and histological modifications with glyphosate (active ingredient grlyphosate, purity 90%). ☐- Dallegrave et al. (2007), "Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats", Arch. Toxicol. 81, 665-673: the authors found a significant increase of the percentage of abnormal sperm at the puberty, a significant decrease of the daily sperm production and sperm number during adulthood, a dose-dependent decrease in testosterone concentration at puberty and histological changes in the testis. -☐ Cassault-Meyer et al. (2014), "An acute exposure to glyphosate-based herbicide alters aromatase levels in testis and sperm nuclear quality", Environmental Toxicology and Pharmacology 38, 131-140: the authors reported alterations in sperm parameters. In conclusion, BE CA suggests to consider a potential classification as REPR. 2.
Dossier Submitter's Response
Thanks for the comment. However, the discussion on classification and labelling is not about the NOAELs/LOAELs in individual studies. The inconsistencies could not be verified by the DS. The rabbit findings have been reported and discussed in length in the RAR and in the CLH dossier. The corresponding arguments have not been listed here. Published research cannot be taken into account when the test items were formulations.
RAC's response
Noted. See response to comment no 259.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	269
Comment received				
effectivity always depends on the presence of surfactants which enable glyphosate to penetrate cellular barriers in plants and even more in lungs.				
Dossier Submitter's Response				
People are always exposed to formulations of glyphosate containing surfactants but not to the active substance. However, there is no evidence of respiratory sensitisation.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	France		Individual	270
Comment received				
Please include all studies and make them public to make sure none of them could be only representative of (very) profitable interests.				
Dossier Submitter's Response				
There are no available studies on respiratory sensitisation. All other studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	271
Comment received				
The GTF agrees with the CLH report stating no classification for respiratory sensitization is warranted (CLP report, page 30). There is no information supporting a classification for respiratory sensitization. The last 40 years of glyphosate use has not yielded evidence of respiratory sensitization in humans.				
Dossier Submitter's Response				
Noted. Thanks for the support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Italy		Individual	272

Comment received
I am one of 2 million citizens who have signed a petition calling on you to ensure that your review of glyphosate is "transparent, based on independent studies, and evaluated by independent researchers without conflicts of interest". I urge you to go beyond business as usual and help restore public faith in the EU. This requires a process that adheres to the highest scientific standards and recognises the extraordinary interest in glyphosate. As recommended in an open letter by 94 top scientists, your assessment should include all studies used in the International Agency for Research on Cancer's report, and all studies you cite should be available for public scrutiny. This assessment will define your and ECHA's reputations, and have tremendous consequences for us and our environment: we look forward to hearing details of how you will conduct this review, and to seeing your results.
Dossier Submitter's Response
There are no available studies on respiratory sensitisation. All other studies have been thoroughly reviewed as can be seen in the CLH dossier and the RAR, including studies from the scientific literature and also those not commissioned by the manufacturers. The studies and their results are reported in detail and justifications are given as to why glyphosate is not considered a carcinogen. Whether the studies provided by industry could or should become publically available in full, is a legal, not a scientific question. The decision on that is not up to the competent authorities of the DS nor up to ECHA's RAC.
RAC's response
Noted. See response to comment no 4.

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Germany		Individual	273
Comment received				
Benachour, N., Séralini, G. E. (2009): Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells. Chem. Res. Toxicol. 22, 97–105.				
Dossier Submitter's Response				
The paper is known to the DS and was mentioned in the RAR.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Spain		MemberState	274
Comment received				
We agree with the dossier submitter to maintain the current classification in CLP Regulation: "Eye irritation Category 1" with the signal word "Danger" and the hazard statement H318 "Causes serious eye damage".				

Dossier Submitter's Response
Thanks for the support.
RAC's response
Noted. RAC agreed to retain the classification for Eye Damage, category 1, H318.

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	275
Comment received				
In the CLH report, glyphosate was classified as an eye irritant and labeled with the hazard phrase H318 ("Causes serious eye damage"). Eye irritation is not unexpected for a neat acidic material such as glyphosate acid. When glyphosate is used in realistic exposure scenarios such as ready-to-use formulations, which contains mostly water, there may be slight eye irritation but it generally fails to meet the criteria for classification. Furthermore, glyphosate acid is not commercially available by itself but is sold as a formulated product. All glyphosate based formulations contains glyphosate salts of a more neutral pH, as reflected in the eye irritation study results of "slightly irritating" with glyphosate salts (RAR Vol 3, Table B.6.2-25), which do not trigger classification for eye irritation.				
Dossier Submitter's Response				
Classification of the active substance, i.e., glyphosate acid is needed. The proposal of the DS is maintained.				
RAC's response				
RAC agreed to retain the classification with Eye Damage, category 1, H318. The evaluation of the classification of formulations is not relevant to the discussion of the classification of glyphosate.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	276
Comment received				
The available eye irritation studies show a dependency of the severity of the effects on the washing of the eyes. Washing of the eyes after 1 hour (allowed for solids under certain conditions for OECD TG 405 (paragraph 18)) resulted in slight or no irritation. Washing after 24 hours seem to induce moderate and reversible irritation but without washing severe and irreversible effects were observed. The CLP and GHS criteria do not define whether the scores for washed or unwashed eyes should be determinative. Therefore, we agree with category 1 based on the effects observed in the unwashed eyes.				
Dossier Submitter's Response				
Thanks for the support.				
RAC's response				
Noted. RAC agreed to retain the classification with Eye Damage, category 1, H318.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	277
Comment received				
Eye Dam. 1, H318 more details see: attachment				
Dossier Submitter's Response				
Thanks for the support.				
RAC's response				
Noted. RAC agreed to retain the classification with Eye Damage, category 1, H318.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	278
Comment received				
The CLH Report refers to maternal rabbit mortality after repeat oral exposures in rabbit developmental toxicity studies only as relevant for STOT-RE Category 2 classification. The rabbit model cited as a basis for the proposed STOT-RE Category 2 classification (CLH report, page 42) is not relevant to humans. In rabbit developmental toxicity studies, nutritional integrity of orally dosed rabbits is compromised by gastrointestinal effects (e.g., loose stools) preventing the animals from performing the essential practice of coprophagy (eating feces). In such instances where coprophagy is not feasible in rabbits, maternal toxicity is a consequence of poor nutrition due to reduced vitamin, nitrogen, protein and sulfur intake, normally available in the nocturnally formed soft fecal pellets. In addition, maternal toxicity observed in rabbits is not consistent with the weight of evidence across multiple glyphosate studies conducted in species not reliant upon coprophagy; mice, rats and dogs. The maternal toxicity finding in orally dosed pregnant rabbits is not a consequence of systemic toxicity, since a complete absence of toxicity is noted in repeat dose dermal toxicity studies in rabbits themselves. These dermal toxicity studies, dosed up to 5000 mg/kg bw/day, result in much higher systemic doses than the oral gavage studies in rabbits. Multiple rabbit dermal toxicity studies consistently report the limit dose as the NOAEL. Systemic glyphosate exposures resulting from 5000 mg/kg bw/day is determined to be 133 mg/kg/day, based on measured dermal absorption values in vitro with rabbit skin (2.66%). Relative to oral dosing, applying the accepted 20% oral absorption for glyphosate (CLH report, page 14), an equivalent oral dose of 665 mg/kg bw/day to reach this systemic dose yields no systemic toxicity when obtained via the dermal route of exposure. Since glyphosate is essentially unmetabolized in mammals, systemic toxicity is independent of the				

route of exposure and therefore the maternal toxicity noted in oral gavage studies is attributable to a local GI tract effect – not systemic toxicity. The CLP guidance section, Annex I: 3.9.2.8.1(e) notes that "substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification". In the case of glyphosate, maternal toxicity in rabbits is species-specific for oral dosing only. The basis of the observed maternal toxicity in orally dosed rabbits is not consistent with dermal rabbit toxicity studies at higher systemic doses, repeat dose toxicity studies in other mammalian species at much higher doses and is not relevant to humans. Unlike rabbits, a balanced human diet does not require the practice of coprophagy. Therefore, the proposed STOT-RE Category 2 classification for glyphosate is neither scientifically robust nor justified. For more details refer to the appended document: "Glyphosate-GTF Response to Toxicology Comments in CLH report_15July2016".
Dossier Submitter's Response
Similar to comment 118. The proposal (STOT RE 2) is kept since mortality is the most severe maternal effect which may occur in a study of this type. The pregnant rabbit turned out to be the most sensitive animal model. There is no reason to disregard these findings. The underlying mechanism and whether the effect is local rather than systemic is not relevant for classification.
RAC's response
Mortality amongst rabbits has been used to justify the proposal for classification of glyphosate for STOT RE 2 by the DS. According to CLP, Annex I, section 3.9.2.7.3, morbidity or death resulting from repeated or long-term exposure can be taken into account for classification as STOT RE. However, CLP further states that "Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites". Following exposure to glyphosate, mortality in rabbits is considered to either be related to mis-dosing, infections or diarrhea and the possible mechanism of caecotrophy and recycling of glyphosate. No mortalities were recorded in the rat studies. In addition, bioaccumulation and over-whelming of detoxification mechanisms by repeated exposure as a mechanism of toxicity is not likely for glyphosate. On the basis of a weight of evidence approach and with due consideration of all data from the short-term, long-term, reproductive and rabbit developmental studies, RAC concludes that classification for STOT RE is not justified for glyphosate.

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Spain		MemberState	279
Comment received				
In agreement with the dossier submitter, the Spanish Competent Authority considers necessary the additional classification as STOT RE, Category 2 for Glyphosate based on maternal mortality observed in the developmental studies in rabbits, with the hazard statement H373 (may cause damage to organs through prolonged or repeated exposure).				

Dossier Submitter's Response
Thanks for the support.
RAC's response
Noted. See response to comment no 278.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	280
Comment received				
- Salivary gland toxicity is a common finding in **industry**'s glyphosate studies, but an industry lab that previously had found some did not report(or it was ignored by industry) more such in newer study; p. 460.				
Dossier Submitter's Response				
This comment relates to the RAR but not to the CLH dossier. It has no relevance for classification and labelling.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
30.06.2016	Germany	Ministry of Environment, Lower Saxony, Germany	BehalfOfAnOrganisation	281
Comment received				
STOT RE 2, H373 - but there is a strong tendency to STOT RE 1, H372 more details see: attachment				
Dossier Submitter's Response				
Based on CLP guidance (values), category 2 is more appropriate.				
RAC's response				
Noted. See response to comment no 278.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	282
Comment received				
BE CA supports the classification as STOT RE 2, H373.				
Dossier Submitter's Response				
Thanks for the support.				
RAC's response				
Noted. See response to comment no 278.				

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France	ANSES, National Autority	BehalfOfAnOrganisation	283
Comment received				
STOT RE p 42: Given the maternal mortality observed in the rabbit developmental toxicity studies and the dose levels at which this effect occurred, classification STOT RE 2 H373 is justified				
Dossier Submitter's Response				
Thanks for the support.				
RAC's response				
Noted. See response to comment no 278.				

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	284
Comment received				
Two new neurotox findings support five known published neurotox findings on technical glyphosate (3 of which EFSA/DE/GTF never found) (see PAN-Europe's 'Missed & Dismissed report). See my attachment of new studies. And among previous neurotox is this low dose one (keyed to the M&D report): - #113: 1:250 dilution LD50, neurotox & synergism w/ 2 common pesticides; detailed mechanism elucidated.				
Dossier Submitter's Response				
Unfortunately we do not understand this comment.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	Netherlands		MemberState	285
Comment received				
We agree with proposed classification as STOT RE 2 without target organ based on the observed maternal mortality in the developmental studies in rabbits at dose levels at or above 100 mg/kg bw/day in multiple studies. No such effects or other effects relevant for STOT RE were observed in rats, mice and dogs at relevant dose levels. As it is unknown which of the test species is more relevant to humans the most sensitive species is determinative for the classification.				
Dossier Submitter's Response				
Thanks for the support.				
RAC's response				
Noted. See response to comment no 278.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
16.07.2016	Belgium	Monsanto Europe S.A.	BehalfOfAnOrganisation	286
Comment received				
Based on reliable long-term (chronic) toxicity data available for three trophic levels, glyphosate does not meet the classification criteria of a "Long-term (chronic) aquatic hazard." The study used for proposed classification as "Long-term (chronic) aquatic hazard, Category 2" is based on a short-term zebrafish study on sac-fry, that does not meet the requirements of a long-term (chronic) early-life stage (ELS) assay, and fails the validity criteria for a reliable toxicity test for chronic aquatic hazard classification. Instead, other available reliable long-term fish studies should be considered, including a 255-day fish full life-cycle study resulting in a NOEC of >25.7 mg/L based on no effects on survival, growth, development and reproduction and an 85-day trout ELS study resulting in a NOEC of 9.6 mg/L based on no effects on growth, development and survival. Therefore, based on the lowest reliable long-term (chronic) toxicity values for glyphosate that are available from three trophic levels (fish, crustacean, algae/aquatic plants), glyphosate does not meet classification criteria of a "Long-term (chronic) aquatic hazard" in accordance with classification categories for hazardous to the aquatic environment. Attached is a comprehensive review of the existing reliable and relevant aquatic toxicity studies that have been evaluated in the context of a weight of evidence approach to conclude that glyphosate does not meet the classification criteria of a "Long-term (chronic) aquatic hazard." For more details refer to the appended document: "Glyphosate-GTF Response to Ecotoxicology Comments in CLH report_15July2016".				
Dossier Submitter's Response				
Thank you for comment. The CLH-report for glyphosate contains valid and reliable acute and chronic toxicity values from studies for aquatic organisms. Based on the lowest reliable long-term (chronic) toxicity values for glyphosate that are available from three trophic levels (fish, crustacean, algae/aquatic plants), glyphosate fulfils classification criteria of "toxic to aquatic life with long lasting effects" in accordance with classification category Aquatic chronic 2 (H411) for hazardous to the aquatic environment (0.1 mg/L <NOEC≤ 1.0 mg/L).				
RAC's response				
RAC agrees with the DS's response.				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Ireland		Individual	287
Comment received				
I have not data to hand regarding hazards to the aquatic environment. However, when a compound is so prevalent in our agricultural ecosystems and is leaking into our aquatic ecosystems, we have to take seriously concerns that such levels of exposure could upset ecological balances. I do not believe there				

has been an adequate effort to assess these hazards. We need such studies, given the very high levels of glyphosate use in our agricultural systems.
Dossier Submitter's Response
Thank you for comment. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008. Classification and labelling provisions for environmental hazards are based on direct effects of substances on the aquatic environment. There is no hazard class in the CLP regulation to classify glyphosate for indirect effects on biodiversity.
RAC's response
RAC agrees with the DS's response. The classification is based only on the hazard properties of the substance. Exposure is not in the scope.

Date	Country	Organisation	Type of Organisation	Comment number
12.07.2016	France	ANSES, National Autority	BehalfOfAnOrganisation	288
Comment received				
P118: FR agrees with the environmental classification proposal (Aquatic chronic 2). FR notes that the data package available in the CLH report does not contain several of the toxicity studies used at European level for the renewal of glyphosate (cf EFSA Journal 2015;13(11):4302). However this does not change the classification proposal.				
Dossier Submitter's Response				
Thank you for your comments and agreement with environmental classification and labelling.				
RAC's response				
Indeed, in the RAR additional tests are reported for each trophic level, which support the environmental classification as Aquatic Chronic Cat. 2				

Date	Country	Organisation	Type of Organisation	Comment number
15.07.2016	Belgium		MemberState	289
Comment received				
BE CA is of the opinion that NOEC is < 1 mg/l. Neurotoxicity in fish : ☐- In an in vitro study (Sandrini et al, 2013) with pure glyphosate, cholinesterase activity was inhibited in a concentration-dependent manner in brain (Danio rerio and Jenysia multidentata), muscle (D.rerio, Jenysia multidentata and Perna perna) and gill (Perna perna) fractions. IC50 ranged from 0.52mM for P.perna muscle to 8.43mM for J. multidentata brain. ☐- In a recent article (Roy et al, 2016) it is was found that glyphosate acid (technical grade) induced neurotoxicity in zebrafish. In this study structural changes to the fore, mid and hindbrain of embryonal zebrafish were considered by examining gross structural morphology as well as morphological abnormalities by studying gene expression changes via in situ hybridization, immunohistological and transgenic approaches. Authors found that loss of				

brain ventricle delineations, general cephalic reduction and reduction in the eye region occurred between 50 and 75µg/l. It is suggested that glyphosate is neurotoxic for the forebrain and midbrain regions by altering the expression of key gene regulators in development but not for the hindbrain. Furthermore, the gene expressions are not attributable to delayed development as treated embryos met developmental milestones accordingly and in sync with control treatment at 50µg/ml.
This study cannot be considered as a chronic study per se as 5h old embryos were exposed for 24h. But despite the sublethal effects seen after such a short exposure period during the most vulnerable stage of fish, it is likely that NOEC will be lower than 50 µg/l.
☐- The toxicity of glyphosate on ovaries of zebrafish (Danio rerio) was examined by Armiliato et al (2014). They found that subcellular and molecular impairments may affect reproduction in female fish. After exposure of 65µg/l of glyphosate for 15 days a significant increase in diameter of oocytes was observed. The presence of concentric membranes, appearing as myelin-like structures, associated with the external membranes of mitochondria and with yolk granules was found when ovarian ultrastructure was examined. Immunohistochemistry and immunoblotting revealed greater expression of SF-1 in the oocytes, which suggests a relationship between oocyte growth and SF-1 expression.

Genotoxicity in fish :
☐- Guilherme et al (2012) examined DNA and chromosomal damage in fish (Anguilla Anguilla L.) after exposure to 17.9 and 35.7 µg/l glyphosate for 1 and 3 days resp. The comet assay was applied to blood cells, either as the standard procedure or with an extra step involving DNA lesion-specific repair enzymes in an attempt to clarify DNA damaging mechanisms. This study confirmed the genotoxicity potential of glyphosate.
Potential non-specific DNA damage in both concentrations of glyphosate, expressed as GDI (Genetic Damage Indicator) was seen.
GDIFPG results demonstrated significantly higher levels of damage for all the treatments in both exposure lengths. This evaluation of the additional breaks resulting from oxidised purine identified also the highest glyphosate concentration (3 days exposure) as genotoxic, which did not occur for GDI parameter.
GDIEndoIII data revealed significantly higher DNA damage for all the treatments in both exposure lengths, when compared with the respective control.
Overall oxidative DNA damage showed significant difference compared to control for all concentrations and exposure times.
☐- Webster et al, 2015 examined the global mechanism of toxicity in the liver of Brouwn trout (Salmo trutta) by exposing these fish for 14d to 0; 0.01; 0.5 and 10 mg/l of glyphosate. Transcriptional profiling demonstrated the induction of alterations of many of the complex, interacting signaling pathways that control cellular stress response, more in particular apoptosis. Also evidence was found that indicates an increase in cell proliferation and cellular turnover and an up-regulation of metabolic process.

Degradation product:
☐- DT50 whole system of glyphosate was determined in several water/sediment studies and ranged from 13.82d to > 301d. The max. amount

of AMPA, the major degradation product of glyphosate, detected in water/sediment system was 16% (water phase), 19% (sediment) and up to 27% (total system) and leads to potential exposure of sediment dwelling organisms to this degradation product. The persistence of AMPA is higher than glyphosate, therefore Guilherme et al (2014) examined DNA and chromosomal damage in fish (Anguilla Anguilla L.) after exposure to AMPA for 1 and 3 days resp. The genotoxicity of AMPA was investigated via Comet and erythrocytes nuclear abnormalities (ENA) assays.
The Comet assay showed potential non-specific DNA damage in both concentrations (11.8 and 23.6 µg/l). Furthermore it was concluded that oxidative damage was more difficult to repair when compared to non-specific damage.
It can be concluded that glyphosate and his breakdown product AMPA show a similar pattern in DNA-damaging effect. However, the recovery capacity from damaged caused by AMPA is different than that by glyphosate. No difference in oxidative DNA damage was shown between AMPA and glyphosate.

Development (oyster and frog)
☐- The study of Akcha et al, 2012 demonstrated a significant increase in abnormal D-larva in oyster versus control after exposure for 24h to 5 µg/l of glyphosate ($p<0.001$). Also here it is likely that NOEC will be lower when exposure period is prolonged.
☐- Lithobates catesbeianus tadpoles , exposed for 96h to 1 mg/l of glyphosate (purity 99.2%) showed significant reduction in V O2 at 80 and 40 mmgHg, significant thickened epidermis and the presence of several layers of overlapping small cells and some chromatid fragmentation (Risoli et al, 2016). The epithelial hyperplasia comprised several layers of undamaged cells, therefore it is suggested that the increase of thickness was a response to avoid systemic absorption of glyphosate.
The epidermal hypertrophy might explain the significant reduction in V O2 as the O2 diffusion distance to O2 uptake increased.

Bioaccumulation :
☐- It is mentioned in the CLH report that no measured bioaccumulation date are available. However a 56d bioconcentration study with Lepomis macrochirus (Forbis 1989) resulting in a BCF = 1.1 ± 0.61 (steady state after 120 ± 59 d, flow-through) is mentioned in the EFSA report and further described in the RAR addenda. Furthermore in the RAR addenda it is recorded that different bioaccumulation studies with glyphosate have been conducted with different aquatic organsisms which achieved a BCF of max. 10.
☐- In a literature study (Wang et al, 1994), bioaccumulation was studied in carp and Tilapia and BCF ranged from 10 to 65.5.
Those values are far below the classification trigger of 500 but a BCF study has prevalence on a octanol-water partition coefficient (logKow) and thus those bioaccumulation studies should be described in the CLH dossier in order to have the whole picture on the potential of bioconcentration in aquatic organisms.
References:
Akcha F., Spagnol C. Rouxel; Genotoxicity of diuron and glyphosate in oyster spermatozoa and embryos, Aquatic Toxicology, 2012, 107, pp 104-113

Armiliato N, Ammar D., Nezzi L. Straliotto M., Muller Y.M.R. & Nazan E.M., Changes in Ultrastructure and Expression of Steroidogenic Factor-1 in Ovaries of Zebrafish Danio rerio Exposed to Glyphosate, Journal of Toxicology and Environmental Health, Part A : Current issues, 2014,Volume 77, issue 7

Guilherme S., Santos M. A., Barroso C., Gaiva˜o I., Pacheco M.; Differential genotoxicity of Roundup ® formulation and its constituents in blood cells of fish (Anguilla anguilla):considerations on chemical interactions and DNA damaging mechanisms, Ecotoxicology, 2012, 21 pp 1381-1390

Guilherme S., Santos M. A., Gaiva˜o I., Pacheco M.; DNA and chromosomal damage induced in fish (Anguilla Anguilla L.) by aminomethylposphonic acid (AMPA)- the major environmental breakdown product of glyphosate, Environ Sci Pollut Res, 2014, 21 pp. 8730-8739

Risoli R.Z., Abdalla F.C., Costa M.J., Rantin F.T., McKenzie D.J. & Kalinin A.L; Effects of glyphosate based herbicides Roundup Original ® and Roundup Transorb ® on respiratory morphophysiology of bullfrog tadpoles, Chemosphere, 2016, 156, pp 37-44

Roy M.N., Carneiro B., Ochs J.; Glyphosate induces neurotoxicity in zebrafish, Environmetal Toxicology and Pharmacology, 2016, 42, pp 45-54

Sandrini J.Z, Rola R.C., Lopes F.M., Buffon H.F., Freitas M.M., Martins C.D.M.G. da Rosa C.E.; Effects if glyphosate on cholinesterase activity of the mussel Perna perna and the fish Danio rerio and Jenynsia multidentata : in vitro studies, 2013, Aquatic Toxicology 130-131, pp 171-173

Uren Webster T.M. and Santos E. M.; Global transcriptomic profiling demonstrates induction of oxidative stress and of compensatory cellular stress responses in brouwn trout exposed to glyphosate and Roundup, 2015, BioMed Central Genomics, 16:32, pp1-14

Wang Y.S., Jaw C.G., Chen Y.L.; Accumulation of 2,4-D and glyphosate in fish and water hyacinth, 1991, Air and Soil Pollution, 74, pp 397-403

Dossier Submitter's Response

Thank you for comment.
The most above mentioned studies (excluding literature study of Wang et al,1991 and literature from 2015) were considered/evaluated in RAR, Appendix to B.9 (evaluation of peer reviewed literature) revised July 2015.
"Several studies investigated changes in the metabolic and enzymatic state in aquatic organisms (Fan, et al. 2013, Sandrini, et al 2013, Syedkolaei, et al. 2013, Gholami-Seyedkolaei, et al. 2013). A few studies associated exposure to commercial formulation with inhibition of AchE activity in brain and/or muscle of aquatic organisms (Cattaneo et al. , 2003, Lajmanovich et al., 2011, Sandrini et al., 2013). These changes in biochemical parameters could be used as biomarkers, because a dose-response association between commercial formulation treatment and enzymtic activity was found in the different tissues.

Available publications studying biochemical, metabolic and histopathological effects were only considered as additional information, since endpoints were not considered to indicate additional implications for growth, survival or reproduction of aquatic vertebrates that are not already covered by the standard risk assessment. Many tests using fish have been conducted in order to investigate the genotoxic and cytotoxic potential of glyphosate towards different aquatic organisms (Nwani et a. 2013, Moreno,et al. 2014, De Souza Filho, et al. 2013, de Castilhos Ghisi, et al. 2012, Vera-Candioti, et al 2013, Guilherme, et al. 2012 and 2014). Most of these studies were performed with ecologically realistic concentration of the herbicide. In most cases, again commercial formulations have been used which does not allow to discriminate, which compound of the commercial formulation could be responsible for the observed effects. Nevertheless, it has also been reported that glyphosate itself caused oxidative DNA damage in cells of *A. anguilla* exposed under laboratory conditions (Guilherme et al.,2012).Taking together, these results revealed that both glyphosate itself as well as the formulated products should be carefully monitored considering their potential impact on aquatic biota. Moreover, it seems that a transition from traditional ecotoxicological methods determining acute toxicity with endpoints on mortality and reproduction can be complemented by methods taking into account biochemical parameters. No concluding informations are available at the moment to decide wether alterations might impair normal organ functioning. Therefore, the studies have limited value to conclude on the relevance at a the population level. Nevertheless biochemical biomarkers allow the examination of specific target organs, including gills, kidney and liver and blood that are responsible for vital functions." Accordingly these results (considered as additional information) were not described at the CLH report for classification and labelling for glyphosate, because valid results of aquatic studies with aquatic organisms (including vertebrates) according to standardised test methods (OECD/EU guidelines) or internationally validated and accepted test methods were available. Regarding bioaccumulation there are validated data available from RAR and EFSA report (Forbis,1989) with BCF = 1.1 ± 0.61 (steady state after 120 ± 59 d, flow-through) and from RAR, Appendix to B.9 additional data from different bioaccumulation studies with different aquatic organisms with BCF of max. 10. By a mistake at the CLH report for glyphosate point **5.3.1.2 measured bioaccumulation data** " no data available" was written. However, all available BCF values are far below the classification trigger of 500.
RAC's response
Thank you for comments regarding the degradation product and bioaccumulation of glyphosate. Relevant information has been added to the RAC opinion. Regarding the toxicity for aquatic organisms, RAC is aware of the Addendum on the assessment of IARC Monographs Part E Ecotoxicology (October 2015) and agrees with the DS response on the relevance of the results on cited endpoints as additional information. In the CLH report, there is valid standard information to conclude on the classification.

Date	Country	Organisation	Type of Organisation	Comment number
11.07.2016	United States	R.I.S.K. Consultancy	BehalfOfAnOrganisation	290
Comment received				
Four new studies (see that attachment) add to the innumerable published findings of glyphosate (technical) on ecosystems (see my attachment). In fact the oxidative impairment finding mirrors a few others that the RAR had earlier missed (see the 'metabolic effects' row in the glyphosate table of M&D report). And amon M&D previous findings is this notable lo dose one: - #41: ~0.2 mg/kg d-: anti- oxidant enzymes (rats, 30-90 d exposure). Well over half of the dozens of published positive findings of aquatic ecotoxicity were initially missed in the RAR, notably #36, #125: Aquatic tox at 0.05 mg/L & 2 ppb.				
Dossier Submitter's Response				
Thank you for comment. There was no possibility to verify the given data or to find the attachment.				
RAC's response				
RAC agrees with the DS response.				

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	Finland		Individual	291
Comment received				
Heavy usage of glyphosate in agriculture, especially in the US, has poisoned waterways and destroyed their ecosystems. The water is used in irrigation and the dose for animals and humans increases to alarming levels. Humans are worst affected near the sprayed areas. The safety limit of glyphosate in the US is a multiple of that in Europe.				
Dossier Submitter's Response				
Thank you for comment. Please note that this information is not relevant for the environmental classification and labelling of glyphosate according to Regulation (EC) No 1272/2008.				
RAC's response				
RAC agrees with the DS's response.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
17.07.2016	France		Individual	292
Comment received				
Vous devez tenir compte des études menées sur des souris qui concluent que le glyphosate est cancérigène; ainsi que les six études tirées de registres de cas de cancer, au moment de déterminer la dangerosité du glyphosate.				
Dossier Submitter's Response				
Thank you for your comments which will be considered in the final discussion of the CLH dossier.				

A more comprehensive answer is submitted in the response on comments number 4 and 21. In support of our answer to this comment on the carcinogenicity of glyphosate, we are providing an additional assessment according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' as an Addendum to the CLH dossier, which is attached at the end of this document.
RAC's response
Noted. See response to comment no 4.

Date	Country	Organisation	Type of Organisation	Comment number
18.07.2016	UnitedKingdom		Individual	293
Comment received				

The potential risks around sub-lethal effects on bacteria from exposure to herbicides have not been widely considered by regulators within hazard identification processes or safety reviews. However, recent studies have found that exposure to some common herbicides can cause bacteria to change their response to antibiotics of clinical importance.

A 2015 report; *Sub-lethal exposure to commercial formulations of the herbicides dicamba, 2,4-D and glyphosate cause changes in antibiotic susceptibility in Escherichia coli and Salmonella enterica serovar Typhimurium* by Brigitta Kurenbach, Delphine Marjoshi, Carlos F. Amábile-Cuevas, Gayle C. Ferguson, William Godsoe, Paddy Gibson and Jack A. Heinemann tested Kamba (dicamba), 2,4-D and Roundup (glyphosate) on E. coli and Salmonella bacteria treated with one of five antibiotics; ciprofloxacin, chloramphenicol, ampicillin, kanamycin and tetracycline.

The herbicides were tested on two species of bacteria: *Escherichia coli* and *Salmonella enterica* serovar Typhimurium, both of which can cause disease in animals and humans.

It was found that the herbicide Roundup (glyphosate) raised resistance of the bacteria to aminoglycoside antibiotics (kanamycin) and fluoroquinolones (ciprofloxacin). When herbicides increased resistance, significant increases in minimum inhibitory concentration (MIC) were found; of 2-fold, and sometimes up to 6-fold, depending on the combination of species, antibiotic and herbicide. The MIC is the lowest concentration of an antibiotic which kills or inhibits the growth of a particular bacteria. Bacteria which survive exposure to an antibiotic above a certain concentration or 'clinical breakpoint' is classed as resistant to that particular antibiotic.

An increase in MIC can lead to direct adverse clinical outcomes, particularly when the MIC of a bacterium to an important antibiotic increases; such as to the fluoroquinolones, which are classified by the World Health Organization as 'critically important' in human medicine due to their importance for treating infections such as Campylobacter, Salmonella and E. coli.

A higher-than-anticipated MIC of a bacteria for an antibiotic can have dramatic effects on the success of therapy, with patients potentially receiving too little antibiotic. For example, one study found that a 2-fold change in the MIC of infecting strains was enough to cause 21% of patients to get a lower than target dose of the recommended antibiotic. And when the MIC reached a 4-fold

increase, 75% of patients failed to receive the target dose (Haeseker et al., 2013). This has implications both in terms of increasing the likelihood of selection for resistance - with numerous recent studies published finding that doses of antibiotics which are well below the MIC have the potential to select for antibiotic resistance - and also for complications arising from failed treatment. [1, 2, 3, 4, 5, 6, 7]

Exposure of bacteria to glyphosate-based herbicide formulations can change the response of common human and animal pathogens to antibiotics. The implications of this effect may also be compounded when humans are exposed to herbicides through other means.

The extent to which this response is induced may result in significant adverse clinical outcomes, and merits due consideration of the risks posed by the sub-lethal effects of glyphosate exposure on bacteria by the ECHA. Such risk assessments may require case-by-case testing of relevant bacteria and herbicides to determine the scale of this changed response.

ECHA note: The comment above was originally submitted as a separate attachment

Dossier Submitter's Response

Due to its unique mode of herbicidal action, some antibiotic activity of glyphosate may be assumed. In fact, there were effects of this compound on bacteria and some other micro-organisms, in particular when tested in isolation *in vitro*. Indeed, a U.S. patent covering antimicrobial use of glyphosate was granted even although the doses necessary to control certain infections in humans were very high. It has been also shown that the vulnerability of various bacteria species is different. These findings have been taken into consideration in the RAR (Volumes 1 and 3) and, thus, for risk assessment, but in the sections dealing with possible effects on animal health. The point of concern was the potential imbalance of the microbial communities in the digestive tract of ruminants. The DS even commissioned additional research activities to investigate a possible impact of glyphosate (i.e., a glyphosate-containing herbicide) on complex microbial communities in cattle at realistic dietary concentrations, but no adverse effects were detected (Riede *et al.*, 2016, see attached article).
A possible impact of glyphosate on the susceptibility of clinically important pathogens to antibiotics is a different and relatively recent issue which was indeed not considered in the RAR. Based on the U.S. patent, no such effects are expected at realistic exposure however research activities are under way nonetheless.
Effects of glyphosate on micro-organisms have not been considered in the CLH dossier since they are not covered by the health-related classifications of chemicals according to CLP. Such effects would be clearly more an issue for risk assessment than for classification and labelling

RAC's response

RAC concurs with the response from the dossier submitter that the effect of glyphosate on micro-organisms are not relevant for the evaluation of the classification.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (GLYPHOSATE (ISO); N-(PHOSPHONOMETHYL)GLYCINE

NON-CONFIDENTIAL ATTACHMENTS:

1. *echa consultation glyphosate.pdf.* Submitted on 18/07/2016 by Jack Heinemann. [Please refer to comment No 19]
2. *Glyphosate pathways to modern diseases.pdf.* Submitted on 17/07/2016 by Rikke Lundsgaard (on behalf of The Danish Society for Nature Conservation). [Please refer to comment No 34]
3. *Analysen und Studien.zip.* Submitted on 14/07/2016 by Christine Vogt (on behalf of Umweltinstitut München e. V.). [Please refer to comment No 69]
4. *Glyphosate-Public.7z.* Submitted on 16/07/2016 by anonymous [Please refer to comment No 118]
5. *Mesnage2015.pdf,* Submitted on 17/07/2016 by Michael Antoniou [Please refer to comment No 121]
6. *Glyphosate-ECHA-Comments-by-Consumer-Schraiber.pdf,* Submitted on 08/07/2016 by Michaela Schraiber [Please refer to comment No 128]
7. *'16 glyphos-only tox-7 selected items - PubMed.rtf,* Submitted on 07/07/2016 by Anthony Tweedale (on behalf of R.I.S.K. Consultancy) [Please refer to comment No 132]
8. *CLH - Glyphosate - BE CA.docx,* Submitted on 15/07/2016 by Els Boel [Please refer to comment No 139]
9. *Avaaz ECHA submission attachments.zip,* Submitted on 18/07/2016 by Pascal Vollenweider (on behalf of Avaaz). [Please refer to comment No 152]
10. *Appendix Greiser 18-7-2016.pdf,* Submitted on 18/07/2016 by Eberhard Greiser. [Please refer to comment No 159]
11. *mBio-2015-Kurenbach-.pdf,* Submitted on 18/07/2016 by Richard Young (on behalf of Sustainable Food Trust). [Please refer to comment No 160]
12. *Internet-Konsultation ECHA.zip,* Submitted on 30/06/2016 by Michael Braedt (on behalf of Ministry of Environment, Lower Saxony, Germany). [Please refer to comment No 168]
13. *Greenpeace_ECHA submission glyphosate_18072016.pdf,* Submitted on 18/07/2016 by Franziska Achterberg (on behalf of Greenpeace European Unit). [Please refer to comment No 179]
14. *Attachments.zip,* Submitted on 17/07/2016 by Helmut Burtscher (on behalf of GLOBAL 2000). [Please refer to comment No 182]
15. *SendToEcha.zip,* Submitted on 08/07/2016 and 15/07/2016 by Christopher Portier. [Please refer to comments No 197 and 219]
16. *Attachments 1-3.pdf,* Submitted on 16/07/2016 by Peter Clausing (on behalf of Pesticide Action Network Germany). [Please refer to comment No 215]
17. *List of References.pdf,* Submitted on 18/07/2016 by Helmut Burtscher-Schaden (on behalf of GLOBAL 2000). [Please refer to comment No 215]
18. *antoniou2012_terat.pdf,* Submitted on 17/07/2016 by anonymous. [Please refer to comment No 260]
19. *ECHA.zip,* Submitted on 18/07/2016 by Angeliki Lyssimachou (on behalf of PAN Europe). [Please refer to comment No 261]

CONFIDENTIAL ATTACHMENTS:

1. *Glyphosate-Confidential.7z .* Submitted on 16/07/2016 by anonymous [Please refer to comment No 118]

Addendum to

CLH dossier

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

Substance Name: N-(phosphonomethyl)-glycine; Glyphosate

EC Number: 213-997-4

CAS Number: 1071-83-6

Index Number: 607-315-00-8

Contact details for dossier submitter:

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Version: 1.0

Date: 28 June 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON (GLYPHOSATE (ISO); N-(PHOSPHONOMETHYL)GLYCINE

1 Introduction

As a result of the ECHA accordance check on the dossier proposing harmonised classification and labelling (CLH) for glyphosate (ISO); N-(phosphonomethyl)glycine a report was submitted to the Dossier Submitter (DS) Germany containing comments and recommendations from the ECHA Secretariat as well as those of the RAC rapporteur. The majority of these comments and recommendations have been considered and implemented into the dossier. However, one comment by the RAC rapporteur regarding Table 52 (*"Table 52: Compilation of factors to be taken into consideration in the hazard assessment"*) of the most recent CLH dossier template (http://echa.europa.eu/web/guest/support/guidance-on-reach-and-clp-implementation/formats) could not be considered due to the short time frame. In order to complete the CLH dossier as provided by Germany, the available long-term studies with glyphosate in rats and mice have now been included in such Tables (see Table 1 and Table 2).

According to the Guidance on the Application of the CLP Criteria (Version 4.1, June 2015, ASB2015-8592) the "*classification of a substance as a carcinogen requires expert judgement and consideration of many different factors (weight and strength of evidence) included in the hazard information on carcinogenicity*". Further it is stated that: "*The guidance provides an approach to data analysis rather than hard and fast rules. A stepwise approach to the classification can be taken where all the factors, both weight and strength of evidence, that may influence the outcome are considered systematically. Such approach, including consideration of these factors is outlined, in McGregor et al, 2009 and Boobis et al, 2006. Also the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical carcinogenesis' (2001), ILSI 'Framework for Human Relevance Analysis of Information on Carcinogenic Modes of Action' (Meek et al., 2003; Cohen et al, 2003, 2004) and the International Agency for Research on Cancer (IARC, 2006 - Preamble Section B) provide a basis for systematic assessments which may be performed in a consistent fashion internationally; however they are not intended to provide lists of criteria to be checked off*". With regard to the three tumour types in mice (renal tumours, malignant lymphoma and haemangiosarcoma) that have been subject to controversial discussions another systematic evaluation according to the above mentioned IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' (2001, TOX2004-2639) is presented to substantiate the DS position on the none classification of glyphosate regarding carcinogenicity.

Therefore, the following addendum consists of two sections:

(1) Two tables according to Table 52 of the most recent CLP report template, summarising the available long-term studies with glyphosate in rats (Table 1) and mice (Table 2).

(2) Systematic evaluation of three tumour types in mice in accordance to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' (2001, TOX2004-2639).

Table 1: Increase in tumour incidences in long-term feeding studies with glyphosate (active substance) in rats.

Strain, study (reference)	Tumour type with increase in at least one treated group	Multi-site responses	Dose response	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
Wistar (Wood et al., 2009; ASB2012-11490)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Wistar (Brammer, 2001; ASB2012-11488)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sprague-Dawley (Enomoto, 1997; ASB2012-11484)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Wistar (Suresh, 1996; TOX9651587)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sprague-Dawley (Bhide, 1997*; ASB2012-11489)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sprague-Dawley (Atkinson et al., 1993; TOX9750499)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Sprague-Dawley (Stout and Ruecker, 1990; TOX9300244)	Pancreas: Islet cell tumours Liver: Adenoma	Yes	No, significant increase at lowest dose only Yes, significant increase over dose range in trend test	No No	No No	Males only affected Males only affected	No	n.a.

Strain, study (reference)	Tumour type with increase in at least one treated group	Multi-site responses	Dose response	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	MoA and relevance to humans
	Thyroid: C cell adenoma		Equivocal, positive trend test at the two upper dose levels but same incidence there	No	No	Females only affected		
Sprague-Dawley (Lankas, 1981*; TOX2000-595 and TOX2000-1997)	Pancreas: Islet cell tumours	Yes	No, significant increase in adenoma at lowest dose; trend test positive for carcinoma	Equivocal	No	Males only affected	No	n.a.
	Testis: Interstitial cell tumours		Increase at the top dose level	No	No	Male-specific organ		
Not specified ("Charles River albino"; Calandra, 1974*; Z35230)	None	No	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.

* Insufficient study, not acceptable according to current standards

n.a.: not applicable

Table 2: Increase in tumour incidences in long-term feeding studies with glyphosate (active substance) on mice.

Strain, study (reference)	Tumour type with increase in at least one treated group	Multi-site responses	Dose response	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Historical control (performing lab)	Historical control data (industry databases, literature)	MoA and relevance to humans
CD-1 (ICR) (Wood et al., 2009; ASB2012-11492)	Malignant lymphoma	No	Yes, increase with dose, highest incidence (9.8%) at top dose level, trend test positive due to "zero" incidence in control	n.a. (malignant neoplasia)	No	Males only	No	Submitted but not suitable	Within (10-20% expected for male CD-1 mice)	n.a.**
Swiss albino (Kumar, 2001; ASB2012-11491)	Malignant lymphoma	Yes	Yes, increase in top dose males (38%) and females (50%) over also high control incidence (20% and 36%); positive in Z-test, negative in Fisher's exact and in trend tests	n.a. (malignant neoplasia)	No	Both sexes affected	No	Outside study control range for males (6-30%) but inside for females (14-58%)	Within (up to 50% but sexes not separated) or above (males 18-27.5%, females up to 36%), depending on source	n.a.**
	Renal adenoma	Yes	Yes, very low incidence but	No	No	Males only	No	not available	not available	n.a.

Strain, study (reference)	Tumour type with increase in at least one treated group	Multi-site responses	Dose response	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Historical control (performing lab)	Historical control data (industry databases, literature)	MoA and relevance to humans
			positive trend test							
Crj:CD-1 (ICR) (Sugimoto, 1997; ASB2012-11493)	Malignant lymphoma	Yes	Yes, increase at top dose level (12%), positive trend test	n.a. (malignant neoplasia)	No	Males only	No	Inside study control range (4-19% for males)	Within (10-20% expected for male CD-1 mice)	n.a.**
	Kidney: adenoma	Yes	Yes, slight increase at top dose level (4%), positive trend test	No	No	Males only	No	Not available	Borderline (up to 4% for adenoma)	n.a.
	Vascular system: haemangiosarcoma	Yes	Yes, slight increase at top dose level (4%), positive trend test	n.a. (malignant neoplasia)	No	Males only	No	Not available	Within (up to 12% but occurring in few studies only)	n.a.
CD-1 (Atkinson et al., 1993; TOX9552382)	Vascular system: haemangiosarcoma	No	Yes, increase at top dose level (8%), positive trend test, pairwise comparison borderline	n.a. (malignant neoplasia)	No	Males only	No	At upper edge of study control range (0-8% in six studies)	Within (up to 12% but occurring in few studies only)	
Balb/c (Bhide, 1988*; TOX9551831)	None	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	not available	not available	n.a.

Strain, study (reference)	Tumour type with increase in at least one treated group	Multi-site responses	Dose response	Progression of lesions to malignancy	Reduced tumour latency	Responses in single or both sexes	Confounding effect by excessive toxicity?	Historical control (performing lab)	Historical control data (industry databases, literature)	MoA and relevance to humans
CD-1 (Knezevich and Hogan, 1983; TOX9552381)	Kidney: adenoma and carcinoma	No	Yes, increase at top dose level (adenoma 2%, carcinoma 4%), trend test positive	Equivocal (one adenoma in the control group; one adenoma and one carcinoma at the high intermediate dose level)	No	Males only	Yes, non-neoplastic kidney and liver lesions and reduced body weight gain	not available	Within (up to 6% for carcinoma***, up to 4% for adenoma)	n.a.
CFLP/LATI, (Vereczkey and Csanyi, 1982; TOX9650154)	None	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	not available	not available	n.a.

* Insufficient study, not acceptable according to current standards
** Mouse-specific oncogenic viruses may play a role but infective status of the colonies not known
*** According to a publication (Baldrick and Reeve, 2007; ASB2016-4639) which was not cited in CLH dossier before
n.a.: not applicable

2 Evaluation of the carcinogenic response in long-term studies with glyphosate in mice, according to the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis'

According to the ECHA Guidance of the Application of the CLP Criteria (Version 4.1, June 2015, ASB2015-8592), for a systematic evaluation of the weight and strength of evidence for a carcinogenic response in experimental animals following long-term administration of glyphosate, a modified form of the IPCS 'Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis' was applied (IPCS, 2001, TOX2004-2639). This modified IPCS framework covers seven of the nine Bradford Hill criteria of causation (Hill, 1965, ASB2013-11494) in order to determine whether an association between exposure and effect might be deemed strong, consistent, specific, temporal, plausible, coherent, and to demonstrate a dose-response pattern.
The IPCS framework was only used for the assessment of the carcinogenic response in male mice regarding kidney tumours (see 2.1), malignant lymphoma (see 2.2) and haemangiosarcoma (see 2.3). For rats of both sexes, no potentially treatment-related increases in tumour incidences have been identified. The same holds true for female mice since the only reported increase in malignant lymphoma incidence in female Swiss albino mice in the study by Kumar (2001, ASB2012-11491) was well covered by the laboratory's historical control data.

2.1 Renal tumours in male mice

In three out of five carcinogenicity studies in mice, a statistically significant positive trend was observed for kidney tumour incidences in male animals when using the Cochran-Armitage trend test whereas the pairwise comparisons of control group and treated groups did not reveal statistically significant differences.

2.1.1. Strength

The actual kidney tumour incidences were 1, 0, 1, and 3 at dose levels of 0, 157, 814, and 4841 mg/kg bw per day in CD-1 mice (Knezevich and Hogan, 1983, TOX9552381), 0, 0, 0, and 2 at dose levels of 0, 165, 838, and 4348 mg/kg bw per day in CD-1 mice (Sugimoto, 1997, ASB2012-11493) and 0, 0, 1, and 2 at dose levels of 0, 15, 151, and 1460 mg/kg bw per day in Swiss albino mice (Kumar, 2001, ASB2012-11491). The association is not strong since the number of affected animals even at the highest dose levels is still low and the higher incidences of renal neoplasms in the high dose groups were not statistically different from the respective control groups when using pairwise comparisons. Furthermore, even the tumour incidence at the excessive dose of 4841 mg/kg bw per day is within the relevant historical control data (HCD) range for CD-1 mice obtained from Charles River Laboratories. The maximum incidences for kidney tumours were 4% for adenoma and 2% for carcinoma (Giknis and Clifford, 2005, ASB2007-5200) or 6% for carcinoma (Baldrick and Reeve, 2007, ASB2016-4639).

2.1.2. Consistency

The association is not fully consistent since in two out of five mouse studies, no renal neoplasms were induced at doses up to 810 mg/kg bw per day (Wood et al., 2009, ASB2012-11492) or up to 1000 mg/kg bw per day (Atkinson et al., 1993, TOX9552382). The "positive" effect was confined to dose levels far above 1000 mg/kg bw per day. Furthermore, in one study (Atkinson et al., 1993, TOX9552382), there was an apparent decrease in kidney tumour incidences (2, 2, 0, and 0 at 0, 100, 300, and 1000 mg/kg bw per day) at the mid and top dose levels. Furthermore, in the study with the highest dose levels tested (Knezevich and Hogan, 1983, TOX9552381), the largest tubular-cell carcinoma was found in the mid dose group (814 mg/kg bw per day) and not at the top dose of 4841 mg/kg bw per day.

2.1.3. Specificity

A numerically higher incidence of renal tumours was only observed in males. Female mice were exposed to similar or higher levels of glyphosate but did not develop any increase in neoplasms of the kidney. There is no explanation of this striking difference because there are no sex-specific differences in toxicokinetic behaviour (e.g., in renal excretion) or with regard to the toxicological effects of glyphosate in general. Accordingly, one might expect a positive response also in female mice if the increase in renal tumours was a true effect of glyphosate. However, no evidence of such an effect was obtained in female mice.

2.1.4. Temporality

A temporal association cannot be judged since all kidney tumours were observed at termination. At least, there is no evidence of a reduced latency or time-to-tumour interval in any study.

2.1.5. Plausibility

A plausible explanation for an association is absent since the mode of action for induction of these renal neoplasms was not established. However, it cannot be excluded that the slightly higher kidney tumour incidence of 3/50 (6%) in the Knezevich and Hogan study (1983, TOX9552381) at the maximum dose level tested (4841 mg/kg bw per day) was an artefact of excessively high doses, since the body weight gain was decreased by more than 15% compared to concurrent controls and the terminal body weight in top dose males was by 11% lower than in the control group. Moreover, there was non-neoplastic kidney pathology at this dose level (i.e., chronic interstitial necrosis in 12/50 high dose males as compared to 5/49 males affected in the control group). These considerations do not exclude the possibility that the slight increase at an exaggerated dose was somehow related to treatment but contradict the assumption of a specific carcinogenic potential. Rather, renal tumours might be a (rare) consequence of excessive toxicity.

2.1.6. Coherence

The coherence of the association is absent since female mice, even though exposed to similar or higher levels of glyphosate, did not develop any increase in renal neoplasms in any study. In addition, male and female rats did not display an association between glyphosate exposure and kidney tumours.

2.1.7. Dose response

There was no statistically significant increase in renal tumours in any study when pairwise comparisons were applied. The positive trend for kidney tumours in male mice in three studies was due to the zero incidence for kidney tumours in the control groups in two of them (Sugimoto, 1997, ASB2012-11493; Kumar, 2001, ASB2012-11491) or a low incidence of 1/49 in the third one (Knezevich and Hogan, 1983, TOX9552381). A higher control incidence of 2/50 was seen in the study by Atkinson et al. (1993, TOX9552382) which is the same as in the top dose groups in studies by Sugimoto (1997, ASB2012-11493) and Kumar (2001, ASB2012-11491). In these groups, male mice received extremely high doses of 4348 mg/kg bw/day or at least of 1460 mg/kg bw/day, respectively. A slightly higher kidney tumour incidence of 3/50 (6%) was observed only at the highest ever dose level tested (4841 mg/kg bw per day in the study by Knezevich and Hogan, 1983, TOX9552381) which is nearly five times above the limit dose of 1000 mg/kg bw per day as proposed by OECD Guidance Document No 116 for the conduct and design of carcinogenicity studies (OECD, 2012, ASB2015-8445).

2.1.8. Conclusion

To conclude, there was no convincing association between exposure to glyphosate and kidney tumour induction in male mice at dose levels not exceeding the maximum tolerated dose since the maximum tumour incidence in animals

treated up to a dose level of 4348 mg/kg bw per day did not exceed the maximum tumour incidence which was observed in concurrent control group animals (2/50, i.e. 4%). For the slightly higher tumour incidence of 3/50 (6%) at the maximum dose level of 4841 mg/kg bw per day in one of the five studies, it cannot be excluded that this was an artefact of excessively high doses. Nevertheless, even at this excessive dose, the maximum kidney tumour incidence as found in a relevant historical control database (i.e., 6%) was not exceeded.

2.2 Malignant lymphoma in male mice

In two out of four carcinogenicity studies in CD-1 mice (Sugimoto, 1997, ASB2012-11493; Wood et al., 2009, ASB2012-11492), a statistically significant trend for malignant lymphoma was observed in male animals when using the Cochran-Armitage trend test whereas the pairwise comparisons did not reveal statistically significant differences between the control group and the treated groups.
In a study in Swiss albino mice (Kumar, 2001, ASB2012-11491), a significantly increased incidence of malignant lymphoma in males and females of the high dose group was stated in the study report, based on the Z-test. However, with the more usual Fisher's exact test and with the trend test, a statistically significant difference or positive trend were not confirmed. In contrast to males, the incidences in females were well covered by historical control data from the performing laboratory.

2.2.1. Strength

In CD-1 mice, the malignant lymphoma incidences were 2, 2, 0, and 6 at dose levels of 0, 165, 838, and 4348 mg/kg bw per day (Sugimoto, 1997, ASB2012-11493) and 0, 2, 2, and 5 at dose levels of 0, 71, 234, and 810 mg/kg bw per day (Wood et al., 2009, ASB2012-11492). The association is not strong since the higher incidences of malignant lymphoma in the dosed groups were not statistically different from the respective control groups when using pairwise comparisons. Furthermore, even the tumour incidence of 12% at the excessive dose of 4348 mg/kg bw per day in the study by Sugimoto (1997, ASB2012-11493) was within the relevant HCD range for CD-1 mice obtained from the laboratory in which the study was performed (maximum 19.2%; Kitazawa, 2013, ASB2014-9146). The 5/51 incidence in the study by Wood et al. (2009, ASB2012-11492) was at least within the HCD range for CD-1 mice obtained from Charles River Laboratories (maximum 21.7%; Giknis and Clifford, 2005, ASB2007-5200).

In the study in Swiss albino mice (Kumar, 2001, ASB2012-11491), there was an increase in malignant lymphoma at the top dose level. However, the high background incidence in this strain must be taken into consideration. Statistical significance was clearly dependent of the test method applied.

2.2.2. Consistency

The association is not consistent since in two further out of 4 studies in CD-1 mice, no malignant lymphoma were induced at doses of up to 4841 mg/kg bw per day (Knezevich and Hogan, 1983, TOX9552381) or up to 1000 mg/kg bw per day (Atkinson et al., 1993, TOX9552382). For Swiss albino mice, consistency cannot be judged since only one study is available. However, it is well known from the literature that this strain is particularly prone to development of this neoplasia (Sher, 1974, Z22020; Roe and Tucker, 1974, ASB2015-2534; Tucker, 1979, Z83266).

2.2.3. Specificity

In CD-1 mice, a numerically higher incidence of malignant lymphoma was observed in males in two out of four studies. Female mice were exposed to similar or higher levels of glyphosate but did not develop any increase in this tumour type. There is no explanation for this striking difference because there are no sex-specific differences in toxicokinetic behaviour or with regard to the toxicological effects of glyphosate in general. Moreover, it is known that female CD-1 mice are usually more prone to develop malignant lymphoma (Son and Gopinath, 2004, ASB2015-2533). In line with that, control incidences in females were in fact higher than in males in glyphosate studies in this mouse strain (compare CLH report Tables 34-36). Thus, one might expect a positive response also in female mice if the increase in malignant lymphoma would have been a true effect of glyphosate but, apparently, this was not the case.

In Swiss albino mice, there was a very high background incidence in both sexes. Only one study is available. Thus, the question of specificity cannot be answered for this strain.

2.2.4. Temporality

A temporal association cannot be judged since most lymphoma were observed at termination. At least, there is no evidence of a reduced latency or time-to-tumour interval in any study.

2.2.5. Plausibility

A plausible explanation for an association is absent since the mode of action for induction of the malignant lymphoma is not established. However, it is well known that oncogenic viruses may play a role and that mouse colonies are often affected by (latent) infections.

2.2.6. Coherence

The coherence of the association is absent since female CD-1 mice, even though exposed to similar or higher levels of glyphosate and, in general, particularly prone to tumours of this type, did not develop any increase in malignant lymphoma. In addition, male and female rats did not display an association between glyphosate exposure and malignant lymphoma.

2.2.7. Dose response

In CD-1 mice, none of the malignant lymphoma incidences in the treated groups was statistically different from the respective control group when using pairwise comparisons. The positive trend for malignant lymphoma incidences in male CD-1 mice in two out of 4 studies was confined to studies with low incidences for malignant lymphoma in the concurrent control groups (i.e. 0 and 4%; Wood et al., 2009, ASB2012-11492; Sugimoto, 1997, ASB2012-11493) whereas the control group incidence for malignant lymphoma in a further study was 8% (Atkinson et al., 1993, TOX9552382). If the studies are looked at in combination, it is obvious that the malignant lymphoma incidences in animals from the 4 concurrent control groups in CD-1 mice were up to a maximum of 4/50 (8%), whereas the incidences at the 4 top dose levels were 9.8%, 12%, 12%, and 4% at 810, 1000, 4348, and 4841 mg/kg bw per day, i.e. without any evidence for a clear dose-response which one would expect when the extremely high doses and the dose spacing are taken into consideration.
In Swiss albino mice, there was some dose response but at least in females the top dose incidence was within the historical control range. In addition, statistical tests revealed contradictory results for both sexes.

2.2.8. Conclusion

On balance, there is no convincing association between exposure to glyphosate and malignant lymphoma induction in CD-1 mice, even at dose levels clearly exceeding the maximum tolerated dose (4841 mg/kg bw per day). In none of the four studies in CD-1 mice, the pairwise comparisons of control group and the treated groups revealed statistically significant differences. Furthermore, if the four studies in CD-1 mice are considered in combination, there is no evidence for a dose-response. All the group incidences were within reliable HCD ranges.
The same holds true for the increase observed in high dose female Swiss albino mice. The higher incidence in top dose males of this strain was above the upper edge of a (small) historical control database but the high background incidence must be taken into account and the effect itself is put into question by more appropriate statistical methods (Fisher's exact test and a trend test) which failed to confirm the positive result of the Z test. To conclude, there is also no convincing association between glyphosate exposure and malignant lymphoma in Swiss mice.

2.3 Haemangiosarcoma in male CD-1 mice

In two out of four carcinogenicity studies in CD-1 mice, a statistically significant positive trend was observed for haemangiosarcoma in the vascular system in male animals whereas the pairwise comparisons of control group and treated groups did not reveal statistically significant differences. No evidence of an increase was found in Swiss mice.

2.3.1. Strength

The actual haemangiosarcoma incidences were 0, 0, 0, and 4 at dose levels of 0, 100, 300, and 1000 mg/kg bw per day in the study by Atkinson et al. (1993, TOX9552382) and 0, 0, 0, and 2 at dose levels of 0, 165, 838, and 4348 mg/kg bw per day in that one by Sugimoto (1997, ASB2012-11493) resulting in a positive trend. The association is not strong since the number of affected animals even at the highest dose levels was still low and the higher incidences in the high dose groups were not statistically different from the respective control groups when using pairwise comparisons. Furthermore, the tumour incidence at the high dose of 1000 mg/kg bw/day was still covered by the historical control data of the performing laboratory even though it was at its upper edge (8%). The 2/50 (4%) incidence at the excessive dose of 4348 mg/kg bw per day is within the relevant HCD range for CD-1 mice obtained from Charles River Laboratories with a maximum of up to 12% (Giknis and Clifford, 2005, ASB2007-5200).

2.3.2. Consistency

The association is not consistent since in two further studies, no haemangiosarcoma were induced at doses up to 810 mg/kg bw per day (Wood et al., 2009, ASB2012-11492) or even up to 4841 mg/kg bw per day (Knezevich and Hogan, 1983, TOX9552381).

2.3.3. Specificity

A numerically higher incidence of this tumour type was only observed in males. Female mice were exposed to similar or higher levels of glyphosate but did not develop any increase in haemangiosarcoma. There is no explanation of this striking difference because there are no sex-specific differences in toxicokinetic behaviour or with regard to the toxicological effects of glyphosate in general.

2.3.4. Temporality

A temporal association cannot be judged since all haemangiosarcoma were observed at termination. At least, there is no evidence of a reduced latency or time-to-tumour interval in any study.

2.3.5. Plausibility

A plausible explanation for an association is absent since the mode of action for induction of haemangiosarcoma was not established.

2.3.6. Coherence

The coherence of the association is absent since female mice, even though exposed to similar or higher levels of glyphosate, did not develop any increase haemangiosarcoma in any study. In addition, male and female rats did not display an association between glyphosate exposure and this tumour type.

2.3.7. Dose response

There was no statistically significant increase in haemangiosarcoma in any study when pairwise comparisons were applied. The positive trend for this tumour in male mice in two studies was due to the zero incidences for this tumour type in the control groups. Moreover, the highest incidence (4/50) was observed at 1000 mg/kg bw/day but in two studies including much higher dose levels of 4348 or 4841 mg/kg bw/day, the respective numbers of affected animals were 2 or even 0. However, if treatment-related, one would expect a further increase in haemangiosarcoma incidence.

2.3.8. Conclusion

To conclude, there was no convincing association between exposure to glyphosate and haemangiosarcoma in male CD-1 mice since the incidences were covered by the historical control ranges and since there was no dose response when all four available studies are taken into account. There were positive trend tests in two out of four studies but pairwise comparisons did not reveal an effect.

3 References

Number	Author(s)	Year	Title Company Report No. Source (where different from company) GLP or GEP status Published or not	Vertebrate study Y/N	Owner
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2	Atkinson, C.; Strutt, A. V.; Henderson, W.; Finch, J.; Hudson, P.	1993	Glyphosate: 104 week combined chronic feeding/oncogenicity study in rats with 52 week interim kill (results after 104 weeks) IRI 438623 ! IRI 7867 ! Page: 1-1510 BVL-1345018, TOX9750499	Yes	BAY CAD CHE DOW MOD MOT NUD
3	Baldrick, P.; Reeve, L.;	2007	Carcinogenicity evaluation: Comparison of tumor data from dual control groups in the CD-1 mouse DOI: 10.1080/01926230701347330 Toxicologic Pathology, 35:562-569, 2007 ASB2016-4639	Yes	
4	Bhide, M. B.	1988	Carcinogenicity and chronic toxicity study of Glyphosate (technical) of Excel Industries Ltd., Bombay BVL-2327344, TOX9551831	Yes	BCL LUX
5	Bhide, R.M.	1997	Combined chronic toxicity / carcinogenicity of Glyphosate technical in Sprague Dawley rat 1231 GLP: No Published: No BVL-2309388, ASB2012-11489	Yes	EXC
6	Brammer, A.	2001	Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats CTL/PR1111 GLP: Yes Published: No BVL-2309368, ASB2012-11488	Yes	SYN
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13	Knezevich, A. L. Hogan, G. K.	1983	A chronic feeding study of Glyphosate (Roundup technical) in mice 77-2061 ! (BDN-77-420) BVL-1345024, TOX9552381	Yes	BAY CAD CHE DOW MOD MON MOT NUD
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15	Lankas, G. P.	1981	A lifetime feeding study of Glyphosate in rats - Data evaluation report 77-2062 BVL-2154319, TOX2000-1997		SYD
16	Lankas, G. R.	1981	Lifetime feeding study of Glyphosate (Roundup technical) in rats 77-2062 ! BDN-77-416 BVL-2309378, TOX2000-595		CAD DOW MON MOT
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25	Tucker, M. J.	1979	The effect of long-term food restriction on tumours in rodents Int. J. Cancer: 23, 803-807 (1979) GLP: Open Published: Open Z83266	Yes	
26	Vereczkey,L.; Csanyi, E.	1992	18 month carcinogenicity study of Glyphosate in mice 24 151/92 ! 8010 BVL-2331365, TOX9650154	Yes	ALK
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28	Wood, E., Dunster, J., Watson, P., Brooks, P.	2009	Glyphosate Technical: Dietary carcinogenicity study in the mouse SPL 2060-0011 GLP: Yes Published: No BVL-2309412, ASB2012-11492	Yes	NUF