01/02/2017

OPINION RESPONSE-TO-COMMENTS TABLE
(following RAC comments on the draft opinion for Glyphosate (ISO), received by 31 January 2017)

RAC Member	Comments	Rapporteurs' response to comments
	General comments	
RAC Member 1	I would like to start congratulating the rapporteurs and members of the ad-hoc working group by their excellent and job developed in this ODD. As you can see below I basically support all the rapporteurs' proposals, although I still keep some doubts for STOT-RE.	Thank you for the support.
RAC Member 2	A big thanks to the Rapporteurs for the excellent evaluation of the dossier and the inclusion of all the comments from the PC. To be short, I agree to all the endpoints. A little remark regarding eye irritation, see below. I remember that glyphosate can exist in at least three commercial stages. The glyphosate acid which is a serious eye irritant, but both the salts, isopropylamine and ammonium salts did not have the same serious eye irritant properties. However, it is not very important as all the preparations are tested for eye irritant properties.	Thank you for the support.
RAC Member 3	ODD is well written and provides clear arguments using weight of evidence analysis. However, the section on reproductive toxicity, particularly developmental toxicity needs to be supplemented with robust study summaries and clear judgment of each study results in weight of evidence analysis how these results contribute to assessment of developmental toxicity hazard. There is a minor need for some language editions, checking of concordance between explanation provided under tables and tables'	Thank you for valuable comments to the ODD. We will look into the developmental toxicity section and do the necessary changes to better justify no classification for developmental toxicity. The checking of the editorials/abbreviations etc. in the ODD will be performed in the final ODD.

RAC Member	Comments	Rapporteurs' response to comments
	content, clarification of abbreviation used to make ODD better to read. For sections covering carcinogenicity and reproductive toxicity I am providing some suggestions to improve clarity of weight of evidence analysis taking into account that many potential readers are not specialists in toxicology and hoping that these suggestions will be useful for rapporteurs.	Thank you for suggestions to improve clarity. They will be looked into.
RAC Member 4	• Human data have been obtained from people exposed to the formulation. POEA is a known ingredient of the pesticide Roundup and is suspected by some of enhancing glyphosate toxicity and of having its own toxic properties. This is frequently mentioned in the ODD. The toxic contribution of POEA to Roundup toxicity is somewhat uncertain but at least some information is available (e.g. USDA, Forest Service: Selected commercial formulation of Glyphosate – *Accord, Rodeo, Roundup and Roundup Pro.* Risk Assessment. Final Report. 1996. Online: https://www.fs.fed.us/r5/hfqlg/publications/herbicide_info/1996_glyphosate.pdf). This information could be briefly summarized in the ODD together with a RAC statement about potential uncertainties. As the information we have about POEA toxicity is limited, I propose not to stress too much the toxic contribution of POEA in the ODD. • As pointed out in another comment, the negative studies have to be subject to the same degree of scrutiny as the positive ones. I have no doubts that the DS and the rapporteurs examined the negative studies properly. Nevertheless, if any significant flaws have been detected in the negative studies, it would be good to mention this in the ODD to prevent suspicion of bias. If no flaws have been found, this should also be explicitly stated.	Due to uncertainties in the data for humans exposed to GBH, information regarding POEA has been deleted from the ODD. See also comments on this issue from [RAC Member 13] and our responses. We have in the ODD to our best knowledge included all relevant information from the studies.
RAC Member 5	First of all great thanks to the excellent and clear ODD prepared by the	Thank you for your comment.

RAC Member	Comments	Rapporteurs' response to comments
	rapporteurs and the ad-hoc group. Some comments regarding carcinogenicity below.	
RAC Member 6	We support the rapporteurs' proposals for no classification of the following endpoints: • acute toxicity • STOT SE • skin corrosion/irritation • skin sensitization • STOT RE • germ cell mutagenicity • carcinogenicity • reproductive toxicity (fertility and developmental toxicity) We also support the proposal of eye damage/irritation category 1.	Thank you for the support.
RAC Member 7	Firstly thanks to the rapporteurs for a good job in evaluating such complicated dossier. I would like to express my support to the Rapporteur's proposal for all evaluated endpoints.	Thank you for the support.
RAC Member 8	Thank you for the very detailed analysis of the available database. Overall, I support rapporteur's analysis and proposals for classification.	Thank you for the support
RAC Member 9	We agree with the conclusions on acute toxicity, skin irritation/corrosion and eye irritation, and these endpoints could be fast-tracked.	Thank you for the support.
RAC Member 10	I would like to thank the rapporteurs and the ad-hoc group for their careful analysis of the extensive data base for glyphosate and the well-elaborated ODD.	Thank you for the support.

RAC Member	Comments	Rapporteurs' response to comments
	I support the proposals for no classification for the following HH endpoints: • Acute toxicity (all routes) • STOT SE • Skin corrosion/irritation • Resp./Skin sensitisation • Reproductive toxicity – fertility	
RAC Member 11	Thanks to the Rapporteurs for excellent work on this huge dossier! I support the Rapporteurs' proposal for all evaluated endpoints.	Thank you for the support.
RAC Member 12	Thank you for the great work and the review of this huge amount of information. <u>General comment</u> - Based on the available evidence on the toxicity of glyphosate and glyphosate based herbicides (GBHs) (IARC assessment, studies on glyphosate and GBHs included in the RAC evaluation) it appears that many of the effects of the formulations are more severe compared to the effects induced by the active ingredient glyphosate on its own. This might be because of a higher availability of glyphosate in combination with co-formulants or because the co-formulants have toxic properties on their own or in combination with glyphosate. However, this is not the focus of RAC's evaluation. We think that it would be important to emphasise in the ODD that RAC considers studies with glyphosate as well as glyphosate-based herbicides and uses the results in a weight-of-evidence analysis, but the proposed classification is only relevant for the active ingredient glyphosate. Such a	For hazard classes where epidemiological data has been assessed, it is clearly stated that these data are related to exposure to GBH, and not the substance itself. Animal studies are performed with glyphosate. We therefore do not consider it necessary to include a statement on this under "RAC general comment." Since this section is for clarifications or other explanations by ECHA, this is up to ECHA to decide.

RAC Member	Comments	Rapporteurs' response to comments
	sentence could be included in the section "RAC general comment".	
	Acute Toxicity (all routes)	
RAC Member 13	I agree with the assessment that no classification should be applied for acute oral, dermal or inhalation toxicity. Perhaps part of the final paragraph (human data) should be deleted from the draft ODD because it becomes rather speculative. Specifically, I would delete the 2 sentences that follow the 2nd sentence: "…it is not possible to distinguish between effects due to intake of glyphosate and those caused by co-formulants". If test data on the co-formulants themselves has not been reviewed systematically, RAC cannot comment on the toxicity of these substances with sufficient independent authority. This endpoint could be fast-tracked.	Thank you for the support for no classification for acute toxicity following oral, dermal and inhalation exposure. We will revise the part describing human data according to your comments.
RAC Member 1	There are lot of studies consistently reporting LD50s in several species well above the respective limits for classification in all three routes. Therefore, **no classification for acute toxicity is well supported**.	Thank you for the support for no classification for acute toxicity following oral, dermal and inhalation exposure.
RAC Member 3	The proposed no classification of glyphosate for oral, dermal and inhalation acute toxicity is supported. These classes of acute toxicity could be considered for a fast-track	Thank you for the support for no classification for acute toxicity following oral, dermal and inhalation exposure routes. As regards fast track of this hazard class it is up to ECHA to decide.
RAC Member 4	I support no classification.	Thank you for the support.
RAC Member 14	The data are very clear for acute toxicity (62 studies, none supporting classification), skin irritation (11/11 studies supporting no classification) and sensitization (14/14 negative), and I thus fully support no classification.	Thank you for support of no classification for acute toxicity following oral, dermal and inhalation exposure.

RAC Member	Comments	Rapporteurs' response to comments
	I understand that ECHA will not allow fast-tracking any end-point for this substance. However, for any other substance, these would be clear cases for fast-track. A detailed presentation of such clear data in plenum seems unnecessary and really a waste of time. Thus, I hope the rapporteurs will keep the presentation of these end-points to a minimum.	We will try to keep it to a minimum.
RAC Member 15	I support the proposal of rapporteurs. This endpoint could be fast-tracked.	Thank you for the support.
Skin corrosion / irritation		
RAC Member 13	Agreed; fast-track.	Thank you for the support for no classification for skin corrosion/irritation
RAC Member 1	Nine studies showing no irritation and two with slight reversible erythema below the cut-off point for classification in only one animal. Thus, **no reasons for classification**.	Thank you for the support for no classification for skin corrosion/irritation.
RAC Member 3	No need for classification is well justified and supported, therefore this toxicity class could also be fast-tracked.	Thank you for the support for no classification for skin corrosion/irritation. As regards fast track of this hazard class it is up to ECHA to decide.
RAC Member 4	I support no classification.	Thank you for the support.
RAC Member 14	The data are very clear for acute toxicity (62 studies, none supporting classification), skin irritation (11/11 studies supporting no classification) and sensitization (14/14 negative), and I thus fully support no classification. I understand that ECHA will not allow fast-tracking any end-point for this substance. However, for any other substance, these would be clear cases for fast-track. A detailed presentation of such clear data in plenum seems	Thank you for support of no classification for acute toxicity following oral, dermal and inhalation exposure. We will try to keep it to a minimum.

RAC Member	Comments	Rapporteurs' response to comments
	unnecessary and really a waste of time. Thus, I hope the rapporteurs will keep the presentation of these end-points to a minimum.	
RAC Member 15	I support the proposal of rapporteurs. This endpoint could be fast-tracked.	Thank you for the support.
	Serious eye damage / eye irritation	
RAC Member 13	It might be helpful to include in the table a conclusion for each study, not just for those that fulfil the cat 2 criteria. I'm unclear why the ODD reached the conclusion that Cat 1 should be maintained. For all other endpoints, a "weight of evidence" approach is emphasised, but here the position simply takes the worst case, strongest evidence. To be consistent, I think a weight of evidence approach should be taken – this might lead to a different conclusion, e.g. Category 2.	Thank you for comments. We have included a conclusion in all studies in the table as well as a weight of evidence of the studies. The rapporteurs still consider that a classification as Eye Damage Cat. 1 is justified.
RAC Member 1	Only two studies fulfilled the criteria for classification in category 1, a third one was stopped before the needed observation time but suggested that this category might be appropriate. Other group of studies fulfilled category 2 but with some of them scoring close to requested to category 1. A third group of studies was performed with technical limitations that suggest that the severity of the effect might be downgraded by early washing. I think the weight of the evidence is on favour of the rapporteurs' proposal and **I support Category 1.**	Thank you for the support for no classification for eye corrosion/irritation and for the assessment of the data available.
RAC Member 3	Eye Dam. 1, H318 is justified and supported based on results of two studies. This class could be considered for a fast-track. On page 12, there is a typo error in a sentence "*These studies were considered as acceptable by the dossier submitter, and in these studies severe effects in the eyes of rabbits were reported and included corneal opacity, iritis, conjunctival hyperemia, edema, chemiosis and secretion that were not reversed after 21 days.* " The sentence needs some	Thank you for the support for no classification for eye damage/irritation and for the proposed changes. As regards fast track of this hazard class it is up to ECHA to decide

RAC Member	Comments	Rapporteurs' response to comments
	editorial changes: e.g. "chemosis" instead of "*chemiosis"; and since* chemosis means "oedema of the conjunctiva" there might be no need to list also "*edema"* without further specification of tissue concerned.	
RAC Member 2	A little remark regarding eye irritation. I remember that glyphosate can excist in at least three commercial stages. The glyphosate acid which is a serius eye irritant, but both the salts, isopropylamine and ammonium salts did not have the same serius eye irritatant properties. However, its not very important as all the preparations are tested for eye irritant properties.	OK
RAC Member 4	I am in more favour of category 1 but a discussion about category 2 may be warranted.	Thank you for the support, some more details are included in the ODD. See also comments on this issue from [RAC Member 13], and our response to his comment.
RAC Member 14	The database is somewhat conflicting, possibly indicating a borderline case between Cat 1 and Cat 2. However, considering the current classification in Cat 1 and that there are at least 2 studies supporting Cat 1, I support the proposed classification (Cat 1, H318).	Thank you for the support for no classification for eye damage/irritation. For further responses to this hazard class, see responses to comments from [RAC Member 13].
RAC Member 15	I support the proposal of rapporteurs. This endpoint could be fast-tracked.	Thank you for the support.
RAC Member 10	It is noted that the studies presented in table 1 of the ODD show varying results (no irritation, slight to severe irritation), even under the same condition (e.g. for studies where the eyes were not rinsed, the effects observed would result in 'no class.' (Arcelin 2007), cat. 2 (Talvioja 2007; Johnson 1997) or cat. 1 (Canabrava 2008)). There were also studies with rinsing after 24 h, or with rinsing after 1 h. These latter studies were negative for eye irritation, but were more or less discounted by the DS	Thank you for the comments. As you correctly point out, the eyes may be rinsed after 1 hour of the instillation of the test substance (for solids) if the solid test substance has not been removed from the eye of the test animal by physiological mechanisms at the first observation time point.

RAC Member	Comments	Rapporteurs' response to comments
	and rapporteurs because rinsing after 1 h would not be compliant with OECD 405. I'm not sure of that though, given what is stated in OECD 405 in paragraph 15 ("*The eyes of the test animals should not be washed for at least 24 hours following instillation of the test substance, except for solids (see paragraph 18), and in case of immediate corrosive or irritating effects. At 24 hours a washout may be used if considered appropriate."*) and paragraph 18 ("*If the solid test substance has not been removed from the eye of the test animal by physiological mechanisms at the first observation time point of 1 hour after treatment, the eye may be rinsed with saline or distilled water.*"). Since neither the CLP criteria nor the guidance define a minimum exposure period, I think the results of all studies in Table 1 should be considered in a weight of evidence approach to decide on the appropriate classification. In this approach also the studies that formed the basis of the current classification as Eye Dam. 1 should be included, as this is not clear from the ODD.	There are no information in the RAR regarding if any test substance were remaining in the eye at 1 hour observation time, and therefore it cannot be concluded if rising was appropriate or not according to the test guideline. We will therefore include all studies included by the DS in the WoE analysis. As regards the studies assessed for the classification of glyphosate as R41, they were not included in the CLH proposal, and have not been available for assessment by RAC.
Respiratory and skin sensitisation		
RAC Member 13	No classification; fast track?	Thank you for the support for no classification for respiratory and skin sensitisation.
RAC Member 1	**No classification is** obviously well-**supported**.	Thank you for the support for no classification for skin and respiratory sensitisation.
RAC Member 3	Skin sensitisation: No need for classification is well justified and supported, therefore this toxicity class can be considered for a fast-track.	Thank you for the support for no classification for skin sensitization. As regards fast track of this hazard class it is up to ECHA to decide.
RAC Member 4	I support no classification.	Thank you for the support.
RAC Member 14	The data are very clear for acute toxicity (62 studies, none supporting	Thank you for support of no

RAC Member	Comments	Rapporteurs' response to comments
	classification), skin irritation (11/11 studies supporting no classification) and sensitization (14/14 negative), and I thus fully support no classification. I understand that ECHA will not allow fast-tracking any end-point for this substance. However, for any other substance, these would be clear cases for fast-track. A detailed presentation of such clear data in plenum seems unnecessary and really a waste of time. Thus, I hope the rapporteurs will keep the presentation of these end-points to a minimum.	classification for acute toxicity following oral, dermal and inhalation exposure. We will try to keep it to a minimum.
RAC Member 15	Skin sensitisation: I support the proposal of rapporteurs. This endpoint could be fast-tracked.	Thank you for the support.
Specific Target Organ Toxicity, single exposure (STOT SE)		
RAC Member 13	Whilst I agree to no classification (fast-track?), the assessment of human data is too speculative. For example, we have insufficient knowledge to conclude whether human exposure to glyphosate, the substance, occurs in industry or not. Similarly, the case described by Burger (2009) could simply be dismissed because exposure was to a mixture, not to glyphosate itself. The authors may have speculated that the alkylamine may have contributed to the hazard, but presumably we have no supportive evidence either way and therefore should simply state that this study does not provide sufficient information to meet the classification criteria.	Thank you for comments and for supporting no classification for STOT SE. Comments regarding the Burger et al., 2009 study are noted, agreed and incorporated. This particular study does not provide any significant information in meeting the classification criteria**.**
RAC Member 1	The rationale for the **no classification** is well explained in the ODD. **I support it.**	Thank you for the support for no classification for STOT SE.
RAC Member 3	No need for classification is well justified and supported, therefore this toxicity class could be fast-tracked.	Thank you for the support for no classification for STOT SE. As regards fast track of this hazard class it is up to ECHA to decide.
RAC Member 4	I support no classification.	Thank you for the support.

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 14	The only effect to discuss is respiratory irritation, since respiratory effects were reported in 7 out of 13 acute inhalation studies. The symptoms included increased or decreased respiratory rate, slight dyspnea, irregular breathing, labored and noisy respiration and gasping. The CLH report as well as the ODD states that it was not possible to distinguish between respiratory irritation and respiratory toxicity in the acute studies. However, according to the CLP guidance, *"respiratory tract irritation covers two different effects: "sensory irritation" and local cytotoxic effects". Classification in STOT-SE Cat 3 for RTI is generally limited to local cytotoxic effects."* (3.8.2.3). Thus, there is no need to distinguish between respiratory irritation and toxicity, and I therefore think that the argument in the ODD need to be rephrased. Furthermore, the guidance states that "*There are no similar guidance values for Category 3. Therefore, if the study shows clear evidence of narcotic effects or respiratory tract irritation at any dose level then this could support classification with Category 3*" (3.8.2.4.2). Unfortunately, no inhalation studies of longer duration including a more detailed investigation of the respiratory tract has been performed to allow assessing if there is "clear evidence" or not. My conclusion of the available data is that respiratory tract irritation has been indicated in half (7/13) of the acute inhalation studies. However, lack of such symptoms in the other 6/13 studies, no histopathological investigation of the respiratory tract, and no human evidence of respiratory tract irritation, preclude defining the available data as the "clear evidence" needed for classification in Category 3. Thus, I support no classification but recommend revising the arguments for no classification in the ODD.	Thank you for valuable comments and for supporting no classification for STOT SE. Vague and general effects on breathing were described as clinical signs in 8 out of 13 inhalation toxicity studies according to the CLH report and the 2013 renewal assessment report. These effects were not consistent. These studies were all performed with glyphosate acid and were all guideline compliant with GLP. Two studies (Rattray, 1996; Nagy, 2011) had mortalities and clinical signs were thus more pronounced, pathology findings (dark lungs, Rattray, 1996) found in one and not in the other. The remaining studies except for Tornai, 1994 (lungs: congestion, haemorrhages and oedema), showed no pathological findings (10 studies). There is no human data to support respiratory tract irritation. There are no objective measurements of clear respiratory tract irritation. A variety of clinical signs have been observed across a number of acute studies (slight dyspnea, decreased respiratory rate, increased respiratory rate, breathing effects, irregular breathing, rales, labored respiration, gasping respiration), but they are not always consistent and do not always occur together but in isolated studies. There is a general lack of pathology (only in 2 out of 13 studies is

RAC Member	Comments	Rapporteurs' response to comments
		lung pathology recorded) and it is difficult to dispel the idea whether isolated idiosyncratic reactions or responses triggered in hypersensitive test subjects are being observed. All effects appear to have been transient in nature. It is therefore not possible to list a definable set of clinical signs that are characteristic amongst all the acute studies reported by the DS. In conclusion there is little evidence amongst these studies to satisfy the CLP criteria for classification.
Specific Target Organ Toxicity, repeated exposure (STOT RE)		
RAC Member 13	As we are not undertaking a risk assessment I would modify the following sentence (page 19): "Altogether, RAC considers that the premature maternal deaths reported in several rabbit developmental toxicity studies are of some concern". I think it would be better to comment on the possible explanations for these findings and, in conclusion, that they cannot be viewed as clear evidence of glyphosate toxicity. In assessing the need for classification, we do not have to comment whether findings are "of concern" – what does this term mean anyway? The clear weight of good quality evidence supports no classification.	Thank you for comments, the ODD has been revised accordingly, and for the support for no classification for STOT RE.
RAC Member 1	**I initially support the no classification** mainly by the following reasons: i) the theory of the overexposure through caecotrophy seems to be plausible and reduces the concern; and, ii) there is a lack of consistence in the results among different studies and curiously, the study with the highest dose (500 mg/kg bw/day) reported no premature fatalities, while the incidences at other high doses are low (1 and 2 dead at 300 and 400 mg/kg bw/day in two different studies, being the mortality	Thank you the support for no classification for STOT RE The duration of the Tasker et al., 1980 study from gd 6-28 compared to gd 6-18 for the other rabbit developmental toxicity studies. However, it is described in the

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	reported at 450 mg/kg bw/day probably attributable to abortion). I am surprised by the duration of the Tasker's study because the exposure seems to be for 22 days! (from gestation day 6 to 27), while OECD Guideline 414 considers 12-13 for rabbits. Therefore, the duration of the exposure in this study is almost twice than in the others. I wonder whether we can conclude that this study did not follow the standard guideline and diminishes its weight in the final balance. The third paragraph in page 19 seems suggest that the studies are relevant for classification as STOT-RE 2 only if the effects are reported below 300 mg/kg bw/day (the top limit for 28-days of exposure). However, the exposures in these studies are 13-days and therefore the limit should be corrected. The other three studies showing mortalities will be within the range for classification, although with lower incidence than the other two. In this same line the sentence *"only two studies may be considered as appropriate for consideration for STOT RE2"* (page 19) is unclear to me. Is this because the low incidence or because the mortalities appear above 300 mg/kg bw/day?	OECD TG 414 the following: "Normally, the test substance is administered to pregnant animals at least from implantation to one day prior to the day of scheduled kill, which should be as close as possible to the normal day of delivery without risking loss of data resulting from early delivery. The guideline is not intended to examine solely the period of organogenesis, (e.g. days 5-15 in the rodent, and days 6-18 in the rabbit) but also effects from preimplantation, when appropriate, through the entire period of gestation to the day before caesarean section". We will include a sentence in the ODD describing that the Tasker et al., 1980 used a longer exposure period than the other rabbit developmental toxicity studies that may have had an influence on the result from this study and make a comparison with the other studies of limited value. We have corrected the Guidance Values for the duration of the exposure in the rabbit developmental toxicity studies (according to Haber's rule) and included the GV for each study in table 2 of the draft ODD. The justification for no classification is changed accordingly.

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RAC Member 3	Repeated dose toxicity The analysis of weight of evidence coming from a substantial number of repeated toxicity studies on mice, rats and dogs performed by the rapporteurs indicate that there are no significant effects in these animals at doses below the guidance value for classification to STOT RE 2. In 2 out of 7 studies of developmental toxicity studies in pregnant rabbits the increased mortality of does was noted. In these 2 developmental toxicity studies to a large extent the mortality of does was due to administration errors as evidenced by pathological findings in lungs of many animals. In addition it was noted that caecotrophy, specific for rabbits, could increase a dose of glyphosate received by pregnant does due to ingestion of cecotropes. Cecotropes, are the material resulting from the fermentation of food in a part of the digestive system called the 'cecum.' Cecotropes are nutrient-rich and are passed out of the body, like feces, but are reingested by the animal so the nutrients can be absorbed. The cecotropes are, most probably, containing glyphosate excreted unchanged from gastrointestinal tract of these animals. It is important to note that no significant pathological alterations were noted in internal organs of the rabbits other than gastrointestinal tract. Therefore, I support the conclusion of rapporteurs that classification of glyphosate to STOT RE is not warranted. In my view this hazard class can be considered for decision by fast-track route.	Thank you for the support for no classification for STOT RE. As regards fast track of this hazard class it is up to ECHA to decide.
RAC Member 4	I support no classification. Whereas the unexplained mortality in the studies Tasker et al. (1980) and Suresh et al. (1993) warranted proper evaluation, mortality in the remaining developmental rabbit studies is much lower or absent. So already the effect in the rabbit is equivocal.	Thank you for the support. As regards guidance values, see our response to the comment from [RAC Member 1].

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	No mortality and no adverse effects were observed in the rat, mouse or dog at doses relevant to classification. The uniqueness of the rabbit gastrointestinal tract and presumably increased exposure due to caecotrophy seems to be a plausible explanation of the increased sensitivity – although this remains a hypothesis. In addition to GI tract irritation, the antimicrobial activity of glyphosate (possibly leading to alterations in gut microbiota) might have played a role. It's a pity that the cause of deaths in studies of Tasker (1980) and Suresh (1993) was not further investigated, so it is not possible to confirm whether the cause of death was directly linked to GIT disturbances. Considering the absence of effects in other species at relevant doses, together with the questionable relevance of the rabbit findings to humans, no classification is the most appropriate outcome of the weight-of-evidence analysis. As to the cut-off value for STOT RE 2, a higher value than 300 mg/kg bw/d could be obtained by a more strict use of the Haber's rule (the dosing period was 12 to 21 days, not 28 days). Still, this does not affect significantly the outcome of the WoE assessment.	
RAC Member 14	I agree with the DS and the ODD that the maternal toxicity in the rabbit studies needs to be considered under STOT RE, and that rabbits seem much more sensitive than the other species studied. The analysis performed by the rapporteurs is very thorough, and I especially note and support that the occurrences of mal-gavage and diseases in the key studies (Suresh 1993 and Tasker 1980, respectively) introduce serious uncertainties in the assessment. Overall, it cannot be concluded with sufficient certainty that substance-related deaths have occurred at doses below the (28 days) GV for STOT RE2. Therefore, I support the ODD and that no classification is warranted.	Thank you for the support for no classification for STOT RE.

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RAC Member 15	The use of the Haber's rule for a study of 28-day is not justified in the ODD or by the DS and restrict the discussion on death observed below ≤ 300 mg/kg bw although effects observed up to 400 mg/kg bw or 750 mg/kg bw in the Tasker et al. study may be considered relevant for classification. The guidance value for STOT RE category 2 is 10 < C ≤ 100 mg/kg for 90-day toxicity. This can be extrapolated by applying Haber's rule to the values of 40 < C ≤ 400 mg/kg bw for 21-day repeated toxicity study (as in Tasker et al., 1980) or 75 < C ≤ 750 mg/kg bw for 12-day repeated toxicity studies (other 6 prenatal developmental toxicity studies). I would therefore propose to add a justification.	The ODD has revised, and corrected guidance values has been added as appropriate. See also response to comment from [RAC Member 1].
	Nevertheless, in the studies performed on GD6-18 or GD7-19, only one death in the Hojo et al. (1995) study and 2 deaths in the Moxon et al. (1996) study can be considered treatment related at 300 mg/kg whereas no mortality was observed up to 400 mg/kg bw in the other studies.	Unfortunately, no further data on this were included in the study report.
	In the study of Tasker et al. (1980) dose related increase in mortality has been observed. At 350 mg/kg 40% of the animals died between GD 14 to 21. The longer treatment period seems to have no impact on the mortality latency as animals died around GD 20 as in the other rabbit studies. It is noticeable that the cause of premature death was not determined. It would have been helpful to know if signs of general toxicity (bw, clinical signs etc…) were observed in these died animals.	
	Overall, I agree with the rapporteurs that **STOT RE for glyphosate is not warranted** based on the followings: - No mortality was observed in other species or study design that would support the proposal; - High mortality rate was only observed in one out of 7 rabbit studies in one particular strain;	Thank you for the support.

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	- Digestive disturbance may have been a cause of premature death and physiology digestion in the rabbit is unique. This endpoint could be fast-tracked.	
RAC Member 8	I fully support no classification for STOT RE endpoint. According to the CLP, substances are classified as specific target organ toxicants following repeated exposure by the use of expert judgement and on the basis of the weight of all evidence available. The guidance values given in CLP are intended only for guidance purposes, i.e. to be used as part of the weight of evidence approach, and to assist with decisions about classification but they are not intended as strict demarcation values. Although morbidity or death resulting from repeated or long-term exposure can be taken into account in STOT RE classification, this refers to situations in which there is accumulation of the dose and/or an effect in long term exposure, which finally results in the pre-term death of the animal. This kind of situations may be relevant for human low level exposures. (See CLP: "(a) morbidity or death resulting from repeated or long-term exposure. 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.*"). In this case, it is clear that mortality in rabbits is either related to dosing (mis-dosing resulting in aspiration and lung effects) or due to local osmotic effects of gavage doses resulting in diarrhea. When taking into account that these deaths occurred only in animal species (rabbit), which has rather unique digestive physiology and in other animal species no mortality occurred even at 10-times higher levels, it can be concluded (on the basis of weight-of-evidence) that these findings are very unlikely to be	Thank you for the valuable comment, which has now been reflected in the ODD.

RAC Member	Comments	Rapporteurs' response to comments
	relevant to humans. In addition, bioaccumulation and over-whelming of detoxification mechanisms by repeated exposure as a mechanism of toxicity is not likely in this case especially since the main effects were local (osmotic) effects in gi-tract.	
RAC Member 9	First of all, thanks to the Rapporteurs and the ad-hoc group for the huge amount of work done. We agree with the conclusions on acute toxicity, skin irritation/corrosion and eye irritation, and these endpoints could be fast-tracked. Concerning STOT RE, we would like to highlight some points which, in our understanding, could worth a little bit more consideration and thus a discussion in plenary would be welcome: • We agree that Rabbit seems to be the most sensitive species • In Tasker et al, 1980: after 22 days of exposure (0, 75, 175 and 350 mg/kg bw/d), 0, 1, 2 and 10 premature maternal deaths occurred. Out of these, 1/1, 1/2 and 3/10 were not considered substance-related and thus 1 and 7 deaths in the two highest dose groups might be due to treatment. Furthermore, at the highest dose, 7 of 17 does died during the treatment period, which is not negligible (+- 41%). As it is mentioned in the Guidance on the Application of the CLP criteria, page 459, version 4.1, June 2015 : **Annex 1 3.9.2.9.5.**The guidance values refer to effects seen in a standard 90-day toxicity study conducted in rats. They can be used as a basis to extrapolate equivalent guidance values for toxicity studies of greater or lesser duration, using dose/exposure time extrapolation similar to Haber's rule for inhalation, which states essentially that the effective dose is directly proportional to the exposure concentration and the duration of exposure. The assessment shall be done on a case-by-case basis; for a 28-day study the guidance values below is increased by a factor of three.	The guidance values has been corrected for the duration of the study. See further response to

RAC Member	Comments	Rapporteurs' response to comments
	Then the range should be adapted for the study duration which is of 22 days, the cut-off value is of approximatively 380 mg/kg bw/d and thus all dose groups are relevant for the assessment.	comment from [RAC Member 1].
RAC Member 9 [contd.]	• In Suresh et al., 1993: after 13 days of exposure (0, 20, 100 and 500 mg/kg bw/d), 2, 0, 4 and 8 premature maternal deaths (=7.7, 0, 25, 53.3 % of mortality) were observed. It is mentioned in the ODD that, except for the deaths in control group, they were treatment-related (with possible gavage error in 5/8 premature deaths in the highest dose group, still leading to approximatively 17% of mortality in the aforementioned dose group). Considering the range, for a 13-day exposure, a cut-off value of approximatively 645 mg/kg bw/d can be set, meaning that these preoccupying premature deaths should be taken into account.	The guidance values has been corrected for the duration of the study. See further response to comment from [RAC Member 1].
	• In the ODD, page 22, "*5. The majority of deaths were associated with very high doses of glyphosate and the majority of deaths were associated with two old studies were the cause of death is unclear*". We would like to emphasize that all studies were conducted between 1980 and 1996, thus there seems to be no good reason to point out that the two following studies showing premature deaths: Tasker et al. in 1980 and Suresh et al., in 1993 are in a way "older" than the others. Furthermore, as mentioned above, these highest doses can be considered as acceptable and relevant to classify after applying Haber's rule. Perhaps this sentence should be deleted.	The paragraph now reads: " The majority of deaths were associated with high doses of glyphosate and the majority of deaths were associated with 2 studies where the cause of death is unclear". See also response to comment from [RAC Member 8] regarding corrected guidance values.
	• Concerning the caecotrophes, it should be stated that rabbits suffering from diarrhea or soft/liquid stools do not produce caecotrophes as their bowel movements are increased and thus there is no time for digestive fermentation. Diarrhea/soft/liquid stools were observed in many studies and thus the hypothesis of the caecotrophes for the higher sensitivity of rabbits due to overexposure may be precarious.	The paragraph now reads: " The majority of deaths were associated with high doses of glyphosate and the majority of deaths were associated with 2 studies where the cause of death is unclear". See also response to comment from [RAC Member 8] regarding corrected guidance values.
	• We cannot deny that the mortality rate is not sufficient enough to classify	We do not agree to that the uncertainties are

RAC Member	Comments	Rapporteurs' response to comments
	glyphosate as STOT RE or that there is many uncertainties arising from this data set. • It should be clearly stated in the conclusions of the RAC's opinion that uncertainties in this case are numerous and do not allow the committee to classify. Furthermore, again in the conclusions, it should be mentioned that this opinion do not reflect on the safety of any formulation containing glyphosate in order to avoid any confusion.	so many that it is impossible for the committee to classify for STOT RE. There are numerous rat, mouse, dog and rabbit studies available with relevant duration for a classification, and based on a weight of evidence assessment, no classification can be justified. We do not agree, since the classification only reflects intrinsic properties of the substance and not formulation containing the substance, and for STOT RE only animal data with exposure to glyphosate has been assessed.
RAC Member 16 ***RAC Member 17***	First we would like to thank the R's for a great job in the ODD. We have some comments regarding the STOT RE endpoint. **STOT RE:** We support no classification based on the following: 1. Analysis of a large number of repeated dose toxicity studies showed no significant effects at doses below the GV for STOT RE 2 2. In 2/7 studies developmental toxicity studies in pregnant rabbits, increased deaths in does were observed in doses below the GV for STOT RE 2 but there was evidence for administration errors and infections thus rendering the evidence weak for classification purposes. 3. The toxicokinetics of glyphosate as well as the rabbit specific caecotrophy support the higher dose of glyphosate in rabbits as compared to other species (rabbits being more sensitive) and the probable non-relevance to humans.	Thank you for the support for no classification for STOT RE.
RAC Member 10	It is clear that the effects seen in other species than rabbits do not warrant classification. As to the mortality observed in rabbit dams in 5 out	Thank you for the support.

RAC Member	Comments	Rapporteurs' response to comments
	of 7 studies at doses below relevant GV for STOT RE 2 (300/600 mg/kg bw/d, for 28/14 d study), this in principle may warrant classification. However, some deaths could be explained, by mis-gavage, diseases or effects related to g.i. tract disturbance. Rabbits appear much more vulnerable for the consequences of these latter effects than rodents, with some doubts on human relevance. There were also some unexplained deaths, in particular in the Tasker et al. 1980 and Suresh et al. 1993 studies; the level of detail provided on necropsy was however insufficient to establish a possible relation with treatment. Clinical signs related to g.i. tract disturbance (such as soft stool, diarrhea) were however often seen in these studies (just like in others). All in all, I support the weight of evidence approach taken in the ODD and the conclusion that there is insufficient evidence for classification.	
RAC Member 12	Based on the repeated dose studies testing glyphosate in rats, mice and dogs no classification as STOT RE is supported. - The only relevant effects are the deaths observed in some of the 7 developmental toxicity studies in rabbits. The doses at which mortalities were seen are relevant for classification as STOT RE 2. It has to be noted that Haber's Law should be applied strictly and the actual duration of exposure should be considered. Exposures ranged from gd 6/7 to 18/19/20/27 in the mentioned studies, however, the actual day of death has to be used for the calculation. When looking at the exact exposure duration it becomes obvious, that some of the deaths occurred after very short exposures (after only 1, 2 or 5 doses in the Suresh et al., 1993 study or after only 8 doses in the Tasker et al., 1980 study). This indicates that the effects could also be of acute nature. However, both studies (Tasker and Suresh) report some indications of mis-gavage, which could also explain the deaths observed after only one or few doses applied. - It is further noted that the results of the studies are rather heterogeneous,	Thank you for the support. Corrected guidance values according to duration of studies has been included, see also response to comment from [RAC Member 1].

RAC Member	Comments	Rapporteurs' response to comments
	ranging from no death up to 500 mg/kg bw/day (Bhide & Patil, 1989) to more than 50% mortality in Tasker et al., 1980 and Suresh et al. 1993 at 350 and 500 mg/kg bw/day, respectively. - Additionally, the caecotrophy hypothesis described in the ODD could be relevant in this case, leading to actually higher doses of glyphosate taken up by the rabbits. On the other hand it was described that soft/liquid stool and diarrhoea was induced by glyphosate in the rabbit studies (also seen in other species), which could have interfered with caecotrophy in rabbits. In turn this could have been the cause for or could have contributed to the observed reductions in body weights and body weight gains in rabbit does (though this link is not consistent either). The ODD states, that caecotrophy is very important for normal growth in rabbits, but not always essential for survival, as concluded from studies in which rabbits were completely deprived of caecotrophs (Robinson et al., 1985; Phiny et al., 2006). However, in combination with the glyphosate exposure deprivation of caecotrophs could be relevant. Overall, it appears that oral rabbit studies are not adequate to test glyphosate and there is a great heterogeneity among the available studies and therefore no classification as STOT RE is supported.	Further information regarding the impact of caecotrophy has been included in the ODD, see also response to comment from [RAC Member 9].
Germ cell mutagenicity		
RAC Member 13	I agree that the WoE from the best available in vitro and in vivo studies (including standard tests employing the sensitive i.p. route) strongly suggests that glyphosate is not a mutagen. If the standard studies do not provide a clear mutagenic profile, the mechanistic studies would seem to be of limited relevance. I suggest amending the 2nd paragraph of the assessment to read as follows: "In contrast to the view expressed by IARC (Monograph 112), glyphosate is not electrophilic and is only metabolised to a limited degree. ADME studies show a wide tissue distribution of non-metabolised	We have revised the text and the reference to IARC is now included in the section "Comparison with the IARC evaluation". However, IARC (in the Monograph 112 p.77 and in their presentation at the RAC 39 meeting) clearly states that glyphosate is not electrophilic. We believe it is valuable to show that there is no difference in the evaluation of the reactivity (and of the limited metabolism) of glyphosate between RAC and IARC.

RAC Member	Comments	Rapporteurs' response to comments
	glyphosate following oral administration." After this, is it possible to explain why the position of IARC is erroneous? As the text stands at the moment, the reader might conclude that IARC simply had different data available and that there position is still a valid one. I agree with the interpretation of the bacterial and mammalian cell gene mutation tests. I can accept that the result of in vitro micronucleus test in human lymphocytes be described as negative, but am less convinced about the "positive" test result in buccal carcinoma cells (species, human?). Were criteria for a positive result in this unusual cell type described adequately; has the cell type been shown to discriminate reliably between genotoxic substances and others? Had the methodology been developed adequately? From the information provided in the ODD, it is unclear why either of the 2 "positive" in vitro chromosome aberration studies should be disregarded. Can more detail be included to explain what aspects of the protocols were criticised by the expert genetic toxicologist. Further, if the positive results can be doubted because of such weaknesses, are we sure that the negative results all come from studies that were conducted perfectly? We should apply the same level of scrutiny to all the studies. Overall, I think we have to conclude that a wide range of genotoxicity studies are available and that they do not provide a totally reassuring negative profile. As such, the in vivo data are key to deciding whether classification is appropriate. In the ODD, I suggest discussing the animal studies before the human data.	A human derived buccal carcinoma cell line (TR146) was used in the study by Koller et al., 2012 with reference to procedures described in a published protocol (Fenech M et al., 2007. Cytokinesis-block micronucleus cytome assay. Nat Protoc 2:1084–1104). The nuclear division index was reported to be unaltered by glyphosate exposure, whereas apoptosis and necrosis was reported from the low concentrations of 20 ug/ml. An international project (HUMNxL) is working with the performance of buccal epithelial cells as a complementary method for measuring human MN frequencies. The in vitro micronucleus test can in principle be applied to any primary cell or cell line. However, to our knowledge, the performance of the TR146 cell line in the in vitro micronucleus test has not been validated and the study in question is not supported with reference to HCD. We agree that for these reasons it may be reasonable to put more weight on the results obtained in the study with human lymphocytes. The text has been revised to ensure a more balanced presentation. Agree. The human data has been placed after the in vivo mutagenicity data in animals.

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 13 [contd.]	It may be possible to discount the Suresh (1993) MN study completely. In well conducted tests, only small numbers of micronuclei are seen per 1000 cells. In contrast, Suresh is reporting MN per 100 cells, even in controls. This could be checked by looking at the original study report. I agree with the interpretation of the comet assays. As discussed previously at RAC, positive results from these tests have less meaning when they are set alongside negative results in standard in vitro and in vivo tests for chromosome damage and point mutation. Were the studies of Bolognesi (1997) and Manas (2013) both conducted well enough to meet the standard described by the recently validated OECD guideline? The negative post-labelling result should not be given much weight – unless it was demonstrated that the chromatography used was able to pick up adducts from a "non-bulky" substance such as glyphosate. I think all of the tests for oxidative stress should be covered in a section with sub-heading: Mechanistic studies – oxidative stress (or something similar). The mechanistic study by Mlandici (2009) was an in vitro study, not in vivo. Please explain the conclusions that can be reached from the tests with Ogg1-glycosylase. Comparison with the IARC evaluation – a table summarising the scope of the data and the similarities and differences in the assessments made would help make this section more accessible. I suggest making separate comparisons (i.e. separate tables) for in vitro data, in vivo data, mechanistic data, and human data before summing up with the general conclusions reached.	Table 23 in the CLH report gives the frequencies of 0.69% and 0.51% MN-PCEs for control male and female mice, respectively, which is higher than expected in controls. In the RAR it is stated that the study is regarded as acceptable. The Rapporteurs do not have access to the original report, but a comment is now added in the ODD. The evaluation of whether the studies meet current standards is made difficult by the limited methodological reporting. The study by Manas (2013) is unfortunately poorly reported which lowers the confidence of the reported comet assay results and their statistical evaluation. A sentence is now added to the UDS paragraph to clarify the limitations of the test with respect to the DNA-lesions observed following glyphosate exposure. The section has been renamed. Thank you. The text has been revised to avoid misunderstanding concerning the study by Mladinic and the implications of using the Ogg1 glysosylase has been added. We have discussed how to best present the comparison of the IARC and RAC evaluations. So far, we have chosen to give a detailed explanation of the RAC argumentation in the cases where the conclusions diverge and not to interpret the IARC evaluation. We have now sought to simplify the text by adding a separate section for mechanistic data as suggested.

RAC Member	Comments	Rapporteurs' response to comments
	Proposed alternative text under the Cat 1A sub-heading: "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 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".	Thank you for this very helpful suggestion. The alternative text now replaces the former description in the ODD.
RAC Member 1	**I support the proposal of no classification** for the substance by the following reasons: ☐ The two *in vivo* germ mutagenicity tests with very high concentrations were negative; ☐ There are no conclusive evidences confirming that glyphosate was able to induce *in vivo* mutagenicity in somatic cells. One might think that the 7 negative results in the micronucleus tests using oral route are due to lack of bioavailability (especially after reporting positive results *in vitro* in this same test). However, the micronucleus tests by ip route were also negative (5 negative tests and 2 positives with methodological deficiencies). In addition, the 2 negative chromosomal aberration tests also support the negative results *in vivo*. ☐ Positive results were obtained *in vitro* with 2 different micronucleus	Thank you for the comments and the support

RAC Member	Comments	Rapporteurs' response to comments
	tests and with 3 sister chromatid exchange tests. However, it cannot be considered enough for classification as Category 2 because these results are counterbalanced by the negative results found in the 16 bacteria tests, in the 3 gene mutation tests, in the 5 chromosomal aberration tests (the 2 positive displayed methodological deficiencies due to non-standard protocols) and in the USD. ☐ The *in vivo* and *in vitro* indicator tests do not support concentration-dependent increases in DNA damage and oxidative stress demonstrated at levels for warranting classification. The Comet tests were positive *in vitro* concurrently with apoptosis and necrosis and/or absence of dose-response and the *in vivo* data suggest that breaks are repaired immediately after the exposure. The reported oxidative stress might therefore also be a secondary or adaptive response to cytotoxicity. ☐ The human data are not un-equivocal due to limitations as uncertainties in exposure, co-exposure with other PPP, low number of individuals involved in the studies, etc.	
RAC Member 3	The analysis of weight of evidence of genotoxicity performed in the draft opinion takes into account all available data in mammals, using larger database than that in IARC Monograph 112, and assigning a proper weight to various study results depending upon reliability of the study, uncertainty in exposure assessment, possible exposure to other toxic chemical in case of human studies, and biological significance of the endpoint measured. Therefore the rapporteurs and DS conclusion on lack of sufficient evidence of mutagenicity of glyphosate in mammalian germ and somatic cells is supported. As proposed by the rapporteurs glyphosate does not warrant classification for germ cell mutagenicity.	Thank you for your comments and your support.
RAC Member 4	I support no classification. Several observations not explicitly mentioned in the ODD or in the comments by other members:	

RAC Member	Comments	Rapporteurs' response to comments
	• As to the positive result in the in vitro micronucleus test by Mladinic (2009a), it is surprising that genotoxicity was observed only with metabolic activation; glyphosate is known not to be significantly metabolized in mammals. It is also interesting that addition of S9 mix also increased cytotoxicity (measured by a vital staining technique; no effect on CBPI). Biological relevance of this finding thus remains questionable. • In the micronucleus test by Koller (2012), frequency of micronuclei was significantly increased from 15 mg/l while a significantly increased cytotoxicity was observed at an only slightly higher concentration of 20 mg/l. This suggests that cytotoxicity might also have played some role at 15 mg/l. In addition, the cell line used (human-derived buccal epithelial cells) is a non-standard one and its false positive rate in comparison to established in-vivo genotoxicity tests has probably not been investigated. • The in vitro comet assay is a relatively simple test, presumably with higher sensitivity than standard regulatory tests. However, it still has serious limitations; one of them is the difficulties with addressing the confounding effect of cytotoxicity. The presumed high sensitivity of this assay raises concerns about low specificity (high false positive rate). Validation efforts have not been successful so far. Therefore results from this test are of very limited value in regulatory context. • The sister chromatid exchange assay is no longer considered as a valid indicator of genotoxicity. Therefore the positive findings in this test have no bearing on classification.	The description of this study has been slightly expanded. The comet assay is a sensitive method for detection of single strand breaks and alkalilabile sites, but is unspecific and will also detect lesions introduced due to cytotoxicity and during cultivation and sample preparation. However, performed correctly and with prober control for cytotoxicity it is a reliable measure of chemical induced DNA strand breaks. The in vivo method has been validate and accepted for regulatory use mainly as a replacement of the UDS. As one has a battery of in vitro mutagenicity tests available, the in

RAC Member	Comments	Rapporteurs' response to comments
		vitro comet assay may give limited additional information with respect to evaluation of mutagenesis.
RAC Member 4 [contd.]	• The in vivo micronucleus by Suresh (1993) was followed by a chromosomal aberration test (Suresh 1994) which was negative at 5000 mg/kg bw and showed bone marrow cytotoxicity (mitotic index decreased by 40%), which can at least partly explain the previous positive finding. The dose of 5000 mg/kg bw is above the limit dose of 2000 mg/kg bw according to the current OECD guideline. • Oxidative stress: Mañas (2009) reported a weak increase in liver SOD activity upon i.p. administration, which was not reproduced in a subsequent study using oral administration (Mañas 2013). • Human data, Paz-y-Miño (2007): According to the OECD TG for the in vivo comet assay, DNA should be sampled shortly after exposure because the strand breaks are short-lived (they are quickly removed, repaired or lead to cell death). The optimal sampling time is at the peak plasma concentration. Upon oral absorption, glyphosate is completely eliminated by 3-7 days, with the major part being excreted within 48 hours (CLH report, p. 14). The presence of POEA does not significantly prolong the elimination time (USDA report. p. 3-7). Upon dermal absorption the elimination phase may last slightly longer, but not substantially longer. So it is questionable what measurement 2 weeks to 2 months post-exposure can reflect. Furthermore, the low variance in the negative control group is at least interesting. Blind reading of slides is not stated. I have some doubts about reliability of this study.	We agree that the use of the comet assay in human biomonitoring has limitations with regard to the unspecific nature and the rapid repair of the lesions measured (if the increases measured does not reflect a prolonged reduction of DNA repair capacity).

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 4 [contd.]	A brief summary of my assessment: 1. In vitro data: The substance is unlikely to cause gene mutations. As to clastogenicity data, at least 1 standard study (Lioi 1998b) was clearly positive. In vivo studies are needed to elucidate the findings. 2. In vivo data: I agree to give less weight to the studies by i.p. route as this route is not recommended by the current guidelines. I also agree to give less weight to the in vivo comet assay as it is an indicator test (the strand breaks need not necessarily be fixed) and the potential confounding effect of cytotoxicity is still under discussion. All the remaining tests are negative. 3. Oxidative stress: Evidence not convincing, less weight to the i.p. studies. 4. Human data: The study of Paz-y-Miño (2007) is of limited reliability. The study of Bolognesi (2009) reported a weak increase but not corresponding to application rates and degree of direct contact. Overall, no convincing evidence. Minor comments: • Oxidative stress markers, p. 27: In the study of Astiz (*Environmental Toxicology and Pharmacology.* 2009, 28:465-473 – reference in the ODD would be appreciated), vehicle controls were not missing, see p. 467 of the article. The vehicle control data are not reported in the article as they are claimed to be similar to those of untreated controls. • Human data, p. 25: As to the study of Bolognesi (2009), I am not sure that the word "transient" is appropriate as the affected cells may disappear by 4 months due to normal cell turnover; likewise,	Thank you for this comment. The text has been revised as we see that our interpretation of the study design is probably incorrect. In the methodology section it is stated that "Animals were randomly divided into nine groups of four rats each, assigned as control rats without any treatment (C), or injected i.p. with polyethylene-glycol 400 (PEG-400) (V), 15mg zineb/kg body weight (b.w.) in PEG-400 (Z), 10mg glyphosate/kg b.w. (G), or 15mg dimethoate/kg b.w. (D)". Probably not only zineb, but also glyphosate was dissolved in PEG-400, although this is not stated clearly. However, it is still a problem that the vehicle control data

RAC Member	Comments	Rapporteurs' response to comments
	no glyphosate is expected to be present in the blood 4 months post-exposure. The 4mo measurement may be useful as a control for baseline drift.	are not presented. The last part of the sentence has been deleted.
RAC Member 14	It is a huge data base, with most studies being negative. There are, however, some indications of effects when it comes to the micronucleus test, the Comet assay, and DNA-lesions. Two out of 2 *in vitro* micronucleus tests are positive, but in contrast 6 out of 7 *in vivo* tests are negative after oral exposure (and only one possibly positive). Also after i.p. administration, most studies were negative (5/7). The exceptions were 2 weak studies by Mañas 2009 and Bolognesi 1997. Overall, I agree with the ODD that the findings are not sufficiently robust to warrant classification. All five *in vitro* Comet assays are positive, but their relevance in relation to mutagenicity is decreased by the very high concentrations used (mM range) and indications of cytotoxicity. Interestingly, both *in vivo* Comet assays were positive in the liver (Mañas 2013, with exposure via the drinking water for 14 days, and Bolognesi 1997, 4 hours but not 24 hours after i.p. administration). One study has also indicated hepatic DNA lesions 24 but not 4 hours after i.p. administration (Bolognesi 1997). These indicator studies are of concern, but it is questionable if they are sufficiently robust as basis for classification, especially in light of the negative standard tests. In addition, I note that in spite of such a big data base, the few positive studies seem to come from mainly 2 research groups (Mañas and Bolognesi, respectively), which is a little odd. Overall, and in spite of indications of hepatic DNA damage, I presently support no classification.	Thank you for your present support.
RAC Member 15	I agree with the rapporteurs that there is no strong evidence that	Thank you for your comments and your

RAC Member	Comments	Rapporteurs' response to comments
	Glyphosate induce oxidative stress as inconsistent results were observed *in vivo*. With regard to the genotoxicity of glyphosate, the ODD is clear and I agree with the conclusion of rapporteurs.	support.
RAC Member 8	I support no classification for mutagenicity. Bacterial mutagenicity studies were clearly negative showing that glyphosate is not reacting with DNA directly. Mammalian cytogenetic studies gave variable results. However, CA studies were mostly negative. I suppose we cannot put too much weight on positive results from *in vitro* Comet assay since this test is rather unspecific and may show effects which do not progress as irreversible genetic damage. In addition, cytotoxicity and lack of dose-response limit the relevance of Comet data. What comes to *in vivo* animal genotoxicity data, I think that overall weight of evidence shows that *in vivo* mutagenicity is negative or at most equivocal, since only 2 studies out of total of 14 *in vivo* MN studies showed positive results and the other positive study (Manas et al., 2009) involved low number of scored cells (*about* 1000/animal). Regarding Manas et al (2009) it should be noted that possible scoring of all erythrocytes (instead of PCE) does not explain the possible wrong positive result (scoring of all erythrocytes instead of PCE will rather result in diluted effect). Anyway, I do not really believe that Manas et al 2009 have been so incompetent that they have counted all erythrocytes instead of PCE; at least in their discussion they refer to immature erythrocytes. However, although in the case of chromosomal aberration test Manas et al state that the scoring was performed blindly by two individual observers, in the case of MN test there is no mention of this. This might be a problem. The main problem of the human study by Paz-y-Mino et al (2007) is in my opinion that the effect of other, confounding factors to the DNA strand	Thank you for your comments. We agree that one cannot assume that Mañas and co-workers (2009) counted mature erythrocytes and not PCEs and that scoring of erythrocytes would rather dilute the effects. However, counting only 1000 PCEs reduces the power of the study. In addition, the MN frequency reported at the top dose of glyphosate is surprisingly high and at odds with all the other observations without any apparent explanation related to dose or protocol. In light of all the other in vivo MN tests and the poor reporting of the study, we do believe that this study is of low confidence. The ODD text has been revised to increase the clarity of the evaluation of the Mañas 2009 study.

RAC Member	Comments	Rapporteurs' response to comments
	breaks cannot to be ruled out. If the subjects suffered from clinical symptoms of poisoning it is likely that they have been exposed also to some other compounds, which may have contributed to the symptoms (as well as DNA strand breaks) since glyphosate itself is of low acute toxicity. The results of the study by Bolognesi et al (2009) cannot provide clear evidence of genotoxicity as the effect was only minor and showed no real association with exposure.	
RAC Member 10	There is a large amount of mutagenicity data available on glyphosate. Although a few studies seem to indicate that glyphosate may have effects on DNA and induce oxidative stress, quite a lot of other, more standard studies are predominantly negative (both in germ cells and in somatic cells). The overall weight of evidence from the available data support the conclusion that there is insufficient evidence for classification.	Thank you for your comments and the support.
RAC Member 12	Glyphosate has been tested in a large number of studies to assess its mutagenic potential. The majority of these studies gave negative results, however, there are also positive studies. Here are some thoughts on the results of these studies: - There are two in vitro micronucleus tests included in the CLH dossier, both positive. One RAC member criticized the positive micronucleus assay by Koller et al. (2012) because of the observed cytotoxicity. Cytotoxicity has been determined using the MN division index, which is very sensitive and is according to OECD test guideline (487) used to determine cytotoxicity. There were no indications of cytotoxicity at 15 mg/L (nor apoptotic or necrotic bodies). Moreover, in the publication of Koller et al. (2012) the cytotoxicity (cell integrity) was tested in various different assays and the outcomes indicate that glyphosate does not effect these parameters to a doses up to 200mg/L (exept LDHe assay). However, it has to be admitted that this study was conducted in a	The description of the study by Koller (2012) has been expanded.

RAC Member	Comments	Rapporteurs' response to comments
	system (buccal carcinoma cells) not previously assessed for its suitability to assess the induction of micronuclei (degree of false positives). The second in vitro micronucleus test (Mladinic et al., 2009a) was conducted in human lymphocytes. It gave positive results with, but not without metabolic activation. Although there are drawbacks in both in vitro micronucleus studies, they indicate that glyphosate may have the potential to induce micronuclei *in vitro*.	
RAC Member 12 [contd.]	- There is a long list of oral and i.p. in vivo micronucleus studies included in the dossier, all assessing the formation of micronuclei in the bone marrow. All oral studies are negative, but there are two positive i.p. studies. The CLH report states that there is sufficient evidence that the bone marrow was exposed to the test compound in these studies. It is referred to toxicokinetic studies reporting that glyphosate has a high affinity to bone tissue, however, in our few this does not necessarily mean that glyphosate also enters the bone marrow, which is high in lipids, while glyphosate is a highly polar compound. The CLH report also states that bone marrow toxicity was seen in toxicity tests and cites a long-term toxicity study in rats (Wood et al., 2009), in which a very high dose of 1077/1382 mg/kg bw/day (m/f) induced bone marrow hypoplasia (degree is not presented in the dossier) and the chromosome aberration test (Suresh, 1994) which reports some decrease in the mitotic index in the bone marrow after exposure to 2 doses of 5000 mg/kg bw within 24 h. It is noted that these doses are extremely high and were possibly not comparable to the doses used in the in vivo micronucleus tests. In addition it is important to look at the PCE/NCE ratios, in order to assess whether the bone marrow was reached in the respective test. While in none of the oral studies this ratio was affected, some effects (though not statistically significant)	Thank you for drawing attention to the ADME study described by EPA 1993. The text is modified with regard to tissue distribution. In the RAR B.6.1 several adme studies are referred to and they seem to indicate that glyphosate distributes broadly in the body including to lipid rich tissue like brain, testis and bone marrow. It is not straightforward to compare the tissue levels from the data given, but muscle and adipose tissue both tend to be at the lower end of the scale, whereas kidney and bone have high levels (ug equiv/g). From Table B.6.1-4 it appears that bone marrow is exposed at a low level comparable to several other tissues, but the levels here are given as % of applied dose.

RAC Member	Comments	Rapporteurs' response to comments
	were seen in the positive i.p. MN test (Bolognesi et al., 1997) as well as in the 600 mg/kg bw group of the study by Duward (2006), which also showed a statistically significant increase in micronuclei, but within HCD. Slight effects on the PCE/NCE ratio were also reported in the negative i.p. micronucleus study by Costa (2010). Furthermore, an investigation indicates that very little glyphosate reaches the bone marrow (after ip injections in rats).[1] So in conclusion we are not totally sure if glyphosate enters the bone marrow in sufficient amount and - looking forward to other experts opinions on this - in the available in vivo micronucleus studies. The assessment of micronucleus formation might have been more relevant in other tissues, like liver or kidneys (there are protocols available). We think that this needs further discussion.	
Carcinogenicity		
RAC Member 13	In general, I think we should take care not to focus too heavily on the statistical nature of the animal study findings. For transparency, could an explanation be provided in the ODD for the re-calculations using the Fisher and Cochran-Armitage tests? This is not done routinely by DS and RAC for studies in CLH dossiers. The lack of consistent tumour findings across most of the carcinogenicity studies in rats and the absence of a clear dose-response in those reporting	This information has now been added.

[1] Male and female Sprague-Dawley rats received single intraperitoneal injections of radiolabeled (14)C-glyphosate. The dose level of glyphosate used for male and female rats was 1150 mg/kg. Blood samples were collected 0.25, 0.50, 1, 2, 4, 6 and 10 hours after injection. Femoral bone marrow samples were collected from one third of the male and female rats sacrificed at 0.5, 4, or 10 hours after injection. Thirty minutes after injection of glyphosate, the concentration of radioactivity in the bone marrow of male and female rats was equivalent to 0.0044% and 0.0072%, respectively, of the administered dose. These findings indicate that very little glyphosate reaches bone marrow, that it is rapidly eliminated from bone marrow and that it is even more rapidly eliminated from plasma. (from: USEPA; Reregistration Eligibility Decision (RED) Database for Glyphosate (38641-94-0). EPA 738-R-93-014 (September 1993). Available from, as of January 25, 2006: http://www.epa.gov/pesticides/reregistration/status.htm

RAC Member	Comments	Rapporteurs' response to comments
	increases in pancreatic tumours suggest that any "positive" findings are incidental and should not be used to support classification. The sex-specific nature of the findings can also be taken into account. However, I look forward to an in-depth discussion about the biological significance of these findings at the next plenary meeting. Generally, in my experience, when a carcinogenic substance produces a carcinogenic response in the liver and thyroid of rats, the findings are evident across different studies conducted under similar conditions. Similarly, it is often possible to suggest a possible mechanism of action for such carcinogens. In the case of glyphosate, the finding of slightly increased benign tumours has not been replicated across the available studies and there doesn't appear to have been a plausible mechanistic explanation for this observation. Therefore I agree with the rapporteur's assessment of these 2 tumour types. I'm not convinced that a decreased weight gain of approx. 15% could account for the renal tumour findings in some of the mouse studies. Can more detail be included to emphasise the lack of a plausible mechanism and relevant pathology, in association with the very high doses employed and unexplained apparent sex-specificity of this observation? The lack of a consistent profile across studies suggests that the haemangiosarcoma and lymphoma findings were incidental. I agree with the rapporteur's conclusion about the possibility of a genotoxic mechanism being demonstrated for glyphosate – i.e. this does not seem plausible. No plausible mechanisms appear to have been found. I would welcome plenary discussion about the epidemiological data, especially a compare and contrast analysis of the papers by Chang and Delzell (2016) and Schinasi and Leon (2014), but am generally in favour of the points made in the draft ODD. Presumably the findings of Fortes et	The text has been revised to clarify that the reduced weight gain is not proposed as an explanation of the increase in renal tumours, but is rather related to evaluation of human relevance.

RAC Member	Comments	Rapporteurs' response to comments
	al (2016) can be dismissed because of a lack of specificity to glyphosate?	*These are the published meta-analyses which come to the same result. This is also the case after using the most adjusted numbers as in the IARC monograph. Please see added text in the ODD. We look forward to*

RAC Member	Comments	Rapporteurs' response to comments
		the discussion in RAC.
RAC Member 1	I basically share most of the arguments stated in the ODD. Classification as 1A is not possible because, despite the large data base, bias and cofounding factors cannot be ruled-out in none of the available study. Solomon estimated in 2016 (doi: 10.1080/10408444.2016.1214678) the worst exposures in the order of tenths of µg/kg bw/day, while the lowest exposure causing presumably significant carcinogenesis in animals were in the order of units of mg/kg bw/day. These several orders of magnitude of difference between human and animal exposures do not contribute to make plausible the possibility that glyphosate was carcinogenic for humans. Classification as 1B or 2 should not be supported because there are lot of concerns regarding the biological relevance of the reported tumours. The weight of the evidence plays, in my opinion, in favour of the no classification by the following reasons, **see the Table in the attachment below**. In conclusion, the carcinogenicity reported in these studies does not warrant classification due to lack of consistence (the results are not reproducible in different species but also within the same species), the statistical significance is weak (only statistically significant trends were reported in a few cases), the effects were reported in some cases at extraordinarily high concentrations and the incidences were always low (only slightly above and sometimes even within the historical control data). Thus, **I support the rapporteurs' proposal for no classification.**	We agree that Carc Cat 1A is not justified.
RAC Member 3	Carcinogenicity in rats Pancreatic islet cell tumours	

RAC Member	Comments	Rapporteurs' response to comments
	The incidences of pancreatic islet cell tumours in concurrent control group of male rats ranging from 0% to 14% in all 7 rats studies as presented in a table below indicating the considerable variability of this tumor incidence in control animals. In four studies (Wood et al., 2009; Enomoto, 1997; Suresh, 1996; Atkinson et al., 1993) the incidence of pancreatic islet cell tumours in rats exposed at the highest dose was lower than in concurrent control groups respectively: four, four, three and seven times. The highest incidence of pancreatic islet cell tumours was observed in Stout and Ruecker study (1990) and the Lankas study (1981) respectively 17.8% and 10.2%) in rats exposed to glyphosate at lowest dose, with no further increase of tumors incidence with the increased of the dose. The incidence of this tumor in the control group in these studies (4.6% and 0%) was the lowest among concurrent control group (0% to 14%). Therefore even these two studies (Stout and Ruecker, 1990; Lankas, 1981) do not provide sufficient evidence for the glyphosate treatment related increase of pancreatic tumors in rats. In none of the 7 studies a dose-response was observed. The analysis of the data from all studies indicates that glyphosate does not increase an incidence of pancreatic islet cell tumours in rats. **Table about the incidences of pancreatic islet cell adenomas and carcinomas combined in male rats, see the attachment below.** <u>Liver tumours</u> No significant dose-dependent increase in glyphosate-related liver tumours was observed in the 7 long-term studies in rats. Only in the study by Stout and Ruecker (1990) a positive trend for increase in incidence of liver adenomas (4.5%, 4.4%; 6.1% and 14.6% in 0, 89, 362 and 940 mg/kg groups) was noted when evaluating with Cochran-Armitage trend test, but the increased incidence of liver adenoma was not noted in the pairwise testing against concurrent control (Fisher exact test). There was no	

RAC Member	Comments	Rapporteurs' response to comments
	progression to malignancy in the exposed groups as the incidence of liver carcinomas was slightly higher in controls than in the glyphosate treated groups. The hepatocellular adenoma incidences in the glyphosate treated animals were within the historical control range from the test facility (1.4%-18.3%) as cited by EPA (EPA 2015).	
RAC Member 3 [contd.]	No statistically significant trend increase was reported for liver adenomas and carcinomas combined. The analysis of the data from all studies indicates that glyphosate does not increase an incidence of liver tumours in rats. Thyroid C-cell tumours Out of seven available long-term carcinogenicity studies on rats only in the study by Stout and Ruecker (1990) a positive trend for increase in incidence of thyroid C-cell adenomas (3.5%, 3.3%; 10.2 % and 10.9 % in 0, 89, 362 and 940 mg/kg group) was noted in female, but not in male rats when evaluating with Cochran-Armitage trend test, but the increased incidence of thyroid C-cell adenomas in female rats was not noted in the pairwise testing against concurrent control (Fisher exact test). **Table about female rat adenomas and carcinomas, see the attachment below.** For males, the increased incidences of adenomas or combined adenomas/carcinomas in the study by Stout and Ruecker (1990) were not statistically significant. No progression from adenoma to carcinoma is indicated in this study. The thyroid C-cell adenoma incidences in the high dose glyphosate treated animals were slightly higher than the historical control range (3.3%-10.0% in females) as referred by EPA (EPA 2015). No increase in thyroid C-cell adenomas was reported in the other 6 long-	

RAC Member	Comments	Rapporteurs' response to comments
	term studies in rats. In these other studies, there were no increase in pre-neoplastic histological lesions and no thyroid weight change noted in response to glyphosate exposure. Conclusion: **The rapporteurs and DS conclusion on lack of sufficient evidence of carcinogenicity of glyphosate in rats is supported**.	
RAC Member 3 [contd.]	Carcinogenicity in mice Renal neoplasms The incidence of tubular-cell renal adenoma /carcinoma in male, but not in female rats, was slightly above historical incidence value for these type of tumours in CD mice only at a highest doses above 4000mg/kg, which was higher than MTD due to weight loss bigger than 10% during the study period. So these incidences alone should not be taken as sufficient evidence of carcinogenicity of glyphosate. Since no increase in incidence of these tumours were seen at lower doses of 1000mg/kg the existing evidence is not sufficient to indicate that the substance pose a hazard by increasing a frequency of tubular-cell renal adenoma/carcinoma in male mice. Haemangiosarcoma in liver and spleen In male mice exposed at the highest dose of 1000mg/kg bw/day the incidence of haemangiosarcoma reached the upper range of historical control value of 8% in the Atkinson et al. 1993 study. The incidence of haemangiosarcoma (4%) in the Sugimoto study at the highest dose of 4348mg/kg bw/day were within historical control for this laboratory (0-12%). These increases were not statistically significant when compared with concurrent controls, although the trend was statistically significant, but only due to incidences observed at the highest doses in both studies. No haemangiosarcoma were observed in both studies at the medium doses of 300 and 838mg/kg bw/day. In three other studies, no increases	

RAC Member	Comments	Rapporteurs' response to comments
	in the incidences of haemangiosarcomas were reported in response to glyphosate treatment. Thus, there is a positive trend in two studies only created by the incidence at the top doses still being within historical control values for the same labolatories. In addition this finding is not consistent across the five studies evaluated. In addition, the increase in haemangiocarcomas in the study by Sugimoto et al. (1997) was only observed at the very high dose of more than 4000 mg/kg bw/day.	
RAC Member 3 [contd.]	<u>Malignant lymphoma</u> A trend to increase an incidence of malignant lymphoma in male, but not in female mice, was observed in two out of five carcinogenicity studies in mice. No statistical increase of lymphoma incidence was observed in any treated group in any study when compared with Fisher exact test with concurrent controls. The highest incidences of malignant lymphoma were within historical control values. <u>Conclusion:</u> **Taking into account the weight of evidence approach I agree with the rapporteurs and DS that there is no sufficient evidence of carcinogenicity of glyphosate in mice. I also support a comparison of RAC and IARC evaluation showing that IARC evaluation focused mostly on positive findings giving minimum weight to evidences suggesting lack of carcinogenicity, while RAC evaluation used both types of findings in a weight of evidence approach.** <u>Human data – epidemiological studies</u> The evaluation of epidemiological studies is well written and indicates that at present a causal relationship between exposure to GBH and any type of cancer cannot be confirmed. The coverage of available epidemiological data seem to be good and their interpretation is appropriate in my opinion.	Thank you for your reflections and viewpoints on the animal carcinogenesis studies. Thank you!

RAC Member	Comments	Rapporteurs' response to comments
	However, only for the cohort study (the U.S. Agricultural Health Study (AHS) there is information how the exposure information was collected. It is also important to provide information how the information on time length of exposure and level of exposure if any was collected for the case-control studies. As far as I know most frequently such information does not exist for the case-control studies carried out with questionnaires where such information depends only on memory of the respondent. Still in the discussion at last meeting of RAC it was noted that for the U.S. Agricultural Health Study the exposure time was too short to cause cancer, while in fact in most of the case-control studies the time of exposure and time between exposure and a time of interview is unknown and most probably much shorter than in case of AHS study.	More information on how information was collected has been added in the ODD. Usually in the case-control studies use of a certain pesticide is reported as ever/never, but sometimes also an exposure-response is described, e.g. as number of events per year. More information is added to the ODD. It will be interesting to follow the AHS further to see how more cancer cases develop. For the case-control studies, the starting point are the cases, and one cannot assume that the preceding exposure time is shorter than in cohort studies.
RAC Member 3 [contd.]	Also a meaning of " exposed case of NHL and control case of NHL" e.g. used in the sentence on page 46: - *"In the Swedish case-control study based on 29 exposed cases and 18 exposed controls NHL was associated with reported exposure to glyphosate (initial OR 2.02/CI 1.10-3.71, Eriksson et al., 2008),"* - could be better explained as many readers of the RAC opinion are not trained epidemiologists. In the CLH report these numbers are more informative: "Eriksson et al. (2008, ASB2012-11614) reported a case-control study which included 910 cases of NHL and 1016 controls living in Sweden. The highest risk was calculated for MCPA. Glyphosate exposure was reported by 29 cases and 18 controls, and the corresponding odds ratio (OR) was 2.02." So it is proposed to rephrase this sentence to"	We agree! Text has been changed accordingly!

RAC Member	Comments	Rapporteurs' response to comments
	"In the Swedish case-control study which included 910 cases of NHL and 1016 controls living in Sweden 29 persons with NHL and 18 control persons reported exposure to glyphosate giving an initial OR 2.02/CI 1.10-3.71,(Eriksson et al., 2008)," In general the case-control studies are designed to detect an association of the disease with exposure and not to detect a causal relationship between a case of disease and exposure. The higher odds ratio does not mean the same as higher risk characterisation ratio, although they look similar at the first glance.	We hope the text is clear on these points.
RAC Member 3 [contd.]	<u>Comparison with the CLP criteria for carcinogenicity</u> I support no classification of glyphosate for carcinogenicity as proposed by the rapporteurs. However, I propose to re-think a sentence in justification for not classifying to category 2 on page 51 e.g. ". *For pancreatic tumours, no clear dose response became apparent in the two studies in which an increase was observed (Lankas, 1981, Stout and Ruecker 1990). Moreover, these tumours could not be reproduced in any of the other long-term studies."* This sentence does not seem to reflect a weight of evidence approach used by the rapporteurs throughout ODD by emphasising *"an increase was observed (Lankas, 1981, Stout and Ruecker 1990)".* My proposal is "*The incidences of pancreatic islet cell tumours in concurrent control group of male rats in all 7 rat studies ranging from 0% to 14% indicate the considerable variability of this tumor in control animals. In four studies (Wood et al., 2009; Enomoto, 1997; Suresh, 1996; Atkinson et al., 1993) the incidence of pancreatic islet cell tumours in rats exposed at the highest dose was lower than in concurrent control groups, respectively: four, four, three and seven times. The highest incidences of pancreatic islet cell tumours in Stout and Ruecker study*	Thank you! The text has been expanded in an attempt to strengthen the argumentation in the section "Comparison with the CLP criteria".

RAC Member	Comments	Rapporteurs' response to comments
	(1990) and the Lankas study (1981) respectively 17.8% and 10.2%) were observed in rats exposed to glyphosate at the lowest dose, with no further increase of tumors incidence in groups administered two higher doses of glyphosate. The incidence of this tumor in the control groups in Stout and Ruecker study (1990) and the Lankas study (1981) (respectively, 4.6% and 0%) was the lowest among concurrent control group (0% to 14%). Therefore these two studies (Stout and Ruecker, 1990; Lankas, 1981) do not provide sufficient evidence for the glyphosate treatment related increase of pancreatic tumors in rats. In none of the 7 studies a dose-response was observed. The analysis of the weight of evidence from all studies indicates that glyphosate does not increase an incidence of pancreatic islet cell tumours in rats. "	
RAC Member 4	I support no classification. Animal studies Although the OECD TG 451 does not specify a limit dose, OECD TG 453 (combined chronic toxicity and carcinogenicity study) does specify a limit of 1000 mg/kg bw/d. This limit dose is further mentioned in the OECD GD 116 (p. 66). I do not support consideration of effects seen above 4000 mg/kg bw/d as substances are not normally tested at such levels and the levels of human exposure to glyphosate by no means indicate the need to test such levels. If the limit dose is 1000 mg/kg bw/d is accepted, then only the following tumours and studies remain: • Pancreatic islet cell tumours in male rats (Stout and Ruecker 1990, Lankas 1981) • Liver tumours in male rats (Stout and Ruecker 1990) • Thyroid c-cell tumours in female rats (Stout and Ruecker 1990) • Renal tumours in male mice (Kumar 2001)	Thank you for these reflections.

RAC Member	Comments	Rapporteurs' response to comments
	• Hemangiosarcomas in male mice (Atkinson 1993) • Malignant lymphomas in the mouse (Wood 2009, in males; not significant in Kumar 2001 and Atkinson 1993) The overall picture is very inconsistent with most tumours limited to only one study, one species and one sex. Exceptions are pancreatic tumours in male rats and malignant lymphomas in the mouse. As to the pancreatic tumours, the study of Lankas (1981) used very low concentrations (up to 31.5 mg/kg bw/d); all of them can be viewed as "controls", which is supported by the lack of dose-response. Then we are left with only one study (Stout and Ruecker 1990) where the incidence lacks dose response (2-8-5-7) and the finding is limited to one sex. As pointed out in the ODD, malignant lymphoma is a common tumour in mice with high and highly variable background incidence. Oncogenic viruses and environmental factors (e.g. diet, cage position) are likely to contribute to this variability (*Greaves: Histopathology of Preclinical Toxicity Studies*). Taking this into account, I consider the historical control data presented in the CLH report to cover the incidences observed in all the above-mentioned studies.	
RAC Member 4 [contd.]	As to the statistical analyses presented by [the IARC representative] at RAC 39, I do not support his method of pooling the data from individual studies without due interpretation of the individual studies first. Crucial information such as lack of dose-response in an individual study, high background incidence and other is simply lost, and misleading numbers are likely to result. <u>Human data</u> The meta-analyses by IARC (2014) and Chang and Delzell (2016) both show a weak, barely statistically significant positive association for NHL	We agree that chance, bias or confounding cannot be ruled out.

RAC Member	Comments	Rapporteurs' response to comments
	(meta-RR 1.3, CI 1.0-1.6). I consider co-exposure to other pesticides as a potentially significant confounder as many of these pesticides (and their formulations) are probably much more toxic than glyphosate and it may be difficult to distinguish effects of the many pesticides the subjects were exposed to. I support the conclusion in the ODD.	
RAC Member 14	As regards the rat data, they do not support classification. Although pancreatic islet cell tumours were noted in 2 studies, they occurred without any dose-response, and therefore I think that the 5 negative studies carry more weight. Liver tumours were observed in one study out of, 7, but it was only adenomas and seemingly within the historical control data (HCD). There was possibly an increased incidence of benign thyroid C-cell tumours in one study, but there were also 6 negative studies carrying more weight. Five studies in mice are available. For the renal neoplasms, Knezevich and Hogan (1983) indicate an increased incidence outside the HCD, and the study by Kuman (2001) indicate a dose- response related increase in renal neoplasms. On the other hand, very high dose levels were used, and there are no indications of tumours at dose levels below 1460 mg/kg/day. As to HCD, there are problems with the comparison with the HCD published by Giknis and Clifford. The data is not relevant as they represent too many years (13 whereas the guidance states within 5 years), only 2 of the 5 studies were conducted within this period, and they represent adenomas and carcinomas separately whereas the study data are given for the combined incidence of adenomas and carcinomas. Thus, I don't think we should use the HCD by Giknis and Clifford (2005) in this ODD, and if the rapporteurs still decides to use them, the limitations should be clearly stated. In principle, we should not comment on the relation to HCD if we don't have proper HCD. Although I possibly find the mouse renal neoplasms being the tumour of highest concern in this data base, I can support that the data is not sufficiently consistent as basis for a	We agree that preferentially, only correct HCD values should be used. However, for several of the studies they are not available to us. We believe that the information in reports from the Charles River lab on CD-1 have some value, especially for the evaluation of malignant lymphomas as it lists data from both 18 and 24 month studies separately, but will specify clearer that they are not proper HCDs.

RAC Member	Comments	Rapporteurs' response to comments
	classification (with 2 clearly negative studies up to doses of 1000 mg/kg/day), and in addition the tumors are only occurring at very high exposure levels. According to the CLH report, the general toxicity of these high dose levels (1460-4800 mg/kg/day) seems limited, but I note that the ODD mentions body weight gain reductions greater than 15%. In addition, the 4 acute oral toxicity studies in mice report piloerection and hypoactivity at 2000 mg/kg in Charles River and NMRI mice and at 5000 mg/kg in ICR mice, and more importantly, mortality, lethargy, and ataxia as from 2500 mg/kg in Swiss albino mice (also used in the Kuman study). I agree with the ODD that the relevance of the highest doses can be questioned.	
RAC Member 14 [contd.]	For the haemangiosarcomas, very low incidences were observed in 2 out of 5 studies, but at the same time there were 3 negative studies and I therefore think the haemangiosarcomas are of low relevance. For the malignant lymphomas, there are 4 studies with increased incidences in male mice although only 2 are statistically significant, with the study by Wood (2009) as the most convincing (0, 2, 4, and 10% incidence at 0, 71, 234, and 810 mg/kg/day, respectively). The other statistically significant finding was a 12% incidence at a dose level of 4348 mg/kg/day (with a 4% control incidence), but it didn't exceed the HCD. The HCD by Giknis and Clifford (2005) is not relevant (as it represents a period prior to the conduct of the Wood study), so we don't know how the observed incidences relate to HCD from the Wood laboratory (if it would be available). The control incidences in the other studies in CD-1 mice were 4 and 8% in males, and 12-28% in females. However, the overall results from the mouse studies are not very consistent, the increases are small and observed at high exposure, in some cases within the HCD, and it is therefore questionable if the data are sufficiently robust for classification.	

RAC Member	Comments	Rapporteurs' response to comments
	[The IARC Representative] presented at the last RAC meeting dose-responses combined for all studies, but per tumour type and clustered by similar doses. These graphs may suggest substance-related effects, but the dose-responses are in that case extremely shallow, possibly indicating effects at 4500 mg/kg/day, but with too large variations to allow firm conclusions.	
RAC Member 14 [contd.]	Concerning the comparison with IARC (page 44 of the ODD), I have 2 editorial comments. I would recommend deleting the second sentence as it may indicate that IARC is not using WoE or expert judgement. I would also recommend deleting the word "independent" on the third last line, as it may suggest that RAC is of the opinion that IARCs statistical assessments are not being independent. As to the human data, I support that they are difficult to evaluate, e.g. because the studies are small, the exposure is often unclear and the exposure to glyphosate is mediated via different commercial products. Thus, they may not prove a causal relationship between glyphosate and increased incidences of tumours in humans. However, the suggested relation between exposure to glyphosate and occurrence of non-Hodgkin's lymphomas is interesting in light of the possibly increased incidences of lymphomas in many of the mouse studies. Overall, although the animal data possibly suggest increases incidences of many different tumours in two different species, the increases are generally very small, often within the HCD, not consistently observed among the studies, and only observed at very high exposure levels. The concern for findings at such very high exposure levels is decreased by the doses being at, or close to MTD, and that there is no robust evidence for a mutagenic MoA. Still, the hepatic DNA-damage, the mouse malignant lymphomas, and the human non-Hodgkin's lymphomas are possibly causes for some concern. At present, though, not fulfilling the criteria for	Agree, changes made accordingly. Agree. We have added a new sentence about our concern in the end

RAC Member	Comments	Rapporteurs' response to comments
	classification.	of the section on epidemiology.
RAC Member 5	**Animal data:** I appreciate the clear overview on studies, their outcomes and also the discussion on differences in IARC classification and that of RAC under CLP. I have the impression that statistics are weighted much. Statistical analysis is important as tool to aid in inferring whether experimental manipulations caused an effect, but biology is rather difficult. Biological relevance of effects at excessive high doses, i.e. > MTD, lack of plausible MoA, inconsistency throughout the studies, and high and/or variable background incidences certain tumours are important points to consider in the overall weight of evidence. Please find some remarks on the individual findings: <u>Rat studies - Pancreatic islet tumors:</u> Pancreatic islet tumour are reported for 2 studies but no dose-response relationship is evident. The Lankas study used quite low dose levels and control incidences of the various rat studies is variable and in 4 studies higher than the Glypho groups. This is mentioned in the ODD p. 37, but maybe it could be more clearly highlighted that comparing to control incidences in the other rat studies, these low dose Glypho groups in the Lanka study (with 2 adenoma and one carcinoma in a single male in the high dose) would reflect rather spontaneous (control) incidences. On page 38 of the ODD in the summary paragraph for rat studies, it is said "*in male rats increased incidences of benign pancreatic and liver tumours was reported in the study by Stout and Ruecker (1990) with some support for pancreatic islet cell adenoma form an older, non-valid, study (Lankas, 1981).* Could the rapporteurs please clarify what is meant with "*non-valid*"	The study by Lankas is non-valid in the sense that the doses are too low and in the RAR it is stated that it has severe reporting deficiencies. It is included in the ODD as a supporting study for the evaluation of potential increases in pancreatic adenomas. The text has been revised for clarification.

RAC Member	Comments	Rapporteurs' response to comments
	and why this study then has been included in the assessment? In the last paragraph p.37 it is said that the findings are not found in additional guideline compliant rat studies. It could be also mentioned that pancreatic tumour were also not found in mice and also not in females in the rats. I agree to the conclusions of the rapporteurs that the studies do not provide s evidence for carcinogenicity.	
RAC Member 5 [contd.]	Rat studies - Liver tumors: The ODD brings clearly the arguments forward but maybe to add that no liver tumours have been found in the mouse studies either. I fully agree to the conclusions of the rapporteurs without any reservations. Rat studies – Thyroid C-cell tumors: An increase in the incidence of thyroid cell C-cell adenoma was reported for both sexes in one study (Stout and Ruecker). Although not statistical significant for males, could these data be included in the table for transparency issues? The high dose incidence is close to the HCD from EPA (2015) – could it be made clear whether it is the HCD of the same laboratory? Since these tumours are not reported for any other rat study and mice, no increase in pre-neoplastic lesions or thyroid weight change and importantly also no malignancy progression, I agree with the rapporteurs´ conclusion that it is not sufficient evidence for carcinogenicity. My overall conclusion on rat studies is that all these findings including pancreatic, liver and thyroid tumours appear to be spontaneous in nature and not treatment related and thus I support the rapporteurs. Mice studies – renal neoplasms: In 3 out of 5 studies in the top doses renal tumours are reported. Renal tumours in CD-1 mice are rare and for rare findings, statistical significance might not be obtained although the differences between groups might be nonetheless biological significant. For the Knezevich study, incidence of	The data for males are now included in Table 5. The EPA report gives the following reference: *Stout, L. D. and Ruecker, P.A. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. Laboratory Project No. MSL-10495; September, 26, 1990, MRID No. 41643801;* ***Historical Controls; MRID No. 41728701***. We have not found any reference to these HCD in the CLH report and can therefore not verify their appropriateness. However, we have chosen to refer to the data in the EPA report to give some support to the evaluation of biological relevance.

RAC Member	Comments	Rapporteurs' response to comments
	top dose was above the HCD of the same laboratory (EPA, 2015). However, the top dose was almost 5000 mg/kg bw*d which questions the relevance of this finding. Same applies to the study of Sugimoto with the top dose > 4000 mg/kg bw*d – here also no dose-response is evident. The ODD refers to Charles River HCD – please see my comment on these data below in the comments for lymphoma. Consideration of these data can be criticised. Relevance of findings at such high dose for humans is highly questionable, looking forward to discussion at the plenary whether to consider these findings for Glypho (MTD might be exceeded but rather marginal toxicity at these top doses).	The human relevance (or lack of relevance) of high dose findings especially when they are not supported by tumourigenicity at lower dose levels, is indeed an important issue for RAC to agree upon. The text is expanded slightly for increased clarity.
RAC Member 5 [contd.]	P. 40 of the ODD states that tumours were observed at termination. Is there information regarding interim sacrifice and can long latency be concluded for these tumours? Conclusion from this statement is left up to the reader. No relevant chronic nephrotoxicity / pre-neoplastic lesions are reported in these studies. Absence of such findings and absence of genotoxic MoA gives further confidence in the assessment. Overall considering that renal tumours appeared in 2 studies at such high doses and in the third studies also exceeding 1000 mg/kg bw*d, only in one sex and not in rats, I agree with the rapporteurs that overall evidence is weak. However, I think we should make our mind more clear up as to whether consider these high dose findings. The OECD guidance document 116 elaborates on the top dose selection and may give further indication, e.g. beside body weight gain depression of no more than 10 %, toxicokinetic nonlinearity should also be considered in the selection of the top dose. <u>Mice studies – Haemangiosarcoma:</u> Increase in haemangiosarcoma were found in two studies in mice in the top dose in males, not in the rat studies. In the Sugimoto study the top dose-only increase was within the HCD of Charles River Lab. Again the relevance of the high dose (< 4000 mg/kg bw*d) finding for humans is	Thank you, text is corrected.

RAC Member	Comments	Rapporteurs' response to comments
	questionable. At the Atkinson study the top dose-only finding was at the upper edge of the relevant HCD of the laboratory and may be discounted. I agree that the finding is of low significance considering effects in one sex, one species / one strain, at/within HCD range. In line with the HCD ranges given in the ODD (8 % upper edge for the Atkinson study and 0-12 % for Charles River Lab, see also my comment on Charles River HCD below for lymphoma), literature reports that haemangiosarcoma occur spontaneously in rats and mice, higher in mice, and higher in males and higher in certain strains including CD-1 mice (see a review of Cohen et al, 2009). Editorial remark: p- 41 second paragraph below the table refers to increase in renal tumours. Is this a typo?	
RAC Member 5 [contd.]	<u>Mice studies – malignant lymphoma:</u> Increase in malignant lymphoma was reported for overall 4 studies, 3 studies in CD-1 mice and one study in Swiss albino mice. Statistical significant trend was obtained only for two of these studies, i.e. Wood et al and Sugimoto in CD-1 mice. For the Atkinson study in CD-1 mice, no dose-response is clear (4-2-1-6). For the Sugimoto study the trend is attributable to the top dose only, showing 12 % incidence obtained at > 4000 mg/kg bw*d - this with questionable relevance of the finding for humans due to extra-high dose, while the incidence was within the HCD of the laboratory, and thus maybe discounted. The lower doses were comparable or below the concurrent control. For the Wood study a very flat dose-response appears and this seems to be the most relevant study, however only the high dose (810 mg/kg bw*d) has very weak statistical significance (Fisher test p slightly > 0.05), but is still within the HCD of Charles River lab (Giknis and Clifford 2005). I understand that these HCD are from different laboratory environments and their use might be criticised as regards to relevance. The IARC	

RAC Member	Comments	Rapporteurs' response to comments
	preamble states:" *It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals*.	
RAC Member 5 [contd.]	I did not check the reference HCD (Giknis and Clifford). Since lymphoma is higher in females it would be interesting to know HCD specific for males? It needs nevertheless to be taken into consideration that for CD-1 mice lymphoma is a common finding and that females are more prone to develop lymphoma. No increase in lymphoma in females is reported in the Wood study or in the other studies with CD-1 mice. In the study with Swiss mice from Kumar, males showed increased incidences in all groups and females at the top dose. The study results confirm that lymphoma background incidences are high in this strain. I agree that the relevance of this finding may be rather unlikely and acknowledge that no statistical significant trend is reported. Overall, the evidence in these mouse studies regarding lymphoma seem not to be sufficient for classification, but it is debatable and may be of concern in my point of view. **Human data:** In general epidemiology studies showing a clear association are highly	The use of the general control data from Giknis and Clifford is revised in the ODD. It is the data for male animals that are given in the text, but both male and female values may be derived from the publication and separated in accordance to study duration and initiation date. The malignant lymphoma range is up to a maximum of 21.7% in males and 50.0% in females.

RAC Member	Comments	Rapporteurs' response to comments
	relevant, but it may be difficult or rather impossible to quantify exposure or to associate exposure with a disease coming years later. Although a weak statistical significant association appear for NHL and GBH, chance and bias cannot be ruled out. In particular pesticide application by professionals is always characterised by exposure to several pesticide in the course of a year or season with quite some of them bearing considerable toxicity. Notably, per culture 1-2 applications are done in the course of a year for Glypho, while for e.g. fungicides several applications, almost regular during seasons, are applied. Just to be clear that exposure to other pesticides is important. The application scheme for Glypho did not really change in the last decades and I think it also comparable for GMO with the only difference that it is applied as selective herbicide here. Since the association is rather weak and no causality can be demonstrated with these Epi data, they do not support classification of Glypho based on these data. I support the discussion and conclusion in the ODD. **To conclude, I agree with the evaluation of the rapporteurs.**	Thank you for the support. Thank you for your support.
RAC Member 15	▪ *Rat tumours*	

RAC Member	Comments	Rapporteurs' response to comments
	Pancreatic islet cell tumours As the increased incidence was not dose-related, consistent with other control values in Sprague-Dawley rats, without progression to malignancy and only in males, without evidence of pre-neoplastic lesions, I agree with the rapporteurs that the increase tumor may be considered limited. Do you have information if the Sprague-Dawley rats from the Atkinson and Stout and Ruecker studies came from the same source? Moreover, is the number of control females showing pancreatic cell tumours available in the Atkinson study? ***Liver tumours*** The increase in hepatocellular adenoma in only one out of seven studies, in one sex and inside HCD is not considered to demonstrate consistent evidence. ***Thyroid C-cell tumours*** The increase in C-cell tumors was observed in both sexes in one study and was only slightly outside HCD. C-cells are involved in calcium homeostasis. In sub-chronic toxicity studies, lower blood calcium levels were observed in a 90-day, one-year and 52-week toxicity study in dog, sub-chronic and chronic toxicity in rats. Nevertheless, decrease calcium content was not reported in this study. As pre-neoplasic lesions were not observed in any studies l agree with the rapporteurs that the tumours in thyroid observed in the rats studies are of limited relevance. ▪ *Mice tumors* ***Haemangiosarcoma*** I agree with the rapporteurs that this tumor was of low consistency.	Two different laboratories performed these studies. Female incidences of pancreatic islet adenomas: 1, 2,2,2,1 (ctrl to high dose).

RAC Member	Comments	Rapporteurs' response to comments
	Renal neoplasms The kidney tumor is a rare tumor. Increase incidences were observed in 3 studies. In the study of Kumar et al., 2001, a trend was observed in the incidence and historical control data are not available for this strain. The findings observed at very high dose above 4000 mg/kg bw are considered of less concern but support the relevance of the increase tumors observed in the Kumar study at 1460 mg/kg bw.	
RAC Member 15 [contd.]	As the renal tumors were observed at termination, without pre-neoplasic lesions, only in male mice and observed at very high doses above 1000 mg/kg bw, the overall evidence could be considered weak. ***Malignant lymphoma*** A dose-related increase in malignant lymphoma was observed in males in the Kumar et al. study that may be treatment related. Trend was observed in 3 out of the 4 studies in CD-1 but inside historical control values and without dose-relation. It is known that this type of tumors is very common in mice. Moreover, in two studies the increase was only observed at very high dose (>4000 mg/kg bw) and within HCD that lowered the concern. In the Kumar study, no historical controls data are available and therefore it is not clear whether the dose-related increase incidence in males and the increase in females at the high dose is treatment related or may be due to the high background incidence in this strain. Moreover, there is no historical control data for this strain of mice. Moreover, the results were not statistically significant. I suggest deleting the sentence "mostly negative findings in female mice is regarded as a sign of reduced consistency of the mouse carcinogenicity data" because the sex difference for this type of tumors was consistently seen in the five mice studies and in historical controls. In conclusion, in mice, increase renal neoplasms and malignant	The text has been altered to specify that all CD-1 studies were neg for females.

RAC Member	Comments	Rapporteurs' response to comments
	lymphomas were observed in one study (Kumar et al., 2001). These effects are supported by two other studies but only at very high dose levels (> 4000 mg/kg bw). **Based on the overall database, I agree with the rapporteurs that no hazard classification is warranted for carcinogenicity of glyphosate.**	
RAC Member 8	I support no classification for carcinogenicity. Epidemiological data do not show clear evidence on carcinogenicity of glyphosate, therefore, classification should be based on animal data. Five rat studies did not show any increase in tumors. One old study (Lankas et al., 1981) shows only dose independent increase in benign pancreatic islet tumors, which is statistically significant only at the lowest dose level. Since no dose-response is observed, tumors observed in this study cannot to be judged as treatment related. It is stated in the draft opinion that Lankas et al (1981) suffers from several flaws. For transparency reasons, I suggest to describe more in detail what are these flaws. If Lankas et al (1981) study cannot provide any evidence on carcinogenicity the only study showing carcinogenicity is the study by Stout and Ruecker (1990). Also in this study, no dose-response was seen for pancreatic adenomas and increases in hepatic and thyroid adenomas were only minor; within or close to historical control levels. Since these findings were not replicated in five other, more recent studies, casts this doubt over these findings. Regarding mice studies, I fully agree that we should not put weight on the findings at the highest doses of >4000 mg/kg – they are such a high doses that they are likely to compromise animal's health in long-term exposure, which may have an impact on tumor incidence. When these high doses are not taken into account, only noteworthy finding in mice studies was a small increase of malignant lymphoma in male mice – in females no consistent increase in lymphomas was observed in five studies. The high background incidence of this tumor type in mice decreases the	We agree that the epidemiology data do not show clear evidence of carcinogenicity (rather very limited evidence). However both animal and human data must be taken into account in the final classification. The text concerning the Lankas study has been slightly revised.

RAC Member	Comments	Rapporteurs' response to comments
	importance of this finding. Taking into account both the rat and mice carcinogenicity data and lack of genotoxicity, overall weight-of evidence does not support the carcinogenicity of glyphosate.	
RAC Member 18	We appreciate the detailed and comprehensive ODD prepared by the rapporteurs and the ad hoc group. We understand the overall conclusion of the rapporteurs that classification of glyphosate for carcinogenicity is not warranted when all available data is evaluated according to CLP criteria by weight of evidence determination. Furthermore, we agree that the tumour findings in the rat studies do not justify classification for carcinogenicity. However, since epidemiological data suggested slight concern with respect to lymphomas in humans we would appreciate more detailed discussion on malignant lymphomas observed in mice studies. Increased incidence of malignant lymphomas in males at the high doses were observed in total of 4 mice carcinogenicity studies. Two studies, Kumar (2001) and Wood *et al.* (2009) show a dose related increase in malignant lymphomas in male mice. In the study of Kumar (2001) also in the high dose females there was a marked increase in malignant lymphomas. Increased incidences of lymphomas appeared to be sex-specific, the MoA is unknown (although there is some concern on genotoxicity, e.g positive Comet assays) and there are no ADME data to explain sex specificity. Thus, the biological significance of the finding is questionable. However, in our view the increased incidence of malignant lymphomas in male mice seem to be related to glyphosate treatment and thus the concern on carcinogenicity of glyphosate cannot be unequivocally excluded. We note that also in the ODD it is stated: "We agree thus, the lymphoma data appears fairly consistent across the male animals." and furthermore: "Across the five studies, all report a positive trend in males for one or more of the tumour types evaluated suggesting a potential	We agree that the lymphoma data in male mice is of potential concern, but in our view the strength of the evidence and human relevance is not strong enough to warrant classification. We hope for a fruitful and critical discussion of the WoE at the RAC meeting. The text has been expanded to clarify the arguments.

RAC Member	Comments	Rapporteurs' response to comments
	concern for a tumour effect at high glyphosate doses." In the section comparison with CLP criteria it is only briefly stated: "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 and biological significance of the findings, including comparison with historical control data and sex differences." Altogether, we would appreciate more detailed justification in the ODD why increased incidences of malignant lymphomas are not considered strong enough to warrant classification (e.g. human relevance, increase in spontaneous tumours).	
RAC Member 19	I would like to thank the rapporteurs and the team for their excellent work. The same applies to all the RAC members for their in depth analysis of the ODD/data. At this moment and time I have no additional comments and I do agree with the proposed classifications. As noted by several RAC members the epi-data on glyphosate NHL-association and findings in mice might deserve some further attention in the upcoming RAC meeting/discussion, for reasons indicated in the various RAC comments. Once again, thanks to the rapporteurs for their excellent work.	Thank you for the support.
RAC Member 16	I would like to thank the Rapporteurs' for their concise and precise presentation of the results in the ODD. Regarding the Carcinogenicity endpoint, I have noticed that the various kind of tumors (pancreatic tumors in male rats, in mice renal benign and malignant neoplasms, haemangiosarcoma and malignant lemphomas) observed in the animal studies are not consistent among all studies, and comparison with the HCD range is important. Statistical significance is rare, usually high doses are required and the MoA is not clear, after having overruled mutagenicity. Nevertheless there are still incidences of tumorigenesis in two different species in both sexes, which renders any decision for classification of the substance rather difficult. In addition, the association between glyphosate	There is no association between exposure to glyphosate and NHL in the cohort study (AHS), only a weak

RAC Member	Comments	Rapporteurs' response to comments
	exposure and Non-Hodgkin`s Lymphoma (NHL) in the Agricultural Health Study (AHS) in relation to the malignant lymphoma in mice, makes me more prone towards classification to category 2 for carcinogenicity. Overall, it is a border line case.	association in a few case-control studies and the meta-analysees.
RAC Member 10	From the large number of studies available in rats and mice it seems as if glyphosate induces tumour formation in a number of different organs/tissues in two species. However, from a closer look the significance of the increased tumour incidences observed is questionable, given a.o. that: - increases are very small, and often without dose-response relation; - increases are mostly observed at very high exposure levels (>1000 mg/kg bw/d); - tumour findings are not consistently observed over the studies (within and between species) or over the sexes (without explanation for the apparent sex-specificity); - there is absence of pre-neoplastic lesions, or no progression to malignancy (for the benign tumours); - the mechanism(s) by which glyphosate would induce the various tumours is not clear, although a genotoxic mechanism is not very likely. The most consistent findings are probably those for malignant lymphomas, that is to say, in male mice only. But mice have a relatively high, and very variable, background incidence of these tumours, particularly Swiss mice. Without proper HCD it is difficult to assess the biological relevance of especially the lymphoma seen in the Wood study, which differed statistically significantly from controls at a dose that was not extremely high (810 mg/kg bw/d).	Thank you for these comments.

RAC Member	Comments	Rapporteurs' response to comments
	In themselves the animal data are probably not sufficiently robust for classification. The same can be concluded for the human data, which suggest a (weak) relation between glyphosate and NHL, but where there might be a problem with confounding and co-exposure. In the ODD however the human data have not been compared with the criteria for limited evidence for carcinogenicity for human data. This should be included, and also what the influence on the outcome is when considering in the comparison also the lymphoma data from the mouse studies.	Agree, changes made accordingly in the paragraph Comparison with the criteria.
RAC Member 11	More specifically, regarding human carcinogenicity data I agree with the Rapporteurs' conclusion that evaluated epidemiological studies do not confirm a causal relationship between exposure to glyphosate and cancer, since "chance, bias and confounding could not be ruled out with reasonable confidence". In addition to justification given in ODD, I find that this conclusion is supported and justification nicely elaborated in a systematic review of Acquavella et al. published in September 2016. Regarding potential association between glyphosate exposure and non-Hodgkin lymphoma (NHL), the authors included 7 studies in their analysis – all 6 studies included in Schinasi and Leon (2014) and Chang and Delzell (2016) meta-analyses and in IARC evaluation, plus one additional study, Cocco et al. (2013). Acquavella et al. (2016) concluded that their review does not indicate causal relationship with glyphosate exposure and NHL. According to validity considerations for these studies, **recall bias** was not likely only in the U.S. Agricultural Health Study (AHS), which is a cohort study. Other studies were case-controls, and therefore prone to this type of bias (which occurs when cases, trying to explain to themselves a cause of their illness, tend to be more likely to remember or report exposures than controls; this issue also applies to proxy, i.e. next-of-kin who participate in epidemiologic studies in place of deceased or disabled family member). Further, **selection bias** (e.g. poor response of controls;	Thank you for your support. The review from Acquavella et al. (2016) was not submitted by the DS or by anyone in the public consultation, and therefore cannot be cited in the ODD. But many of the various aspects you raise have been better highlighted now, in the ODD.

RAC Member	Comments	Rapporteurs' response to comments
	hospitalised patients as control subjects less likely to have strenuous occupations, including farming, than the general population) was unlikely in 3 (out of 7) publications**.** Bias from **sparse data** (at least in some analyses) was possible in the majority of studies (5 out of 7). **Adjusting for co-exposure to other pesticides and other potential confounders** was clearly present in 4 studies. **Proxies** (for deceased or disabled family member) were present in 3 studies, in 21% to 31% of cases and 0% to 40% in controls. **Blinding of interviewers** was clearly known to be present in 4 studies, and latency period (time period between first or last glyphosate exposure and health outcome) was considered only in one study.	
RAC Member 11 [contd.]	The authors point out (as also described in Chang and Delzell 2016) issues related to **exposure self-assessment** performed in these studies. For example, by comparing farmers' self-reports and suppliers' records of purchases for specific pesticides it can be concluded that up to 40% of study participants may incorrectly report their exposure to pesticides. Also, it was stressed out that **application of a specific pesticide**, such as glyphosate, is in most cases seasonal, during only few days per year, which is reflected by exposure categorisation in the literature – high exposure group was, for example, designated as glyphosate application during 10 or more days per year in Eriksson et al. (2008), or even as two or more days per year in McDuffie et al. (2001). Another point is a route of exposure. Namely, since inhalation of spray droplets appears to be a minor route of glyphosate exposure, the main route is dermal. However, based on experimental animal data and *in vitro* human skin data, only approximately **1% - 2% dermal absorption** was indicated (Wester et al. 1991, Final addendum to the RAR October 2015). Low exposure to glyphosate, both for farmers and general population, was shown by Niemann et al. (2015) who performed a critical review and comparison of glyphosate biomonitoring data (human urine samples) from seven studies	The Niemann study has been mentioned in the revised ODD as it was mentioned by the DS on the

RAC Member	Comments	Rapporteurs' response to comments
	from Europe and the US, and concluded that "no health concern was revealed because the resulting exposure estimates were by magnitudes lower than the ADI or the AOEL" (details available in the Final addendum to the RAR October 2015). Based on these considerations, the authors conclude that case control studies are inadequate for the assessment of a relationship between glyphosate and NHL, and consider "the AHS cohort study as the only reliable evaluation of NHL risk from glyphosate", despite its limitations (small number of NHL cases, and that the length of follow-up after enrolment was less than a decade). I agree with the review authors that described limitations of epidemiological studies significantly affect evaluation of glyphosate-NHL association, and that overall evidence from human data does not support glyphosate carcinogenicity in humans.	RCOM. Thank you for your support.
RAC Member 11 [contd.]	Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL. Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol. 2016;46(sup1):28-43 Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. J Environ Sci Health B. 2016;51(6):402-34. Cocco P, Satta G, Dubois S, Pili C, Pilleri M, Zucca M, Mannetje AM, Becker N, Benavente Y, de Sanjos S, et al. 2013. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med. 2013;70:91–98. Eriksson M1, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer. 2008;123(7):1657-63. McDuffie HH, Pahwa P,	

RAC Member	Comments	Rapporteurs' response to comments
	McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 2001;10(11):1155-63. Niemann L, Sieke C, Pfeil R, Solecki R. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. J Verbr Lebensm. 2015;10:3–12. Schinasi L, Leon ME. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. Int J Environ Res Public Health. 2014;11(4):4449-527. Wester RC, Melendres J, Sarason R, McMaster J, Maibach HI. Glyphosate skin binding, absorption, residual tissue distribution, and skin decontamination. Fundam Appl Toxicol. 1991;16(4):725-32.	
RAC Member 12	We have some specific concerns, which need probably further consideration or more in-depth explanation in the present version of ODD to strengthen the line of argumentation. **<u>Human epidemiological studies (NHL and glyphosate exposure):</u>** - <u>Cohort study (AHS Study):</u> Cohort studies have from a scientific point some advantages compared to case control, however, for diseases with long latency it needs to be evaluated if the follow up period is considered long enough. An explanatory statement in regard to the follow-up period of 6-7 yrs should be provided in the ODD. It is stated in the ODD, that RAC notes, that individual exposure is longer than follow up time (as exposure precedes the start of the study), however we do not have appropriate data on that assumption.	Info is actually available in EPA Glyphosate Issue Paper, Sept 2016, p. 67, from an email from NIEHS. "At the time of enrollment the average and median times of exposure were 7.5 years and 8 years." However, we cannot include any information not submitted by the DS or in the PC into

RAC Member	Comments	Rapporteurs' response to comments
	- Case-control studies: *Epidemiological case-control studies are by nature prone to confounders (recall bias, co-exposure to other pesticides). In reviews and meta-analysis those confounders have been partly taken into account. A discussion on reliability of outcomes of these studies (e.g. Chang and Delzell (2016), Schinasi and Leon, 2014) is needed to conclude on the strength of evidence in humans.* - *Overall the Rapporteurs conclude that* ***available epidemiological case-control studies, reviews, re-analyses and meta-analyses show weak associations between exposure to GBH and finding of cancer, especially NHL. This indicates a potential concern for human health. However, chance, bias and confounding could not be ruled out with reasonable confidence. A causal relationship can thus not be confirmed by RAC. More specifically this is due to a number of factors.*** *The conclusion of the Rapporteurs might implicit that RAC assumes that* ***limited evidence of carcinogenicity in humans is given for GBH based on CLP definition.*** **Comparison Table: "Limited evidence of carcinogenicity in humans" (CLP Regulation) and RAC Conclusion, see the attachment below.**	the ODD.
RAC Member 12 [contd.]	Since the conclusion of human data on strength of evidence - limited evidence (IARC) vs very limited evidence (EU experts) of carcinogenicity in humans has been matter of discussion[2], RAC needs to be precise in its conclusion and a clear statement on credibility of the causal relationship needs to be provided for the compound glyphosate.	

[2] EFSA_Executive Director_13 January 2016. Subject: Open letter: review of the carcinogenicity of glyphosate by EFSA and BfR.

RAC Member	Comments	Rapporteurs' response to comments
	In our opinion, for **glyphosate based herbicides limited evidence for carcinogenicity of humans** can be assumed. It is important to interpret human findings in relation to other findings. In the present version of ODD human data findings are not mentioned in the section of comparison with the CLP criteria (Category 2) - although limited evidence of carcinogenicity in humans might be assumed for GBH based formulations. In this regard biological significance of the findings in animals and humans, mainly with regard to lymphoma, should be discussed. In our view, it is an important finding that same cell types (white blood cells) are of concern in mice studies carried out with pure glyphosate. **Studies with laboratory rodents:** **Rats:** Assessment based on seven long term studies carried out with Sprague Dawley and Wistar rats. Following tumourigenic findings have been assessed in details: - Pancreatic islet cell tumours, - liver tumours, - thyroid C-cell tumours have been analysed In summary, we agree with the assessment of the rapporteurs, that the sporadic tumorigenic findings in rats do not indicate a strong association between glyphosate exposure and adverse effects in rats. **Mice:** Assessment based on five long term studies (CD mice, Swiss albino mice). Following tumourigenic findings have been assessed in details.	Thank you for your comments. More arguments have been entered into the paragraph on Comparison with the criteria for carcinogenicity in the ODD. We propose not to classify in Carc Cat 2, but agree that a better discussion of findings in animals and humans together was needed in the ODD.
RAC Member 12	- **Renal tumours (adenomas and carcinomas combined):** In three out	The reference to the 15% reduction of

RAC Member	Comments	Rapporteurs' response to comments
[contd.]	of five studies alteration in renal tumour formation has been detected at very high doses. Data indicate that tumorigenic findings are observed at dose levels of 1400 mg/kg bw and above. The absence of any effect in the other two studies (Atkinson et al. 1993 (up to 1000 mg/kg bw) and Wood et al. 2009 (up to 810 mg/kg bw)) might be due to lower doses applied. It is argued that at very high dose levels general toxicity might be involved. Thus, it is important to verify if 15% reduction in bw (high dose vs control) have been observed in single affected animals in the study of Knezevich and Hogan, 1983 and Sugimoto et al., 1997. To date, it is not clear to readers of ODD if 15% reduction is referred to the group as such (high dose group vs control) or for individual animals. However, we agree on the final conclusion to give less weight to findings at very high dose levels, since the biological relevance of reported tumours is questionable. - **Haemangiosarcoma:** we agree with the assumption that the findings of haemangiosarcoma are not consistent. - **Malignant lymphoma:** In four out of five studies a tendency in increased tumour formation only in CD-1 **male** rats, not in females, have been observed. Statistical dose-dependent significance has been observed in two out of the four studies applying the trend test, in one of these two studies Fischer test failed only marginally to demonstrate significance (p=0.056). We agree on the final conclusion that the lymphoma data appears fairly consistent across the male animals. Since the argument that incidences are within historical control is inter alia out-weighing the concern a **thorough analysis of the HCD data is very important** and is partly provided by DS. Malignant lymphoma is a common tumour in mice with high and highly variable background incidence, this is supported by the historical control data, which indicate a hugh variability of spontaneous incidence. Nevertheless, since the findings of the present mouse studies in males are regarded to be consistent, it would be of an advantage to have further information on distribution of used HCD data.	body weight gain in comparison with controls is not intended as an explanation of the increased tumour incidence per se, but rather show that this very high exposure levels is associated with general toxicity. The human relevance of findings only at very high doses are considered to be low and thus given less weight. The text has been clarified on this point.

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 12 [contd.]	The presentation of the median and interquartile range of historical control data (and the application of an outlier test) is an advantage as described by Elmore and Peddada (2009)[3] (cited in OECD 2012)[4] in order to make an appropriate comparison is of interest. For two studies appropriate HCD data are available (Kumar, 2001 and Sugimoto, 1997), for the other studies data from open literature published by industry has been used. The Charles River database has been used for comparison (59 studies, from 1987 and 2000) – incidences of 1.45% up to a maximum of 21.67%, mean 4.5%. It would be helpful to include the data of historical control in table 8. In the case of Kumar (2001) the incidence at high dose (38%) was above the HC range (6-30%) , in case of Sugimoto (1997) the incidence at high dose (12%) was within the range (3.85-19.23%), but two fold higher compared to the mean incidence (12% vs. 6.33%). It would be helpful to have median values of the HCD data for further consideration. In Wood et al. (2009) the incidence rate at high dose (10%) is within the range (1.45-21.67%), but 2fold over the mean of 4.5%. As well as the study of Atkinson (1993) the incidence at high dose (12%) is within the range (1.45-21.67%) but more than 2fold higher as the HCD mean of 4.5%. Since the incidences at high dose levels (but within the recommended high dose of 1000 mg/kg bw) are 2 fold (or even more) higher than the mean of HCD. Again a comparison with median HCD values would be necessary to clarify whether the findings might be of biological relevance. With regard to the Atkinson et al. (1993), study it is important to consider that only those lymphnodes were investigated histologically which showed macroscopic changes. This is certainly a drawback of the study and might have lead to underestimation of the actual tumour numbers.	Thank you for these detailed comments on the important aspect of HCD. The text regarding the HCD has been expanded to provide more detail where available. The text has been revised.

[3] Elmore and Peddada, 2009. Points to consider on the statistical analysis of rodent cancer bioassay dat when incorporatin historical control data. Toxicol Pathol. 2009 37(5): 672-676.

[4] Guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453

RAC Member	Comments	Rapporteurs' response to comments
	We take into consideration, that increased incidences of lymphoma have been only seen in males (except one study, in which also females had a statistical significant increase in the high dose compared to controls – Kumar, 2001), which questions the consistency of findings. However, it should be kept in mind, that there is no requirement for the mechanistic understanding of tumour induction. In summary, we agree with most of the conclusions drawn by the rapporteurs, however it would be good to have some further discussion, especially in relation to biological significance of the lymphoma findings in male mice (based on comparison with HCD) as well as on the rapporteurs analysis of the epidemiological case-control studies concluding they indicate a potential health concern.	
RAC Member 17	First I would like to thank the R's for a great job in the ODD. I have some comments regarding the Carcinogenicity endpoint. **Carcinogenicity**: **Rats** There were seven chronic toxicity/carcinogenicity studies in rats. I support no classification based on the following analysis: *Pancreatic tumors in male rats* The tumors were observed in 2 out of the seven rat studies (Stout & Ruecker 1990, Lankas 1981). In the Lankas (1981) study there were low doses used, reporting deficiencies, no OECD compliance, no dose-response, no progress to malignancy and there were no pre-neoplastic lesions observed. In addition, there was no trend test significance and pairwise significance only at the low dose in male animals. The frequency of incidences though was outside the HCD data and the concurrent control. In the Stout & Ruecker (1990), the benign tumors were observed only in the male animals, at the low dose with no dose-response, no progress to malignancy and with no pre-neoplastic	Thank you for these reflections

RAC Member	Comments	Rapporteurs' response to comments
	lesions observed. In addition, there was no trend test significance and pairwise significance only at the low dose in male animals. The frequency of incidences though was outside the HCD data and the concurrent control. The above observations and the fact that in five more recent OECD compliant studies, there were no pancreatic tumors observed, the control group incidences were higher than in the high doses and there were no pre-neoplastic lesions observed, indicate that glyphosate does not increase the incidence of pancreatic islet cell tumors in rats. *Liver tumors* Liver tumors were observed only in 1/7 studies (Stout & Ruecker 1990) which showed no dose response, no progression to malignancy, no pre-neoplastic lesions, the frequency of the incidences were within the HCD of the group and the statistical significance was noted in the trend test but not in the pairwise test. Therefore, analysis of all the data indicates that glyphosate does not increase the incidence of liver tumors in male rats. *Thyroid C-cell tumors* Thyroid C-cell tumors were observed in female rats in 1/7 studies (Stout & Ruecker 1990) which showed no dose response, no progression to malignancy and no pre-neoplastic lesions. The frequency of the incidences were slightly higher than the HCD and the statistical significance was noted in the trend test but not in the pairwise test. Therefore, there was possibly an increased incidence of thyroid C-cell tumors in one study but analysis of all seven studies indicate that glyphosate does not increase the incidence of thyroid C-cell tumors in male rats.	

RAC Member	Comments	Rapporteurs' response to comments
	Overall, I agree that the Stout & Ruecker 1990 data is rather inconsistent and that glyphosate does not induce neoplasia. **<u>Mice</u>**: There were five (4 CD-1 & 1 Swiss Albino) chronic toxicity/carcinogenicity studies in mice. I support no classification based on the following analysis: *Renal Benign and Malignant Neoplasms* Combined renal benign and malignant neoplasms were observed in 3 out of 5 studies in male mice. The frequency of the incidences were slightly higher than the HCD for a rare type of tumor for mice and the statistical significance was noted in the trend test but not in the pairwise test. In two out of three positive studies (CD-1 mice) the incidences occurred only at the high dose which was at MTD levels since the weight gain decrease was higher than 15%. At the mid dose (about 820 mg/kg bw/d) in the same studies no incidences were observed. In the third study (Swiss albino mice, the renal combined tumors were observed again at the high dose which was 1460 mg/kg bw/d. Overall, considering that the tumors are seen at doses above 1000 mg/kg bw/d in one sex and one species (mouse) renders the evidence not sufficient for classification. *Haemangiosarcoma* I support no classification based on the following analysis: The Haemangiosarcomas in male mice were observed in two studies (Atkinson and Sugimoto) out of five only at the high dose. The high dose in the Sugimoto study (4348 mg/kg bw/d) was at MTD levels. At the mid doses in both studies (300 and 838 mg/kg bw/d respectively) no tumors were observed. In the Atkinson study, the incidences occurred at the upper limit of	

RAC Member	Comments	Rapporteurs' response to comments
	the HCD of the group while in the Sugimoto study the incidences were observed within the HCD of the CD-1 mice. In both studies, statistical significance was noted in the trend test but not in the pairwise test. Overall, the tumors are observed within or close to HCD, only at the high dose and the findings are not consistent among all five studies. *Malignant lymphoma* I support no classification based on the following analysis: The incidences in male mice were observed in 3/4 studies in CD-1 mice and in one Swiss albino mouse study. The statistical significance was not noted in the pairwise test in any of the studies. In the Wood and Sugimoto CD-1 studies the trend test was significant for malignant lymphoma. In mice, lymphoma is a common spontaneously occurring neoplasm. The tumor incidence of 12% at the high dose of 4348 mg/kg bw per day in the study by Sugimoto (1997) was within the relevant HCD range for CD-1 mice obtained from the laboratory in which the study was performed, and at an MTD dose level. The 10% incidence in the study by Wood et al. (2009) was within the HCD range for CD-1 mice obtained from Charles River Laboratories (mean incidence of 2.7% and a range of 0-14% for the 18 month studies; Giknis and Clifford, 2005, ASB2007-5200). In the Kumar (2001) Swiss albino study, the incidences were high both for male and female animals but the high background incidence makes the statistical analysis non-significant. Thus in conclusion, although there were findings in four 4 studies, two were statistically significant but within the HCD range. In addition, in one out of the two studies the findings were at MTD levels. **Overall Conclusion:** Although I agree based on the weight of evidence approach that the tumors observed in the animal studies are **mostly** not consistent among all studies,	

RAC Member	Comments	Rapporteurs' response to comments
	within the HCD range, with no statistical significance, at high doses and with no robust evidence for mutagenic MoA, nevertheless there are various tumors in two different species in both sexes which makes the classification of the substance rather complicated. In addition, although the evaluation of the human data is difficult, the association between glyphosate exposure and Non-Hodgkin`s Lymphoma (NHL) in the Agricultural Health Study (AHS) in relation to the malignant lymphoma mouse findings causes some additional concern. Overall, I support the R's but it is not an easy one!	
Reproductive toxicity (effects on fertility)		
RAC Member 13	No classification, as discussed in the ODD.	Thank you for the support for no classification for fertility.
RAC Member 1	Four of the six studies showed no effects on fertility at doses of 668, 800, 985 and > 2000 mg/kg bw/day, while other two studies reported effects at 1000 and 2000 mg/kg bw/day. However, these effects were of low severity, appeared concurrently with parental toxicity, were not consistent among different generations of the same study and in general did not affect the reproductive performance. Therefore, **I support the rapporteurs' proposal for no classification of the substance.**	Thank you for the support for no classification for fertility.
RAC Member 3	I support the conclusions of rapporteurs and DS on lack of sufficient evidence of effect of glyphosate on fertility in rats, therefore classification is not warranted.	Thank you for the support for no classification for fertility.
RAC Member 4	I support no classification and the conclusion in the ODD.	Thank you for the support.
RAC Member 14	There is no effects on fertility, so no classification is obviously supported	Thank you for the support for no classification for fertility.
RAC Member 15	I agree with the rapporteur's conclusion on the fertility endpoint	Thank you for the support.

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 8	I support no classification for fertility effects. Only study showing some effects was the study by Dhinsa et al (2007) and the effects were either not consistent across generations (sperm count) or did not show impact on reproductive performance (sperm count/preputial separation). In other studies, no reproductive effects were seen. Although in the study by Suresh et al., (1993) no effects were seen in the parental animals or in the offspring, I wouldn't say that the study should be dismissed since it used *too low doses*: anyway the dose of ˜800 mg/kg bw is not far from the general limit dose of 1000 mg/kg for reproductive studies.	Thank you for the support for no classification. The Suresh et al. (1993) study was considered as supplementary in the RAR since no LOAEL could be derived. This has been included in the ODD.
Reproductive toxicity (effects on development)		
RAC Member 13	Overall, as discussed in the draft ODD, the absence of a clear, reproducible developmental effect across species or studies on the same species points towards no classification. However, I think it would be helpful to review each of the rabbit developmental toxicity studies in plenary. As noted in comments from another RAC member, some of the findings as described in the draft ODD could in themselves be sufficient for classification: e.g. heart related defects in the rabbit, including at doses apparently without significant maternal toxicity. For example, Bhide and Patil, 1989: table 12 implies no adverse developmental or maternal effect at the mid dose of 250 mg/g (NOAEL), but the summaries of this study on pages 66 and 69/70 indicate increased malformations at this dose. This uncertainty makes it difficult to reach a clear view for this endpoint.	We look forward to a discussion of this hazard class in RAC plenary. As regards the Bhide and Patil, 1981 study, this study has serious deficiencies including that aborted foetuses were included in the assessment of malformations, therefore this study has not been taken into account in the weight of evidence assessment of developmental toxicity. The ODD has been revised accordingly.
RAC Member 1	Three studies in rat showed no treatment-related developmental toxicity at doses up to 1000 mg/kg bw/day. Increases in post-implantation losses, delayed ossification and skeletal abnormalities were found in rats exposed to 1000 or 3500 mg/kg bw/day. However, in only one of the studies the delayed ossification was found in absence of maternal toxicity (incidence not reported), while in all other cases the developmental toxicity was	Thank you for the support for no classification for developmental toxicity.

RAC Member	Comments	Rapporteurs' response to comments
	reported concurrently with severe maternal toxicity (including mortalities). Thus, in my opinion, the results in rats do not warrant classification. The different studies in rabbit shoed an array of adverse effects as increases in post-implantation losses and visceral malformations. Post-implantation losses were detected altered regarding the controls in 2 of 7 studies, although in both cases the effects were not dose-related and in presence of severe maternal toxicity, which notably reduced the concern. The main concern for visceral malformation was the impairments in the development of heart. This alteration was reported in 3 different studies, although two of them with methodological deficiencies that makes very difficult the interpretation of the results and always with presence of maternal important toxicity. It is also remarkable that these visceral alterations were not reported in the rat studies at doses around twice the dose employed in the rabbit studies. In summary, the most concerning effects in rabbits were not convincingly reported among different available studies, were found in presence of confounding factors as excessive mortality or methodological deficiencies. Other less concerning effects were found with lower incidence and/or within the historical control values. These are the main reasons that, to my opinion, make the evidences of developmental toxicity not strong enough for warranting classification; and this is because **I support the rapporteurs' proposal for no classification of glyphosate.**	
RAC Member 3	It is possible to support the conclusions of rapporteurs and DS on lack of sufficient evidence for classification of glyphosate as developmental toxicant, however the justification is not clear. I propose to re-write this section in order to present the findings of each study (e.g. robust study summary when possible) in such a way that the comparison of evidence gathered in each study with classification criteria would be clearer. So far it is rather difficult, since presentation of data in	We will do our best to revise the ODD according to your comments below. The text will be changed and will be summarized with a comparison with the CLP criteria. However, we consider that Robust Study

RAC Member	Comments	Rapporteurs' response to comments
	ODD suggest rather classification Repr 2; H361d: Suspected of damaging the unborn child - e.g. on page 59 it is written: "*Overall, RAC concludes that the six studies with rats (Wistar and Sprague-Dawley) included by the DS with doses up to 3500 mg/kg bw/d showed* consistently limited evidence of developmental toxicity following in utero exposure to glyphosate*, including reduced ossification and skeletal malformations at high maternally toxic doses. The LOAEL for developmental effects were ≥ 1000 mg/kg bw/d*." Do we really have "*consistently limited evidence of developmental toxicity"* in rats? I am not sure about this. Therefore there is a need for a clear interpretation of each study results in sequence of studies as shown in Table 10 and Table 12 - one study after another, pointing out whether the study results provide limited or sufficient evidence for classification. It is also advisable that Guidance on the Application of the CLP Criteria (2013) will be taken into account for interpretation of results of each studies and all studies together. The study of Moxon (1996) is listed as a first study in table 10 on page 57, however it is not commented directly under this table. A first sentence with findings and interpretation of this study appears 2 pages after Table 10 on page 59, even after table 11: *"The most recent study by Moxon et al., (1996) showed no effects at doses up to 1000 mg/kg bw/d. One control animal was killed on day 7 as a result of being misdosed. There was no evidence of maternal toxicity or effects on the foetuses. The incidence of foetuses with major defects was 1/284, 1/297, 1/301 and 2/296 in the control and 250, 500 and 1000 mg /kg bw/d groups, respectively. Neither the type nor incidence of major defects provided evidence for an adverse effect of glyphosate. The defects were dissimilar in type and of single incidence. Further, the proportion of foetuses with external/visceral variants and the proportion of foetuses with skeletal variants were lower in the glyphosate acid treated groups than in the control group."* Thus this study does not provide any evidence of	Summaries should better be placed in the CLH report than in the ODD. We will do our best to include a concluding statement in the end of each study. We decided to include the two studies requiring an in-depth analysis in the beginning (meaning not following the sequence of table 10) and include a sentence in the beginning of this section with the following: "In the six developmental toxicity studies in rats only two of the studies reported results that required an in depth analysis of the data by RAC (Tasker and Rodwell., 1980 and Brooker et al., 1991). Four of the studies reported no evidence of developmental toxicity. In the section below we include first the two studies requiring in depth analysis followed by the studies with no evidence of developmental toxicity."

RAC Member	Comments	Rapporteurs' response to comments
	developmental toxicity.	
RAC Member 3 [contd.]	A second study (Hatakenaka (1995) listed in table 10 on page 57 is also commented on page 59 after description of study of Tasker & Rodwell (1980) and Brooker et al (1991). I understand that there is a reason to start with Tasker & Rodwell (1980) and Brooker et al (1991) studies showing some developmental effects, but is would more convenient for the reader to keep a sequence of studies as listed in table 10 for rats and in table 12 for rabbits or clearly say that there are only two rat studies with results which require deep analysis while all the rest indicate lack of developmental toxicity. In the presentation of data and analysis of results of Tasker & Rodwell (1980) it would be convenient to make an initial conclusion whether some of the effects seen in foetuses of the highest dose group 3500mg/kg were or were not related to maternal toxicity or whether malformations observed were or were not related to treatment with glyphosate. Such study conclusions would facilitate later justification of the final, overall conclusion of classification. Similar assessment would be appropriate for the study of Brooker et al (1991). Then we have on page 59 a final RAC conclusions based on the rat studies: ""*Overall, RAC concludes that the six studies with rats (Wistar and Sprague-Dawley) included by the DS with doses up to 3500 mg/kg bw/d showed* consistently limited evidence of developmental toxicity following in utero exposure to glyphosate*, including reduced ossification and skeletal malformations at high maternally toxic doses. The LOAEL for developmental effects were ≥ 1000 mg/kg bw/d.*" I propose to express that conclusions more in line with classification criteria and CLH guidance, to facilitate interpretation of data coming from the developmental toxicity studies on rats in terms of classification. The current conclusion is rather summary of the findings instead of answering	A conclusion of the study has been included in the ODD: "RAC concludes that this study showed effects at very high doses (3500 mg/kg bw/d) including post-implantation losses and malformations. These effects occurred at clearly maternal toxic doses and are therefore considered as secondary to maternal toxicity and no classification for development is justified according to the CLP criteria based on this study." We have changed the text to be in line with the CLP criteria to the following: Summary of rat developmental toxicity studies: In one of the the six studies with rats (Takser and Rodwell, 1908) effects were reported at very high doses (3500 mg/kg bw/d) including post-implantation losses and malformations. RAC concludes that these effects occurred at clearly maternal toxic doses and are therefore considered as secondary to maternal toxicity and no classification for development is justified according to the CLP criteria based on this study. Cardiovascular malformations were reported in two of the six studies with rats as single incidences from 300 mg/kg bw/d in the study by Hatakenaka et al., 1995 not considered related to maternal toxicity and at 1000 and 3500 mg/kg bw/d in the

RAC Member	Comments	Rapporteurs' response to comments
	the question whether glyphosate may cause developmental toxicity effects not being secondary to maternal toxicity. Particularly "skeletal malformations" in rats if really caused by glyphosate would require classification.	study by Brooker et al., 1991 in the presence of maternal toxicity at 3500 mg/kg bw/d. RAC concludes that due to the single incidences of cardiovascular malformations without a clear dose-response and without statistically significance and not reported consistently in the six rat developmental toxicity studies no classification for development is justified according to the CLP criteria based on these studies.
RAC Member 3 [contd.]	<u>Rabbits</u> I propose to adopt the same scheme of presentation of the rabbit study results as suggested for the rat studies. Please reconsider modification of the following sentence on page 61 just below table 12. "*The developmental toxicity studies performed in rabbits clearly showed that rabbit was the most sensitive species following in utero exposure to glyphosate."* The exposure *in utero* is related only to embryos and fetuses and such exposure causes developmental toxicity. Having in mind that rapporteurs do not propose classification of glyphosate to this hazard category, most probably the sentence relates to systemic toxicity of glyphosate to pregnant rabbits. Therefore it is possible to use instead of this the following sentence:	The studies in table 12 is included with the most recent study in the beginning of the table and then followed by decedent order. In the text we have divided the foetal effects observed in the rabbit developmental toxicity studies into "effects on foetal viability" and "foetal pathological findings" and we still consider this as a clear way to present the data Thank you for the suggested modification. The sentence has been modified accordingly. "Late embryonic death" is taken from the CLH report and also used in the original study report, so the rapporteurs consider

RAC Member	Comments	Rapporteurs' response to comments
	"The developmental toxicity studies showed that pregnant rabbits are more sensitive species than pregnant rats following exposure to glyphosate." Please note while discussing the maternal toxicity in pregnant rabbits that in the STOT RE section the rapporteurs noted on page 20 that "*The strategy of caecotrophy ensures that substances predominantly excreted unchanged in the faeces such as glyphosate are readily available for repeated oral uptake and constitute a potentially significant oral dose relative to other species including man. This possible recycling of glyphosate and increased exposure in rabbits might explain the particular sensitivity of this species while at the same time casting doubt over the relevance of oral dosing in rabbit studies for man in this instance.*"	that the use of "late embryonic death" should be ok. In the study report Embryonic/foetal death were classified as: • Early: only placenta visible at termination • Late: both placental and embryonic remnants visible at termination • Abortion: only implantation site scars visible at termination
RAC Member 3 [contd.]	Please reconsider whether "late embryonic death" in table 13 and elsewhere in the text of ODD should be rather changed to "late foetal death" Please consider providing some documentation or description of some internal organ malformations such as "dilated heart" because it might be very subjective. Did authors of this study Suresh et al. (1993) provided any description of this malformation or criteria for classifying a heart as malformed? If not, please just inform about that. Did they provide and historical control data? Were those foetuses alive at C-section or they were dead? There are sentences on page 65: "These included cardiac malformations, evident as intraventricular septal defects at the highest dose, which were	We have already included in the draft ODD that the reporting of the dilated heart was insufficient in the full study report with a lack of measurements of the heart and definition of this diagnosis. So we have no further information that is already included in the draft ODD. No information regarding HCD was included and the foetuses for examination. It is described in the study report that "The fetuses were euthanized using ether anaesthesia. All the fetuses were subjected to visceral and skeletal evaluation."

RAC Member	Comments	Rapporteurs' response to comments
	seen in 4 foetuses from 4 litters and lay outside the HCD. The same effects were seen in one foetus from each of the other dose groups, including the control group. It should be noted that these malformations were considered by the DS to be different from the malformation described as "dilated heart" in the study by Suresh et al., (1993)". Why it is considered necessary to mention in ODD that "dilated heart" is not the same as "intraventricular septal defect". It seem obvious. It could be avoided if more detailed description provided by the authors of these studies would be provided. In table 16 summarizing the study by Brooker et al. 1991 there are data on number of malformed fetuses and affected litters (I presume litters affected are with malformed fetuses). They seem to not differ significantly with controls however these data are not used in weight of evidence analysis? On page 65 there is a sentence: *"Maternal toxicity is included in the section describing effects on fetal viability from the study by Brooker et al. (1991)."* Since this paragraph somehow analyse experimental data would it be possible to provide data on maternal toxicity instead of referring to another section or clarify whether maternal toxicity could contribute to effects in fetuses? There is a clear difference in CLH report and ODD in evaluation and presentation of data from the study of Bihde and Patil (1989):	See comments above. In the summary of the developmental toxicity studies in rabbits and in the weight of evidence analysis and comparison with the CLP criteria the Brooker et al., 1991 study is included. A reference to the maternal toxicity was included to avoid repetition in the draft ODD, however, if preferred, maternal toxicity is now included in the discussion of the fetal pathology from the Brooker et al., 1991 study.
RAC Member 3 [contd.]	CLH report: *"The study of Bhide and Patil (1989, TOX9551960) was seriously flawed by serious deficiencies. Thus, no individual data is given and it is not clear whether statistical analysis of data has been performed and, if so, which statistical tests had been applied. Uterine weights and the results of maternal necropsy have not been reported. It is surprising that no maternal deaths have occurred even though the mid and high dose levels of 250 or 500 mg/kg bw/day had proven clearly higher in the*	In the description of this study we decided to include in the ODD some more information regarding the number of malformations from the original study report that was not included by the DS in the CLH report.

RAC Member	Comments	Rapporteurs' response to comments
	groups receiving the mid and high doses of glyphosate but it is not clear whether they were found in different foetuses or if some foetuses had multiple malformations. The rather high number of visceral malformations at the top dose level was mainly due to absent kidneys or lung lobes, i.e., findings that can hardly be attributed to test substance administration." ODD: *"The study by Bhide and Patil (1989) performed with NZW rabbits was described to have several reporting deficiencies including no individual data, no statistical analysis, no uterine weights and no results from maternal necropsy. In this study the total number of foetuses and litters with malformations were higher at 250 and 500 mg/kg bw/d relative to controls and included ventricular septal defects. The incidences were 0 (0), 1(1), 1(1) and 2(2) in foetuses (litters) from the 0, 125, 250 and 500 mg/kg bw/d dose groups. The total number of foetuses (litters) with malformations were 3 (3), 6 (6), 10 (10) and 20 (14) from the 0, 125, 250 and 500 mg/kg bw/d dose groups respectively. Malformations included abnormal tail, missing kidney, absent postcaval lung lobe and rudimentary 14th rib. No information regarding statistical significance was included in the study and 2 of the 14 litters in the high dose group examined were aborted litters. Maternal toxicity was reported in the high dose group as lower food consumption and reduced bw gain. "* Please provide robust study summary and some conclusions from the study by Bhide and Patil (1989) since current description seem to indicate teratogenic property of glyphosate, at least a study description provided in ODD is focused on demonstration of teratogenicity. If it is so, please provide information what malformations were in the rapporteur's opinion caused by glyphosate in this study.	The number of litters assessed in the high dose group is also considered to not be correct since out of 15 does in the high dose group, 3 were not pregnant and 2 aborted and fetuses from the aborted litters were included in the assessment of malformations. Therefore, we will include in the description of the study in the draft ODD the following to better describe that this study had serious deficiencies" but it is not clear whether they were found in different foetuses or if some foetuses had multiple malformations" as well as information regarding that aborted litters were included in the assessment of malformations.
	Clear judgment how the data from each developmental toxicity study on rabbits are assessed in terms of indicating developmental toxicity hazard of glyphosate would be highly appreciated. The robust study summary for	We will do our best to include a concluding statement in the end of each study.

RAC Member	Comments	Rapporteurs' response to comments
	each study followed by initial interpretation of these results in terms of potential hazard would be appreciated. Please note that in section "In depth analysis by RAC" there are very useful data but not any analysis. In fact a reader is expected to make such analysis for him/herself. These data could be provided earlier and sum up with interpretation and clear conclusion.	According to the "instruction to writers" in the ODD it is described that "This material is additional to what was included under "Assessment and comparison with the classification criteria" above. This may be rearranged data, new graphs, plots or statistical analyses by e.g. Rapporteurs that clarify or **visualise key information** ". So we do not see the need to analyze these data since it was included to visualize the data and no new data is included that are not already assessed and discussed in the Draft ODD
RAC Member 4	There is limited evidence of developmental toxicity in both rabbits and rats, perhaps not sufficient for classification. Still, discussion in the plenary seems warranted on the following and perhaps some other issues: (1) the degree of maternal toxicity in the individual studies, (2) how much lack of consistency among studies decreases the concern, (3) whether rabbit is a suitable model for humans (with regard to caecotrophy as discussed in the STOT RE section), (4) whether effects at 1000 mg/kg bw/d are relevant for classification (in rat studies) and (5) whether delayed ossification without maternal toxicity may trigger category 2 classification.	Thank you for the issues raised, we look forward to discussing this further at the RAC plenary.
RAC Member 14	There are no indications of developmental toxicity in the rat studies. Of the many rabbit studies, only the study by Brooker et al (1991) is suggestive of effects on embryo survival and development	Thank you for the summary of the data and for support.

RAC Member	Comments	Rapporteurs' response to comments
	(malformations). However, the effects on embryo viability were not pronounced and were not seen in 6 other rabbit studies. The findings of cardiac malformations (4 foetuses in 4 litters), with an incidence outside the HCD, is usually a cause for concern. Although the effects on maternal weight gains were modest, one dam died in the high dose group (450 mg/kg/day). Also, based on all rabbit developmental studies one can conclude that rabbits are rather sensitive against glyphosate, and that some maternal mortality has been observed in most studies at dose levels of 300-500 mg/kg/day. Although a rather high incidence of cardiac malformations (31 vs 6% in the control on a litter basis), it is noteworthy that similar malformations were not observed in the other 6 studies, and this is the main argument against considering classification. Also, the possibility that the cardiac malformations were secondary to non-specific maternal toxicity cannot be completely ruled out. Overall, I don't think the findings are sufficiently robust to warrant classification.	
RAC Member 15	I agree with the rapporteur's conclusion on the developmental toxicity in rats. With regards to the seven developmental toxicity studies in rabbit, only four were considered acceptable in the RAR (Brooker, 1991, Coles, 1996; Hojo, 1995; Moxon, 1996). Results of the other three studies should be interpreted with care as only a very limited number of litters were observed at the high doses.	Thank you for the support.
RAC Member 15 [contd.]	<u>Cardiovascular malformations in rabbits</u> A clear increase in cardiovascular malformations (e.g. septal defects) at the high dose of 450 mg/kg bw was observed in the study of Brooker et al., 1991. The cardiovascular malformations were observed in four foetuses in four different litters. At this dose level, one premature death occurred, incidence of soft/liquid stool were increase. Moreover, food consumption and bw gain were slightly reduced. It would be useful to know if there is a link between the severity of the maternal toxicity and the dams having the 4 foetuses with interventricular septal defects. In this study, at 150 mg/kg bw, a clear increase in fetuses with retro-	There do not seem to be a clear link between the severity of the maternal toxicity and the malformed fetuses in the top dose group. The only parameter showed the most pronounced variations was that the does with malformed fetuses were

RAC Member	Comments	Rapporteurs' response to comments
	oesophagial right subclavian artery was observed. If considered as a variation as in many laboratories, this may show that gravity of the effects increase with dose-level. At 150 mg/kg bw, maternal toxicity was lower than at 450 mg/kg bw and couldn't explain the increase incidence of variations observed. According to the of review of Kimmel, 2013[5] (fundings of this study came from the European glyphosate taskforce), malformations relating to disproportionated sized aorta and pulmonary septum, as well as IV septal defects of the upper region are related to the displacement of the developing aorticolpulmonary septum. The authors calculate the total incidence of these types of malformation in control and glyphosate treated-groups. Although this reasoning is far fetched, it gives an estimate of the overall incidence of glyphosate cardiovascular malformations in the four available studies. Using this approach and taking into account the three acceptable studies (Brooker, 1991, Coles, 1996; Moxon, 1996), using New Zealand rabbits, malformations on interventricular septum or aorta sized, the following results are obtained: combined control groups was 1/ 434 (0.23%), and in combined glyphosate-treated groups the incidence was 9/1147 (0.8%). The incidence is only slightly above historical control value of 10/1511 (0.66%). It would also be interesting to compare on a litter-based data but the details of the study summaries does not permit to do so. **Table about cardiovascular malformations in rabbits, see the attachment below.** Overall, although there is a clear increase in cardiovascular malformations in the Brooker et al., 1991 study, this was not supported by other developmental toxicity studies in NZ rabbits.	"off-feed" a slightly higher number of days (1, 1, 4, 13) than the does without malformed fetuses (0, 0, 0, 0, 1, 1, 1, 1, 1, 10). This will be reflected in the revised ODD.
RAC Member 15 [contd.]	<u>Skeletal malformations in rabbits</u> In the Hojo, 1995 study, an increase in skeletal malformations was observed in Japanese rabbits at the low (4 foetus in 3 litters), mid (6	

[5] Kimmer et al., evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development. Crit Rev toxicol. 2013.

RAC Member	Comments	Rapporteurs' response to comments
	foetuses in 2 litters) and high dose levels (5 malformed fetuses in 5 litters). Although individual foetal incidence was not reported, it seems from the results that this was not clustered together in the same foetus at the high dose. At the low and mid-dose level this is more difficult to interpret. Nevertheless, no craniofacial malformations were observed in control whereas 12 treated skull malformations were observed in treated groups. No increase variations on skull were observed at any dose level. **Table showing the summary of cranio-facial skeletal malformations according to table B.6.6-27 of RAR, see the attachment below.** Only slight maternal toxicity was observed up to the highest dose of 300 mg/kg bw. Are the historical control values for the skeletal malformations observed available? In addition, according to table 2 of the ODD, 4 females showed loose stool in the high dose group, was it the same females that had malformed fetuses? No other study is available with this strain of rabbits to support the observed malformations. Skeletal malformations were not seen in the other 6 developmental studies in rabbits. Differences in the type of malformation seen between Japanese and New Zealand (skeletal and visceral, respectively) may be explained by strain differences but there is no data in the dossier to support the hypothesis. Therefore, based on the above considerations, increase malformations were observed in two out of four acceptable studies in rabbits. As the effects were not consistent between the studies and no developmental effects observed in rats, the findings are not sufficiently convincing to place glyphosate in Category 1. Nevertheless, no classification or category 2 for developmental toxicity of glyphosate **need to be discussed at RAC meeting.**	There are no available historical control data for the skeletal malformations observed. No correlation was found between does with loose stool and fetuses with skeletal malformations in any dose group.
RAC Member 8	I support no classification for developmental effects.	Thank you for the support for no

RAC Member	Comments	Rapporteurs' response to comments
	In rat studies, effects were seen only at huge doses (3500 mg/kg) in the presence of maternal toxicity. What comes to rabbit studies, I think the sentence (p. 62, below the table) stating: "*the developmental toxicity studies performed in rabbits clearly shows that rabbit was the most sensitive species following in utero exposure to glyphosate*" is misleading. Rabbit seems to be most sensitive species for the *gastrointestinal dosing and osmotic effects of glyphosate*, but this is not due to in utero exposure. If we then conclude that actually rabbit findings in the offspring are not very consistent, they occur only in the presence of maternal toxicity and only at low incidences, it is a bit contradictory to state that the data clearly shows that rabbit is sensitive to in utero exposure to glyphosate.	classification. This sentence has been rephrased as following: "The developmental toxicity studies showed that pregnant performed in rabbits are a more clearly showed that rabbit was the most sensitive species than pregnant rats following in utero exposure to glyphosate."
	I think Suresh et al (1993) study cannot to be considered in the weight of evidence analysis due to the high maternal mortality at high and mid-dose, which seems to be either due to mis-dosing or gi-intolerance or both. Main findings causing some concern on developmental effects of glyphosate come from Brooker et al (1991) study, in which there was (not dose-dependent) increase in embryonic deaths/post-implantation losses also at low- and mid-doses and cardiac malformations at high dose (however, in the presence of maternal toxicity). When taking into account that the glyphosate related increase in post-implantation losses/embryonic deaths is not supported by other rabbit developmental studies, and the support for cardiac effects from other studies is also limited, the overall data supporting developmental toxicity of glyphosate is limited.	We do not consider that the Suresh study should be completely dismisses in the weight of evidence analysis, but we have clearly stated that it should be treated with caution due to high maternal mortality and insufficient reporting of dilated heart.
	One more note to conclusions: I suggest to clarify the conclusion on rat developmental data. The following sentence is not very clear: "*In conclusion, the six studies with rats with doses up to 3500 mg/kg bw/d showed consistently limited evidence of developmental toxicity following in utero exposure to glyphosate including reduced ossification and skeletal malformations at maternally toxic doses, with LOAEL for developmental*	Thank you for the suggestions, the sentence now reads as following: "In conclusion, the six studies with rats with doses up to 3500 mg/kg bw/d showed some, although consistently limited evidence of developmental toxicity following in utero exposure to glyphosate including reduced

RAC Member	Comments	Rapporteurs' response to comments
	effect >1000 mg/kg bw/d." What do you mean with "consistently limited evidence of developmental toxicity": 1) there were some (although limited) evidence on developmental effects, or 2) the studies did not really show evidence on specific developmental toxicity?	ossification and skeletal malformations at maternally toxic doses, with LOAEL for developmental effects ≥ 1000 mg/kg bw/d."
Aquatic hazards (acute and chronic)		
RAC Member 20	I agree with the proposed environmental classification as Aq. Ch. 2. It is a pity that the CLH dossier failed to include all relevant aquatic plant toxicity data (e.g. green algae and *Myriophyllum*). The opinion mentions that *Myriophyllum* was the most sensitive species, and I think more details about this study should be provided as supplemental information. For example, what was the test substance, was 0.3 mg/L the lowest concentration tested, and what level of effect was observed (e.g. was it a 20 % effect, and was it based on growth rate over a specific time period)? Glyphosate's mode of action means that it acts relatively slowly on plants. Given the unbounded NOEC for *Myriophyllum*, I think the opinion should mention that the classification might need to be reviewed if further relevant aquatic plant data become available (e.g. for rooted emergent macrophytes such as *Glyceria*), particularly over long test durations. I think this would give a suitable signal that the classification is not necessarily based on an appropriate data set in this case.	Thank you for the comment. We will modify the opinion providing supplemental information on the study for the aquatic plant *Myriophyllum*. We agree on the need to clarify in the ODD that the classification might be reviewed if further relevant aquatic plant data become available.
RAC Member 21	I agree with the proposed environmental classification as Aquatic Chronic 2.	Thank you for the comment.
RAC Member 22	I agree with the proposed env classification. Also with [RAC Member 20] comment regarding the study with RAR *Myriophyllum* study where a NOEC<0.3 mg/l is reported being this the lowest concentration tested.	Thank you for the comment. See the above comment.

RAC Member	Comments	Rapporteurs' response to comments
RAC Member 10	For ENV, the classification as Aquatic Chronic 2 is also supported.	Thank you for the comment.

Attachment

1) The following tables belong to the comment on carcinogenicity by [***RAC Member 1]***:

Effects in rats	
In favour of classification	Against classification
Pancreatic islet cell tumours	
· 2 different studies report statistically significant increases for adenoma · 1 study report statistically significant increases for carcinoma · Outside the historical control of the facilities	· 5 different studies do not the effects · No dose response in none of the two positive studies for adenoma · No pass to malignancy of the adenomas · Not found in mice · Very weak (p=0.046) association with carcinoma in one study but with number of cases similar to those reported in controls
Liver tumours	
· Detected in only 1 study · Statically significance positive trend for adenoma + carcinomas · Positive trend for adenomas	· Not detected in 6 studies · Weak significance of the trend for adenoma + carcinomas (p=0.075) · No pass to malignancy of the adenomas (carcinoma incidence in controls higher than in exposed animals) · Incidences within the historical control of the facility · Reported in only one sex · No significance using pairwise comparisons · Not found in mice
Thyroid cell tumours	
· Detected in only 1 study · Statically significance positive trend for adenoma + carcinoma cases	Not detected in 6 studies · Weak significance of the trend (p=0.0435) · No significance using pairwise comparisons

· Incidence higher than historical control data only at the highest dose (940 mg/kg bw/day)	· Not found in mice · Reported in only one sex

Effects in mice	
In favour of classification	Against classification
Renal neoplasms	
· Detected in 3 studies · Statically significance positive trend · Incidences above the historical control of the facility in one of the studies	· Not detected in two studies · No significance using pairwise comparisons in none of the studies · All tumours observed at termination (long latency) · Incidences in the highest dose at the upper end or slightly outside the historical control range from Charles-River laboratory · Reported in only one sex · In two of the three positive studies tumours appear between 4000 and 5000 mg/kg bw/day with body weight gain reduced by more than 15% · Not reported in rats
Haemangiosarcoma	
· Detected in 2 studies · Statically significance positive trend	· Not detected in three studies · No significance using pairwise comparisons in none of the studies · Incidences in one of the studies in the upper edge of the historical control data of the facility · Incidence in the second study within the historical control range from Charles-River laboratory · Reported in only one sex · In one of the three positive studies tumours appear above 4000 mg/kg bw/day · Not reported in rats

Lymphoma	
· Detected in 4 studies · Statically significance positive trend	· Not detected in one study · Very weak significance in three of the four studies (p slightly higher than 0.05) · Common spontaneously occurring neoplasm · No significance using pairwise comparisons in none of the studies · One study with statistically significant trend reported 12% incidence above 4000 mg/kg bw/day within the historical control data of the facility · Second study with statistically significant trend reported 10% incidence at 810 mg/kg bw/day within the historical control data from Charles-River laboratory · Reported in only one sex · Not reported in rats

2) The following tables belong to the comment on carcinogenicity by ***[RAC Member 3]***:

Table: Incidences of pancreatic islet cell adenomas and carcinomas combined in male rats

Study (strain)	Control	Low dose	Mid dose	Second mid dose	High dose	Response** Fisher exact test
Wood et al., 2009 (Wistar)	4 / 51 **(7.5 %)**	1 / 51 (86 mg/kg bw/d)	2 / 51 (285 mg/kg bw/d)	-	1 /51 **(2.0%)** (1077 mg/kg bw/d)	No significant increase
Brammer et al., 2001 (Wistar)	1 / 53 **(1.9%)**	2 / 53 (121 mg/kg bw/d)	0 / 53 (361 mg/kg bw/d)	-	1 / 52 **(1.9%)** (1214 mg/kg bw/d)	No significant increase

Study (strain)	Control	Low dose	Mid dose	Second mid dose	High dose	Response** Fisher exact test
Enomoto, 1997 (Sprague-Dawley)	4 / 50 **(8%)**	1 / 50 (104 mg/kg bw/d)	2* / 50 (354 mg/kg bw/d)	-	1 / 50 **(2.0%)** (1127 mg/kg bw/d)	No significant increase
Suresh, 1996 (Wistar)	3 / 48 **(6.25%)**	0 / 30 (6.3 mg/kg bw/d)	0 / 32 (59.4 mg/kg bw/d)	-	1 / 49 **(2.0%)** (595.2 mg/kg bw/d)	No significant increase
Atkinson et al., 1993 (Sprague-Dawley)	7 / 50 **(14%)**	1 / 24 (10 mg/kg bw/d)	2 /17 (100 mg/kg bw/d)	2 / 21 (300 mg/kg bw/d)	1 / 49 **(2.0%)** (1000 mg/kg bw/d)	No significant increase
Stout and Ruecker, 1990 (Sprague-Dawley)	2* / 43 **(4.6%)**	8 / 45** **(17.8%)** (89 mg/kg bw/d)	5 / 49 (362 mg/kg bw/d)		7 / 48 **(14.6%)** (940 mg/kg bw/d)	Significant increase in adenoma in low dose vs control
Lankas, 1981 (Sprague-Dawley)	0 / 50 **(0%)**	5 / 49** **(10.2%)** (3 mg/kg bw/d)	2 / 50 (10.3 mg/kg bw/d)	-	3* / 50 **(6.0%)** (31.5 mg/kg bw/d)	Significant increase in adenoma in low dose vs control

*including one carcinoma
** Statistics; pairwise Fisher exact test.

Table: Female rat adenomas and carcinomas

Dose (mg/kg bw/d)	Female rats Adenomas (%)	Female rats Carcinomas	Fisher exact test
0	2/57 (3.5%)	0/57	
89	2/60 (3.3%)	0/60	NS

Dose (mg/kg bw/d)	Female rats Adenomas (%)	Female rats Carcinomas	Fisher exact test
362	6/59 (10.2%)	1/59	NS
940	6/55 (10.9%)	0/55	NS
Cochran- Armitage Trend test (p-value)	p=0.0435 (adenomas)	-	

3) The following tables belong to the comment on developmental toxicity by [***RAC Member 15]***:

Table: Cardiovascular malformations in rabbits

	Controls			**Glyphosate (100-450 mg/kg)**		
	Brooker, 1991	Moxon, 1996	Coles, 1996	Brooker, 1991	Moxon, 1996	Coles, 1996
Number of fetuses examined	163	143	128	311	426	410
Interventricular septal defect	1	0	0	6	0	1*
Heart single ventricle, ventricle walls thickened, aorta enlarged, pulmonary artery reduced	0	0	0	0	1	0

*this fetuses was multi-malformed and may thus be excluded from the analysis.

Table: Summary of cranio-facial skeletal malformations according to table B.6.6-27 of RAR

Dose level (mg/kg bw)	**0**	**10**	**100**	**300**
No of examined fetuses	140	130	150	112
Parietal bones,				

- Fusion - Fissure - Splitting	0 0 0	1 0 0	0 3 3	2 0 1
Interparietal bones (hypoplasia)	0	1	0	0
Nasal/frontal/mandibular bones	0	0	1	0
Total	0	1-2* (0.8-1.5%)	4-7* (2.7-4.7%)	3 (2.7%)

*taking into account number of litters as no information if fetuses had several skeletal malformations

4) The following table belongs to the comment on carcinogenicity by [***RAC Member 12]***:

Comparison Table: "Limited evidence of carcinogenicity in humans" (CLP Regulation) and RAC Conclusion

Limited evidence of carcinogenicity in humans (CLP Regulation))	***Conclusion of RAC – 1st draft ODD***
3.2.2.3 Limited evidence in humans is demonstrated by a positive association between exposure and cancer, ***but a causal relationship cannot be stated.***	*Avialable* ***epidemiological case-control studies, reviews, re-analyses and meta-analyses show weak associations between exposure to GBH and finding of cancer, especially NHL. This indicates a potential concern for human health. However, chance, bias and confounding could not be ruled out with reasonable confidence. A causal relationship can thus not be confirmed by RAC…..***
Carcinogenicity in humans: - *A positive association has been observed between exposure to the agent and cancer*	- ***available epidemiological case-control studies, reviews, re-analyses and meta-analyses show weak assosciations between exposure to GBH and finding for cancer, especially NHL***
- *for which a causal interpretation is considered to be credible*	- ***this indicates a potential concern for human health***
- *but chance, bias or confounding could not be ruled out with reasonable confidence*	- ***However, chance, bias and confounding could not be ruled out with reasonable confidence***

Summary of findings; renal tumour findings, haemangiosarcoma, malignant mouse lymphoma:

Studies	Strain	Doses applied mg/kg bw	Renal tumour findings - Males	Haemangio-sarcoma – Males	Malignant mouse lymphoma - Males
Knezevich and Hogan, 1983	CD-1	0, 157, 814, 4841	↑ I: 1 (2%),0, 1 (2%),3 (6%)	No increase -	No increase
			F: 0.617	-	-
			T: 0.0339*	-	-
Atkinson, 1993	CD-1	100, 300, 1000	No increase I: 2 (4%),2 (4%),0,0	↑ I: 0,0,0,4	↑ I:4(8%),2(4%),0(2%),6(12%)
			-	**F: 0.05***	F: 0.741
			-	**T: 0.0004***	**T: 0.0085***
Sugimoto, 1997	CD-1	165, 838, 4348	↑ I: 0,0,0,2 (4%)	↑ I: 0,0,0,2	↑ I: 2(4%),2(4%),0,6(12%)
			F: 0.495	F: 0.495	F: 0.269
			T: 0.0078	**T: 0.0078***	**T:0.0085***
					HCD: range 3.85-19.23%, Mean: 6.33% 112 studies with male mice between 1992 and 1998
Wood, 2009	CD-1	71, 234, 810	No increase I: 0,0,0,0	No increase	↑ I: 0,1 (2%),2 (4%),5 (10%)
			-	-	**F: 0.056**
			-	-	**T: 0.0037***
Kumar, 2001	Swiss albino	15, 151, 1460	↑ I:0,0,1 (2%),2 (4%)	No increase	↑ I: 10 (20%), 15 (30%),16 (32%), 19 (38%)
			F: 0.495	-	F: 0.077
			T:0.039	-	**T: 0.065**
					HCD: range 6-30% mean: 18.4% 250 male mice in 5 studies covering the in-life phase of the actual study

I: Incidences, F: Fischer exact test, T: Trend test