Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Quizalofop-P-tefuryl; (+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate

EC Number: 414-200-4
CAS Number: 200509-41-7

CLH-O-0000001412-86-118/F

Adopted
3 June 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON QUIZALOFOP-P-TEFURYL; (/-) TETRAHYDROFURFURYL (R)-2-[4-(6-CHLOROQUINOXALIN-2-YLOXY)PHENYLOXY]PROPIONATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

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

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

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

Substance name: **Quizalofop-P-tefuryl; (/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate**
EC number: **414-200-4**
CAS number: **200509-41-7**
Dossier submitter: **United Kingdom**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	1

Comment received

1. Substance ID:
In IUCLID section 1.2 some impurities are listed (flagged as confidential). For five of the stated impurities CAS names are given although there are no existing corresponding CAS entries. Therefore, the given CAS names should be deleted.
Furthermore, we like to mention that in most of the reference substance data sets neither a SMILES notation nor an InChI code is given.
The structural formula given in the IUCLID file in the reference substance data set for Quizalofop-P-tefuryl ((RS)-Tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)-phenoxy]propionate; 50:50 SR:RR isomer ratio) does not reflect the stereochemistry of the substance. The structural formula given in Part B, Section 1.1 of the CLH report should be given instead.
The same applies to some of the impurities given in section 1.2 of the IUCLID file. The corresponding structural formulas given in the reference substance data sets not reflecting the stereochemistry of the particular impurity should be amended.

2. In the applicant's statement (Annex II to CLH dossier), it was stated that data from further quizalofop acid generators were also relevant for the evaluation of quizalofop-P-tefuryl. However such data is apparently missing in the CLH dossier.

Dossier Submitter's Response

1. Thank you for your comments. We note the points raised but it is our understanding that we are unable to update the CLH dossier (including the IUCLID) at this stage of the process.
2. Further information on the quizalofop acid generators quizalofop-P-ethyl and propaquizafop, that is relevant to the evaluation of quizalofop-p-tefuryl, is provided

in Part B of Annex II to the CLH report which is appended to Section 13 of the IUCLID dossier.
RAC's response
Thank you for your comments.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2015	Netherlands		MemberState	2
Comment received				
No carcinogenesis was observed in mice. In rats however, neoplasms were increased in liver (adenoma/carcinoma), testis (Leydig cell tumour) and kidney (renal squamous cell carcinoma). Liver P 53: According to the applicant, the liver tumours are the result of activation of PPARα. It is clear that the neoplasms in the liver are preceeded by hypertrophy and hyperplasia. In addition, it has been shown that quizalofop-P-tefuryl increases the number of peroxisomes in the liver of rats. Although this is an indication that the substance activates PPARα, an actual increased peroxisomal activity (i.e. by CN--insensitive palmityl CoA oxidation) by quizalofop-P-tefuryl has not been evaluated. Therefore, based on the provided data for quizalofop-P-tefuryl, there is insufficient ground to dismiss hepatotoxicity and hepatocarcinogenicity for humans on the basis of the argument that the substance is a peroxisome proliferator. Nevertheless, there are structural similarities with other substances which are concluded to be activators of PPARα. We therefore agree that it may be assumed that also quizalofop-P-tefuryl is an activator of PPARα and that the observed liver tumours are not relevant to humans. Testis P 53: Also the Leydig cell tumours are a consequence of an increased PPARα activation according to the applicant. Although this may be a plausible explanation, the hypothesis has not been proven. In addition, Leydig cell tumours may also be induced via other mechanisms (several of which also result in decreased testosterone levels). No evidence has been provided to exclude these mechanisms. It can therefore not be excluded that the Leydig cell tumours are relevant for humans. Kidney P 53: Renal squamous cell carcinoma is a rare tumour type in rats. Only 3 animals were involved, however the incidences were outside the historical control range and the tumours are considered to be treatment-related. Comparison with criteria and conclusion P53-54: Both the renal tumours and the Leydig cell tumours may be relevant for humans. Carcinogenesis has been observed only in 1 species and only in 1 study. Therefore, we agree with classification as Carc. 2; H351.				
Dossier Submitter's Response				
Thank you for your comments. Regarding the relevance of the Leydig cell tumours to humans, it is agreed that further studies could clarify whether the key early mechanistic step involves PPARα and altered metabolism of testosterone. However, taking into account all the available information, including the incidence of comparable testicular findings for other quizalofop acid generators, the relevance to humans appears low.				

RAC's response
Noted. RAC considers that the substance should be classified as Carcinogenic Category 2, as there is evidence of increased tumours in only one species (rats) and there is no genotoxicity.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	France		MemberState	3
Comment received				
4.10.1.1 Carcinogenicity: oral (p.51-52) PPARα activation is considered to be the underlying MoA for liver and testicular tumors observed in the rat. The MoA of rodent tumors induced by PPARα agonists and its human relevance have been extensively studied by a panel of experts (Klaunig 2003 and Corton 2014). The characterization of this MoA for Leydig-cell tumorigenesis observed in rodents exposed to some PPARα agonists is however less well understood than for liver tumors (Klaunig et al, 2003) and the etiology of Leydig-cell tumors of peroxisome proliferator compounds seen in the rat remains unclear (Corton et al., 2014). The human relevance of such tumors could not be ruled out. Based on both kidney and Leydig-cell tumors, Carc. 2; H351 proposal is supported by FR.				
Dossier Submitter's Response				
Consideration of the relevance of the Leydig cell tumours to humans is not straightforward; we recognise that some experts may consider that the available data are insufficient to discount them for classification purposes. Please also see the response to Comment No. 2.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	4
Comment received				
Overall, classification for carcinogenicity in Category 2 can be supported. A chronic study in rats found dose dependent increase in the incidences of hepatocellular adenoma/carcinoma and kidney squamous cell carcinoma in both males and females, and Leydig cell tumours in testes of males. No neoplastic findings were reported from a chronic carcinogenic study with mice. With respect to the liver tumour development, the proposed MOA hypothesis involves activation of PPARα leading to changes of both hepatocyte growth and survival. Sustained PPARα activation results in hepatocyte proliferation, decreased apoptosis, hyperplasia and ultimately tumour formation. Although biologically plausible, this rodent MOA is considered unlikely for humans due to quantitative differences in the response of both species (Corton et al., 2014). No direct measurement of PPARα activation is available to support the proposed MOA, however hepatic peroxisome proliferation can be considered as a strong and reliable indication for PPARα involvement. Further, there is also no experimental data on hepatocellular proliferation at earlier time points as one of the key events for PPARα initiated liver tumour development (i.e., measures of DNA replication such as BrdU or PCNA). Importantly, there is only limited analysis of alternative MOAs (apart from lack of genotoxicity) that can lead to liver tumour induction such as cytotoxic regenerative proliferation (e.g. cytotoxicity markers such as ALT) or the involvement of				

other nuclear receptors (CAR, AhR). Nevertheless, considering the structural similarity to the group of aryloxyphenoxypropionic herbicides known to act as peroxisomal proliferators, it can be reasonably accepted that peroxisome proliferation and the resulting oxidative stress is the likely mechanism of hepatocellular tumour induction. This MOA is considered of no relevance for humans.

Considering the testicular Leydig cell tumours, several other PPARα activators have been shown to induce a triad of tumour types (liver, the exocrine pancreas, and testicular Leydig cell tumours). The postulated MOA for Leydig cell tumours starts with the activation of PPARα leading to induction of hepatic aromatase and increased conversion of testosterone to oestrogen. The resulting sustained low plasma testosterone levels stimulate the release of luteinising hormone which is as a Leydig cell mitogen. Apart the observation that high incidences of Leydig cell tumours are induced at the same doses as liver tumours, there are currently no further mechanistic studies to support this MOA. According to the CLH report, preliminary results from an on-going study show data that are consistent with the proposed MOA (i.e., increased conversion of testosterone to oestrogen, and increased secretion of luteinising hormone). As these changes are secondary to the pleiotropic effects of PPARα activation, they are considered not to be relevant to humans. The TG on the Application of the CLP Criteria discuss Leydig cell adenomas induced by dopamine antagonists or gonadotropin-releasing hormone as one of the mechanisms of tumour formation considered not relevant to humans.

Renal squamous cell carcinoma is a rare type of tumour found only in few animals of the high dose group in the rat study. Although of minimal incidence, their rates are outside the historical control range and these tumours are considered treatment related.

In summary, a plausible MOA hypothesis has been presented to explain the development of hepatocellular and Leydig cell tumours which involves PPARα activation, peroxisome proliferation and sustained oxidative stress; this MOA is considered not relevant to humans. Nevertheless, several weaknesses in the experimental evaluation of the liver MOA (specifically the lack of more complete assessment of alternative MOAs) and the minimal incidence of rare renal squamous cell carcinoma seem to support a classification in category 2 for carcinogenicity.
However, when RAC assesses factors increasing and decreasing the level of concern, a classification into cat. 1B might be possible, also.

Dossier Submitter's Response

Thank you for your comments. The data suggest to our experts that a category 2 classification would be the most appropriate for this substance. It is possible that the substance does not possess a carcinogenic hazard of relevance to humans, but sufficient data are not available to discount all the tumour findings in animals. In our opinion, a much more definitive carcinogenic profile in animals would be needed to support a category 1B classification. The lack of mutagenicity of this substance is an additional factor to take into account.

RAC's response

See response to comment no 2.

Date	Country	Organisation	Type of Organisation	Comment number
13.11.2015	Spain		MemberState	5
Comment received				
The Spanish CA agrees with the dossier submitter that classification for carcinogenicity is necessary for quizalofop-P-tefuryl under CLP classification criteria as Carc. 2; H351. As the UK CA, we also consider the kidney tumours are relevant for classification. Besides, we can´t rule out the relevance for humans of the testicular tumours. Beyond the question on whether biological responses related to activation of PPARα are of relevance for humans, there are uncertainties about the contribution of this mechanism. There is insufficient evidence to link the Leyding cell tumours to PPARα.				
Dossier Submitter's Response				
Thank you for your comments; please see our response to the other similar comments numbered 2, 3 and 4.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Sweden		MemberState	6
Comment received				
The Swedish CA supports classification of Quizalofop-P-tefuryl (CAS No 200509-41-7) in Carc. 2 as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard class.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Noted.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2015	Netherlands		MemberState	7
Comment received				
We agree with no classification for mutagenesis. All available studies (2 Ames tests, 1 cell mutation assay, 1 in vitro and 1 in vivo UDS test, 1 in vitro chromosome aberration and 2 in vivo micronucleus assays) were negative. Only the cell mutation assay showed equivocal results in the absence of metabolic activation. There are therefore no indications that Quizalofop-P-tefuryl is mutagenic, despite the current classification as Muta Cat 3; R68.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Your opinion is supported				

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON QUIZALOFOP-P-TEFURYL; (/-) TETRAHYDROFURFURYL (R)-2-[4-(6-CHLOROQUINOXALIN-2-YLOXY)PHENYLOXY]PROPIONATE

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	8
Comment received				
Based on the presented data, it seems appropriate not to classify quizalofop-P-tefuryl for mutagenicity. However, considering the substance's existing harmonised classification for mutagenicity, the records / minutes of the previous meetings at ECB should be checked, to ensure that no relevant data are missing.				
Dossier Submitter's Response				
Thank you for your supportive comment. We have considered the records from the previous meeting that are available to us. We are not aware of any additional data which would suggest that the current Annex VI entry is correct. It therefore remains our opinion that this was an error and the available data do not support classification in this hazard class.				
RAC's response				
Your opinion on no classification is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
13.11.2015	Spain		MemberState	9
Comment received				
The Spanish CA agrees with the dossier submitter that classification for mutagenicity is not needed.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Your opinion on no classification is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Sweden		MemberState	10
Comment received				
No experimental values are indicated for any of the studies referred to (neither in the summary table of relevant studies, nor in the text). It is therefore not possible for the reader of the CLH report to evaluate the results on mutagenicity other than by taking general statements about an observed effect or no observed effect into account. Based on such general statements we agree that the available results do not support that the substance should be classified for germ cell mutagenicity.				
Dossier Submitter's Response				
Thank you for your supportive comment. In our view, the descriptions in the CLH report are sufficient for RAC to be able to assess this endpoint. There are no grounds to support classification or to raise a doubt about the mutagenicity of this substance. It should also be noted that as this substance was first notified as a new substance (under NONS) and then considered in detail under the pesticide review programme, the studies have been carefully assessed by us and several other regulatory bodies. The "Note" added in table 20 in relation to the study by Putman and Morris (1991) illustrates the detailed nature of the assessments that have been made.				

RAC's response
Your opinion on no classification is supported.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
12.11.2015	Netherlands		MemberState	11
Comment received				
Despite the fact that the observed testicular effects and effects on fertility and development may be explained by the activation of hepatic PPARα, there is insufficient evidence to conclude this is the (only) mode of action for quizalofop-P-tefuryl . Also it is unclear whether the reprotoxic effects of quizalofop-P-tefuryl are secondary to the effects of PPARα that are common to rodents and man like the hypolipidemic response and changes in lipid metabolism and transport genes, or secondary to the rodent specific effects like oxidative stress and hepatocyte growth. Therefore, it cannot be excluded that the observed effects are relevant for humans and quizalofop-P-tefuryl should be classified for both fertility and development. However, for the substance perfluorooctanoic acid, RAC concluded (RAC opinion December 2011) that PPARα related effects may contribute, but other modes of action must also be active for the reprotoxic effects. This shows that more than one mode-of-action is possible. However, it is unclear due to the differences in chemical structure whether this can be extrapolated to quizalofop-P-tefuryl. Although the available studies have several limitations the overall picture shows reprotoxic effects that are consistent with other PPARα inducers and would warranr classification in category 1B. The effects occur mostly only at doses toxic to parental animals and it is unknown whether these effects occur secondary to the primary effects of quizalofop-P-tefuryl or secondary to the hepatotoxicity. Therefore, we agree with classification in Repr. 2; H361fd.				
Dossier Submitter's Response				
Thank you for these comments.				
RAC's response				
Your analysis of data and opinion on classification as Repr. 2; H361fd is supported.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	France		MemberState	12
Comment received				
Fertility and reproductive function. Adverse effects on fertility function are observed in the available data. The potential MoA proposed by the notifier is not considered sufficiently supported by specific data to conclude of the non-relevance to humans As compounds that induce Leydig-cell tumor in rats by disruption of the hypothalamic–pituitary–testicular axis pose a potential risk to human health (Klauning et al, 2003), Based on those uncertainties and the incompleteness of the parameters measured in the 2-generation study, FR is of the opinion that the initial classification "Repr. Category 2 H361f should be maintained, waiting additional research. Developmental toxicity In rat studies effects on development (growth, mortality, and fetal alterations) were observed at dose levels inducing maternal/parental toxicity. According to CLP guidance, "classification shall be considered where there is a significant toxic effect in the offspring, e.g. irreversible effects such as structural malformations, embryo/foetal lethality,				

significant post-natal functional deficiencies". Major malformations were observed, in the rat developmental toxicity study at the high dose level inducing marked maternal toxicity (100 mg/kg bw/d) and hydrocephaly was observed in some dead pups in the 900ppm group. The dose selection for the rat developmental toxicity is questionable and high dose value selected is not appropriate (exceeding the MTD).

Moreover, the dose-ranging of the developmental study on rabbits is neither appropriate, Indeed the study showed no adverse effect at any dose levels, Rabbit were therefore not adequately tested (conclusions peer review EFSA, 2008).
As a specific maternally –mediated mechanism has not been demonstrated for malformations observed in rats and due the uncertainties surrounding the quality of the studies (dose ranging, incompleteness of the parameters, exposure limited to the organogenesis), FR is in the opinion that the initial classification "Repr. Category 1B H360D should be maintained.

Furthermore, it is important to underline that THFA is a major metabolite of Quizalofop-P-tefuryl in rat metabolism and as such could actually contribute to its toxicity. THFA has been classified Repr. Category 1B H360Df (RAC, 2012) which therefore also supports the proposal for classification of Quizalofop-P-tefuryl as Repr. Category 1B H360Df.

Dossier Submitter's Response

In our view it would be inappropriate to apply the inadequacy of the developmental toxicity tests as a weighting factor to support a category 1B classification. The recent reconsideration of the hydrocephaly seen in rats casts some doubt about the relevance of these observations to humans. The observed post-implantation loss, reduced number of viable foetuses and other significant findings in the foetuses of rats all occurred in dose groups where increased maternal death was observed and this prevents a definitive assessment. The increased pup mortality and effects on pup weight described in the 2-generation study is a concern, although we question whether this is sufficient to justify a category 1B classification given the lack of consistency seen between F1 and F2 pups and between the first and second litters.

The observation that THFA is a metabolite of quizalofop-P-tefuryl is correct, but there is no evidence available to suggest that this could have been formed in sufficient amounts and itself have been subject to metabolism and disposition in a way that would have contributed to the observed reproductive toxicity. At most, this would seem to support the case for a category 2 classification.

RAC's response

Your opinion on classification as Repr. 2; H361f is supported. Please note that quizalofop-P-tefuryl has a different toxicity profile compared to THFA, thus the latter is not determining neither toxicity nor effect on reproduction of quizalofop-P-tefuryl. Quizalofop acid, a major metabolite of quizalofop-P-tefuryl, is considered more important in the toxicity of the parent compound.
The existing data provides evidence that quizalop-P-tefuryl affects the development of animals; however, the adverse developmental effects are only seen at dose levels either lethal to maternal organisms or at dose levels initating serious metabolic alterations leading to disturbances in lipid and testosterone/estrogen metabolism through activation of PPARα receptors. Therefore the observed adverse developmental effects may be considered a secondary non-specific consequence of other toxic effects. Taking into account the evidence of developmental toxicity and doubts related to relevance of the postulated mechanism to humans RAC is of the opinion that quizalop-P-tefuryl warrants classification as Repr. 2, H361d.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	13

Comment received

Based on the presented data, it seems appropriate to classify quizalofop-P-tefuryl for reproductive toxicity. Considering the substance's existing harmonised classification for fertility (cat. 2) and development (cat. 1B), the records / minutes of the previous meetings at ECB should be checked, to ensure that no relevant data or information are missing.

In the multi-generation study, adverse effects on fertility were reported (range-finding: small testes, histological findings in seminiferous tubules and epididymis, fail to sire, sperm abnormalities; main study: low male and female fertility, low litter size, hormonal changes). This is supported by adverse effects reported in repeat-dose studies on spermatogenesis / in testes in all tested species (Tables 19 and 21). Considering that effects were reported in several species, classification for fertility (at least with cat. 2) is triggered, however a case could be made easily to classify with cat. 1B.
Remark: considering that similar findings were reported in repeat-dose studies in mice, rats and dogs, the case about the relevance of PPAR-mediated effects in rat testes is questioned.

In the multi-generation study, increased incidences of hydrocephalus were reported for offspring in F1b and F2b generations and low pup viability in F1a generation in top dose groups. In the range-finding developmental toxicity study in rabbits, increased incidences of post-implantation loss were reported. Considering that effects were reported in several studies, classification for developmental toxicity (at least with cat 2) is supported, however a case could be made not to change the existing harmonised classification with cat 1B.

Dossier Submitter's Response

As far as we can ascertain from the meeting records available to the UK CA and from information provided by the Applicant, no studies are missing. Your comments are noted.

RAC's response

In the opinion of RAC there is mechanistic information that raises doubt about the relevance of the effects observed in animals for humans, and thefore classification in Category 2 is considered more appropriate.

Date	Country	Organisation	Type of Organisation	Comment number
13.11.2015	Spain		MemberState	14

Comment received

The Applicant has provided arguments for no classification for an effect on reproduction. In our opinion PPARα-related effects may contribute, but other modes of action can also be active and can´t fully be excluded and developmental effects could not be attributed to liver toxicity as a secondary mechanism. Also the role of PPARα-related mode of action is not fully elucidated for the developmental effects.

In addition the relevance of PPARα expression for humans is well established for the liver, however much less is known for the relevance of PPARα-related effects in other organs and effects in the offspring and juvenile.

Therefore, Spanish CA agrees with the dossier submitter that classification is needed. Evidence is sufficiently convincing to classify for reproductive effects as Repr.2 (H361fd).
Dossier Submitter's Response
Thank you for the supportive comment.
RAC's response
Your analysis and opinion is supported.

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Sweden		MemberState	15
Comment received				
The Swedish CA supports classification of Quizalofop-P-tefuryl (CAS No 200509-41-7) in Repr. 2 for adverse effects on sexual function and fertility as specified in the proposal. SE agrees with the rationale for classification into the proposed hazard class and differentiation. We do not support revision of the current classification of Quizalofop-P-tefuryl in Repr. 1B to Repr. 2 for adverse effects on the development of the offspring. We consider the current classification in Repr. 1B still appropriate and justified. The developmental toxicity studies (pre-natal developmental toxicity studies in rat and rabbit) that were not included in the previous evaluation do not affect the current harmonised classification of Quizalofop-P-tefuryl in CLP Annex VI. We consider that classification in Repr. 1B is warranted mainly based on data from the two-generation reproduction toxicity study where postnatal decrease in pup viability is demonstrated. We note that reduced pup viability and decreased pup weight during early lactation are findings that appear to be consistent across F1a/b and F2a/b litters and that the effects are not considered to be secondary to other maternal toxic effects. We do not think that there is sufficient support from the PNDT studies to disregard these findings. The two-generation reproduction toxicity study reveals delayed death at birth or shortly after birth after in utero exposure during the entire gestation period. In the PNDT studies in utero exposure occurs only between only GD 6-15 and the postnatal period is not covered in the examination. Therefore, the lack of clear effects on foetal viability in the PNDT study is not contradictory to the demonstrated effects in the two-generation study. The lack of developmental toxicity in the PNDT study in rabbit is can be explained by the low doses administered. We consider that the dose levels in this study may not be high enough to explore developmental toxicity of Quizalofop-P-tefuryl since no maternal toxicity were reported at the highest dose level. In addition to the demonstrated effects on pup viability there are further evidence from available studies that support the signal of Quizalofop-P-tefuryl as having potential to cause developmental toxicity. The reported malformations in the two-generation reproductive toxicity study and PNDT study in rat cannot conclusively be disregarded as solely coincidental. Moreover, the mode of action argumentation referring to PPPRα is considered not be relevant for the observed developmental toxicity.				

Dossier Submitter's Response
Thank you for the supportive comment in relation to the sexual function and fertility endpoint and for the further assessment of the relevance of the results of the PNDT studies.
RAC's response
Thank you for your analysis and comments. RAC also supports Repr. 2 for adverse effects on sexual function and fertility as specified in the proposal. For classification of developmental effects according to CLP criteria the classification of a substance in Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on development in the absence of other toxic effects, or if occurring together with other toxic effects, the adverse effect on reproduction should be considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate. The existing data provides evidence that quizalop-P-tefuryl affects the development of animals, however the adverse developmental effects are only seen at dose levels either lethal to maternal organisms or at dose levels initating serious metabolic alterations leading to disturbances in lipid and testosterone/estrogen metabolism through activation of PPARα receptors. Therefore the observed adverse developmental effects might be a secondary non-specific consequence of other toxic effects. In this case these effects cannot be treated as secondary, however taking into account the evidence of developmental toxicity and the doubt related to relevance of the postulated mechanism to humans RAC is of the opinion that quizalop-P-tefuryl should be classified as Repr. 2, H361d.

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	16
Comment received				
Based on the presented evaluation, the relevant data are lacking.				
Dossier Submitter's Response				
Noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	17
Comment received				
Based on the presented data (oral LD50 in rats: ~1012 mg/kg bw; dermal LD50 in rabbits: > 2000 mg/kg bw; LC50 in rats: > 3.9 mg/L), it seems appropriate to classify quizalofop-P-tefuryl with Acut Tox. 4 for the oral route (H302) but not for dermal or inhalation routes.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
13.11.2015	Spain		MemberState	18
Comment received				
With an oral LD50 of 1012 mg/kg bw, the Spanish CA supports the proposed classification as Acute Tox.4; H302.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	19
Comment received				
Based on the presented data, it seems appropriate not to classify quizalofop-P-tefuryl for Skin corrosion/irritation.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	20
Comment received				
Based on the presented data, it seems appropriate not to classify quizalofop-P-tefuryl for serious eye damage/eye irritation.				
Dossier Submitter's Response				
Thank you for your supportive comment.				
RAC's response				
Thank you for your comment.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	21
Comment received				
Based on the presented data, it seems appropriate to classify quizalofop-P-tefuryl for skin sensitisation taking into account the higher severity and incidence of skin reactions in treatment group animals. However, based on the limitations in the study results (quite high number of animals reacting in control group) it is considered difficult to assign the substance to a certain subcategory with confidence. Hence it is proposed to classify quizalofop-P-tefuryl with Skin Sens. 1 (H317).				

Dossier Submitter's Response
Thank you for your comments. Given that an intradermal induction concentration of 20% produced a positive response in only approximately 7/20 (35%) of test animals it seems very unlikely that this substance is a high potency skin sensitiser as defined by the CLP guidance. We take note of your comments, but still think a category 1B classification to be justified by the available data.
RAC's response
Thank you for comment. Given the argumentation provided in the opinion, RAC concluded that classification as Skin sensitization is not justfied.

Date	Country	Organisation	Type of Organisation	Comment number
13.11.2015	Spain		MemberState	22
Comment received				
The Spanish CA supports the proposed classification of quizalofop-p-tefuryl as Skin Sens. 1B; H317: May cause an allergic skin reaction, according to the 2nd ATP of CLP Regulation (in a guinea pig maximisation test with >1% intradermal induction dose a response ≥ 30% of the animals is considered as positive). This classification is based on the results of the maximisation study in guinea pigs (Denton, 1998) not reviewed in the context of the classification decision included in the 28th of Dir 67/548/EEC.				
Dossier Submitter's Response				
Thank you for your comments – see response to comment 21 also.				
RAC's response				
Thank you for your comment.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Sweden		MemberState	23
Comment received				
We agree with the dossier submitter that the data from the first challenge in the GPMT indicates that Quizalofop-P-tefuryl has skin sensitising potential. However, there are skin reactions to the vehicle alone in the test group which compromises the interpretation of the results from the study. Because of these difficulties, we consider that the available data is insufficient for sub-categorisation. Instead, we suggest to classify Quizalofop-P-tefuryl in category 1.				
Dossier Submitter's Response				
Thank you for your comments – see response to comment 21				
RAC's response				
Thank you for comment. Given the argumentation provided in the opinion, RAC concluded that classification as Skin sensitization is not justfied.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	24
Comment received				
Based on the presented data, it seems appropriate not to classify quizalofop-P-tefuryl for STOT SE.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted. RAC consideres that classification for specific target organ toxicity (single exposure) is not required.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	25
Comment received				
DS proposed to remove quizalofop-P-tefuryl's harmonised classification with STOT RE. However, based on the presented data, it seems appropriate to keep quizalofop-P-tefuryl's classification for STOT RE. In the repeat-dose studies in mice and dogs and the developmental toxicity studies in rats and rabbits (range-finding), (higher numbers of) animals died in the later stages of the studies. Additionally, in the studies in mice, liver necrosis was observed. Both, mortality and liver necrosis are severe findings which may trigger classification. The findings were reported in dose levels compatible with STOT RE 2.				
Dossier Submitter's Response				
It is noted that a number of effects were observed in the repeat dose toxicity studies. However, the liver effects in the mouse are considered to be consistent with PPARa activation and not relevant to the classification. With regards the other effects, including the increased mortality, kidney effects etc., there was a lack of consistency across the studies (e.g., from range finding/short duration studies to full/longer term studies) and between the different species. It is therefore considered that these effects are not supportive of a classification for STOT-RE.				
RAC's response				
Noted. RAC however considers that the current classification as STOT RE 2 should remain. See opinion for further argumentation.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	26
Comment received				
Based on the presented evaluation, the relevant data are lacking.				
Dossier Submitter's Response				
Noted.				

RAC's response
Noted. Thank you.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	France		MemberState	27
Comment received				
We agree with the classification and M-factors proposed for Environmental hazards.				
Dossier Submitter's Response				
Thank you for your supportive comments.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.11.2015	Germany		MemberState	28
Comment received				
Page 85, point 5.9.3 algae and aquatic plants, Study 2 (Hoberg, 1992) The study result should not be used for classification purposes because the study does not fulfill validity criteria of the guideline. There is a great loss of test concentration from initial 1.9 mg/L to lower than 0.1 mg/L at the end of the study. During the study at 96 hours and later no exponential growth was observed. After 72 hours the mean cell density was significantly reduced by 72% in relation to untreated control. Therefore this test should be repeated with a range of test concentrations to get real dose-response-related results. The study results are only supplementary information. Results of study 1 (Morris & Latham, 1998) with Navicula pelliculosa is sufficient for assessment of acute aquatic toxicity of Quizalofop-P-tefuryl for algae.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted. RAC assumes that this study (Hoberg, 1992) results do not have any influence on the proposed classification.				

Date	Country	Organisation	Type of Organisation	Comment number
09.10.2015	Denmark		MemberState	29
Comment received				
Denmark agrees with the CLH proposal. The most sensitive species in the acute tests are fish with LC50 for Bluegill Sunfish of 0.23 mg/l and for rainbow trout of 0.51 mg/l. There is only one study on the long-term toxicity to fish, a NOEC for rainbow trout of 20 mg/l. Given there are 2 acute tests, both of which report LC50 in the range of 0.1-1 mg/l the NOEC of 20 mg/l seems to be unreliable. Thus there is no reliable EC10 or NOEC for fish, and therefore the chronic classification must be based on the short-term toxicity combined with degradation and/or bioaccumulation data as done in the CLH report.				

Dossier Submitter's Response
Thank you for your comments.
RAC's response
Noted. RAC assumes that this long-term study was provided for the metabolite QUIZ but not for the parent substance quizalofop-P-tefuryl.