CLH report

Proposal for Harmonised Classification and Labelling

**Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2**

Substance Name: Quizalofop-P-tefuryl

EC Number: **414-200-4**

CAS Number: **200509-41-7**

Index Number: **607-373-00-4**

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Dossier prepared by Chemtura Corporation in accordance with Article 37(6) of CLP.

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Part A.

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	Quizalofop-P-tefuryl
EC number:	414-200-4
CAS number:	200509-41-7*
Annex VI Index number:	607-373-00-4
Degree of purity:	≥ 79.5%; 50:50 RR:SR ratio
Impurities:	There are up to 12 impurities present. The impurities have been taken into consideration and do not add to the classification.

* *CAS number currently included in Annex VI of CLP is 119738-06-6 (EC 414-200-4; Annex VI Index number: 607-373-00-4.)*

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation
Current entry in Annex VI, CLP Regulation	Muta. 2; H341 (Suspected of causing genetic defects) Repr. 1B; H360Df (May damage the unborn child. Suspected of damaging fertility) Acute Tox. 4 *; H302 (Harmful if swallowed.) STOT RE 2 *; H373 ** (May cause damage to organs through prolonged or repeated exposure) Aquatic Acute 1; H400 (Very toxic to aquatic life) Aquatic Chronic 1; H410 (Very toxic to aquatic life with long lasting effects)
Current proposal for consideration by RAC	Carc. 2; H351 (Suspected of causing cancer) Repr. 2; H361fd (Suspected of damaging fertility. Suspected of damaging the unborn child) (*Note: The Applicant (Chemtura,) who drafted this report, proposed no classification for reproductive toxicity based on a proposed mode of*

	CLP Regulation
	action involving a rat specific activation of hepatic PPARα of no relevance to man) Acute Tox. 4; H302 (Harmful if swallowed.) Skin Sens. 1B; H317 (May cause an allergic skin reaction) Aquatic Acute 1; H400 M-factor = 1 (Very toxic to aquatic life) Aquatic Chronic 1; H410 M-factor = 1 (Very toxic to aquatic life with long lasting effects) *STOT RE is proposed to be removed from Annex VI of CLP*
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Carc. 2; H351 (Suspected of causing cancer) Repr. 2; H361fd (Suspected of damaging fertility. Suspected of damaging the unborn child) (*Note: The Applicant (Chemtura,) who drafted this report, proposed no classification for reproductive toxicity based on a proposed mode of action involving a rat specific activation of hepatic PPARα of no relevance to man)* Acute Tox. 4; H302 (Harmful if swallowed.) Skin Sens. 1B; H317 (May cause an allergic skin reaction) Aquatic Acute 1; H400 M-factor = 1 (Very toxic to aquatic life) Aquatic Chronic 1; H410 M-factor = 1 (Very toxic to aquatic life with long lasting effects)

1.3 Proposed harmonised classification and labelling

This proposal addresses the removal of the harmonised classification for STOT-RE and mutagenicity, a change in the classification for reproductive toxicity, and addition of a classification for carcinogenicity. It does not address the other classifications listed in Annex VI to CLP.

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.2.	Flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.3.	Flammable aerosols	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.4.	Oxidising gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.5.	Gases under pressure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.6.	Flammable liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.7.	Flammable solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.8.	Self-reactive substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.9.	Pyrophoric liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.10.	Pyrophoric solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.11.	Self-heating substances and mixtures	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.12.	Substances and mixtures which in contact with water emit flammable gases	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.13.	Oxidising liquids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.14.	Oxidising solids	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.15.	Organic peroxides	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
2.16.	Substance and mixtures	Not classified	Not applicable	Not classified	conclusive but not

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
	corrosive to metals				sufficient for classification
3.1.	**Acute toxicity - oral**	**Acute Tox 4; H302**	Not applicable	**Acute Tox 4*; H302**	Not applicable
	Acute toxicity - dermal	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
	Acute toxicity - inhalation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.2.	Skin corrosion / irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.3.	Serious eye damage / eye irritation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.4.	Respiratory sensitisation	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.4.	Skin sensitisation	**Skin Sens 1B; H317**	Not applicable	Not classified	Not applicable
3.5.	Germ cell mutagenicity	Not classified	Not applicable	**Muta 2; H341**	conclusive but not sufficient for classification
3.6.	Carcinogenicity	**Carc 2; H351**	Not applicable	Not classified	Not applicable
3.7.	Reproductive toxicity	**Repr. 2; H361fd [see footnote]**	Not applicable	**Repr. 1B; H360Df**	Not applicable
3.8.	Specific target organ toxicity – single exposure	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification
3.9.	Specific target organ toxicity – repeated exposure	Not classified	Not applicable	**STOT-RE*; H373****	conclusive but not sufficient for classification
3.10.	Aspiration hazard	Not classified	Not applicable	Not classified	Data lacking
4.1.	Hazardous to the aquatic environment	**Aquatic Acute 1; H400** **Aquatic Chronic 1; H410**	**Acute M-factor = 1** **Chronic M Factor=1**	**Aquatic Acute 1; H400** **Aquatic Chronic 1; H410**	Not applicable
5.1.	Hazardous to the ozone layer	Not classified	Not applicable	Not classified	conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Footnote: *The view of Chemtura Corporation (also referred to as "The Applicant" in this dossier), with due consideration of positions developed previously during expert meeting discussions at EFSA, is that there should be no classification for reproductive toxicity based on a proposed mode of action involving a rat specific activation of hepatic PPARα of no relevance to man. Their rationale has been included in this CLH Report, which has largely been prepared by them. The UK CLP Competent Authority, being responsible for submission of this proposal, is of the view that at least a category 2 classification is appropriate.*

Labelling: Signal word: Danger
Hazard statements: H302, H317, H351, H361fd, H400, H410
Pictograms: GHS07, GHS08 and GHS09

Proposed notes assigned to an entry: None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Quizalofop-P-tefuryl is currently listed in Annex VI of Regulation EC 1272/2008 (CLP Regulation) as Muta. 2; H341, Repr. 1B; H360Df, Acute Tox. 4*; H302, STOT RE 2*; H373**, Aquatic Acute 1; H400 and Aquatic Chronic 1; H410.

The substance was notified in the UK under Dir 67/548/EEC (notification number 94-06-0565) and a classification proposal was subsequently presented to and agreed by the Technical Committee for Classification and Labelling in 1998. It was then adopted in the 28th ATP to Dir 67/548/EEC and incorporated into ATP00 of the Classification Labelling and Packaging Regulation.

Table 4: The original data package submitted under NONS included the following studies:

Study	**Author(s), year**
Acute oral toxicity	Naas, 1991
Acute dermal toxicity	Lilja, 1988a
Skin irritation	Lilja, 1988b
Eye irritation	Lilja, 1988c
Skin sensitisation	Lilja 1989
90 day repeat dose study in the rat	Goldenthal, 1990
90 day repeat dose study in the dog	Crosby Tompkins, 1991b
Ames	San & Springfield, 1990
IVC	Bigger & Clarke, 1991
In vivo mammalian bone marrow micronucleus study	Putman and Morris, 1991
2-Generation study in rats	York, 1993b
1 year chronic toxicity study in dogs	Crosby Tompkins, 1993
Combined 2 year chronic toxicity/carcinogenicity study in rats	Goldenthal, 1993

Subsequent to the adoption of the current harmonised classification, this substance was reviewed under Directive 91/414/EEC as a pesticidal active substance. Additional studies were submitted (by Chemtura: the "Applicant") in the context of this review (e.g. rat and rabbit developmental toxicity studies) which had not been included in the previous NONS submission. It is considered that these additional data significantly impact on the final classification conclusions for quizalofop-P-tefuryl.

In EFSA's Conclusion on the peer review of quizalofop-P (EFSA's Scientific Report (2008) 205, 1-216) the following classification according to Directive 67/548/EEC was proposed for quizalofop-P-tefuryl:

R22 "Harmful if swallowed"
R40 "Limited evidence of a carcinogenic effect"
R43 "May cause sensitization by skin contact"
R63? "Possible risk of harm to the unborn child" (this endpoint was for referral to ECHA).
N, R50/53 "Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment"

The rationale for EFSA's conclusions on the classification of quizalofop-P-tefuryl are discussed under the relevant hazard categories below.

2.2 Short summary of the scientific justification for the CLH proposal

No classification is warranted for physico-chemical hazards.

With an oral LD50 of 1012 mg/kg bw, quizalofop-P-tefuryl warrants the classification Acute Tox. 4; H302. It has a low dermal and inhalation toxicity and therefore no classification is justified for these routes of

exposure. Quizalofop-P-tefuryl is not a skin, eye or respiratory tract irritant or a corrosive substance and therefore no classification is warranted for these hazard classes.

Quizalofop-P-tefuryl has sensitising properties in a Maximisation test, although not in a Buehler test. Differing from the current Annex VI classification (not classified), quizalofop-P-tefuryl is considered to warrant classification with Skin Sens Cat 1B: H317.

In repeat dose studies, effects were observed in the liver and testes. According to CLP criteria, testicular effects (including testicular degeneration, aspermatogenesis and aspermia, as observed with quizalofop-P-tefuryl) should be considered as part of the assessment of reproductive toxicity. For the reported liver effects, these are concluded to result from peroxisome proliferation and therefore not to be relevant to humans. Consequently, no classification for repeated dose toxicity is considered to be justified. This differs from the current harmonised classification which, at the time of consideration, was based on the testicular effects.

Quizalofop-P-tefuryl gave a negative result in an *in vivo* rat hepatocyte UDS assay and in a mouse bone marrow micronucleus assay. It has been thoroughly tested for genotoxicity and is proposed not to be classified for this hazard class. The basis for the existing classification with Muta. 2; H341 classification is unclear.

Increased frequencies of kidney, liver and testicular tumours were seen in rats treated with quizalofop-P-tefuryl. No evidence of carcinogenicity was found in mice. Whilst the kidney tumours are considered to be of potential relevance to humans, and therefore to support classification, the Applicant (Chemtura) has proposed that neither the liver nor testicular tumours should be viewed as relevant for classification.

In the case of both liver and testicular tumours, the action of quizalofop-P-tefuryl as an inducer of the hepatic peroxisome proliferation receptor (PPARα) is considered critical. The increased frequency of liver tumours was judged to be linked to the induction of PPARα, and therefore not considered relevant to humans. Furthermore, as this receptor is known to promote induction of the hepatic enzyme aromatase it can stimulate conversion of testosterone to oestrogen resulting in decreased circulating testosterone levels. This in turn would result in a chronic surge in leuteinising hormone (LH), which is known to be mitogenic to the Leydig cells of the testes. It was argued that chronic cell proliferation as a result of increased LH could account for the carcinogenic response seen. In the absence of activation of PPARα, and the subsequent liver growth that occurs following receptor activation, there is no induction of aromatase, through the pleiotropic effects of PPARα, and hence no increased conversion of testosterone to oestrogen, no LH surge, and no increase in Leydig cell tumours in the treated rats. The Applicant concluded that the testicular effects were a consequence of a generally accepted, increased sensitivity of rats to the pleiotropic effects of PPARα induction, and therefore of little or no relevance to humans.

Quizalofop-P-tefuryl is not mutagenic (see section 4.9 below) and there is no evidence that it has produced tumours in humans. On this basis, with tumours of potential relevance to humans found in rat kidney only, classification with Carc. 2; H351 is considered appropriate.

In the repeated dose studies with Quizalofop-P-tefuryl, testicular damage was observed in the testes of rats, dogs and mice. The Applicant has provided the following explanation as to why these effects are not relevant for classification. Originally, the dog was found to be the most sensitive species, with aspermatogenesis of the testes and epididymidyl aspermia observed in a 90-day study at 51-64 m g/kg/day, the highest dose tested. A targeted pathology review of the dog testes, epididymis and prostate glands, by the original CRO that ran the study, found a common lesion representing immaturity in all three organs and concluded that the lesion was a secondary consequence of the large body weight reductions that occurred in the top dose animals, and not a direct effect of the test item. Further, due to the age of the animals in this study, and lack of sexual maturity, there are expected age related abnormities in testes that are in line with the pathology findings in the 90-day dog study, and support further that the effects in this study are not the result of exposure to the test item (Goedken *et al*., 2008). In addition, the conclusion of the 90-day dog study is supported by the lack of similar findings in the male reproductive organs from dogs in the shorter-term 28 day study conducted at higher dose levels, and in the 12 month study, which was carried out at comparable dose levels to those used in the 90 day study.

Testicular effects were observed in rats, in a 90-day study at 134 mg/kg/day, the highest dose tested. At this same dose level mean body weights were markedly reduced in male rats, with a 30% decrease in body weight noted for this group, when compared to controls, at study termination. A significant reduction in mean body weight in rats, resulting from decreased food intake, has been shown to impact negatively the testes and spermatogenesis (Rehm *et al*., 2008). The significantly reduced mean body weights at the 134 mg/kg/day group in this study suggests that the effects seen in the testes could be due in part to decreased food intake and not the direct effect of the test item exposure. This is further supported by the fact that testicular effects were not seen at the lower dose levels tested, where mean body weights were not notably decreased when compare to control animals.

Information is available in mice from a 28-day study; testicular toxicity was seen at the highest dose tested (285-452 mg/kg/day). Since all of the mice on the top dose level died between days 5 and 7, and they lost weight and were presumably starving, from the first day of exposure, it is clear that they were under extreme conditions throughout their time on study. The testicular necrosis, as described in the report, is minimal, and is consistent with what has been described as a secondary consequence of extreme stress (Everds *et al*., 2013). The conclusion of these mice being under extreme stress is supported by observations of lymphoid atrophy, and adrenal hypertrophy, shown in these animals. Under these conditions it is not appropriate to consider any organ effects in dying animals as being directly related to exposure to the test item.

The proposed mode of action for rat testicular toxicity is through decreased circulating testosterone as a consequence of increased conversion to oestrogen, via PPARα related induction of aromatase. This mode of action (MOA) would account for the changes in the testes and produce the morphological changes observed in these studies where testosterone is needed for the stage-specific maturation of germ cells. These findings, involving quizalofop induced activation of rat hepatic PPARα, involve a MOA that has no relevance to humans and, as such, would justify no classification for reproductive toxicity.

In the only available two-generation reproduction study, conducted in rats, the highest dose tested was 52.8-68.1 mg/kg/day (dosing via the diet). At this dose, there were signs of reduced reproductive performance in F1 males. This was a little below the dose level found to cause adverse effects on the testes in this species following repeated dosing for 90 days. In the 2-generation study, however, parental body weight gain was lower at this dose than in controls during the pre-mating period and increased liver weight and hepatic hypertrophy were seen in the parents at termination. Other endpoints which might clarify or confirm the effect of quizalofop-P-tefuryl on reproduction were not included in this study i.e. oestrus cyclicity, sperm evaluation, reproductive organ weights and comprehensive histopathological examination of the reproductive tract. It could be argued therefore that this study is not sufficiently robust to reliably confirm an effect of quizalofop-P-tefuryl on fertility.

Further to this, the Applicant has provided arguments for no classification for an effect on reproduction. They highlight the observations in treated rats of increased plasma oestrogen concentrations and the decreased circulating testosterone, and comment that other PPARα agonists produce a similar effect. They argue that this results in an altered hormonal "milieu" which would be expected to result in altered reproductive parameters. As they describe in detail in Annex I, this is considered not to be relevant to humans (Annex I). Although the Applicant argued that the 2-generation reproduction study in rats clearly had deficiencies, they observed that some of the reported findings in the exposed animals were not inconsistent with the proposed hypothesis. For example, vacuolar change in cells of the *pars distalis* in the pituitary gland was observed in F0 and F1 male (only) rats at the 2 higher doses. This is considered secondary to the hepatocyte hypertrophy and not a direct effect on the pituitary gland, indicating the presence of so-called 'castration cells' which are leuteinising hormone secreting and support the hypothesis of reduced testosterone; only being seen in male rats. The Applicant concluded "in consideration of a plausible PPARα hypothesis for non-human relevance and consistency of the experimental results related to findings from repeat dose and reproductive studies for quizalofop-P-tefuryl, despite the deficiencies of the two-generation reproduction study, and other quizalofop acid generators (Annex II) it could be considered that there is sufficient reason to preclude the need for any classification for fertility under CLP".

Overall, the UK CLP Competent Authority concluded that the evidence is suggestive, at least, that quizalofop-P-tefuryl presents a reproductive hazard of relevance to humans. It has not been proven that the

"PPARα hypothesis" accounts for the effects on fertility seen in the 2-generation study and all the observations relating to testicular toxicity in rat, mouse and dog repeat dose toxicity tests (although the applicant has presented arguments to suggest that the effects in dogs and mice are not directly related to quizalofop-P-tefuryl exposure). However, as available data show that this potential may only prevail at a systemically toxic dose, classification in Category 2 (with H361f) may be more appropriate than Category 1(with H360F).

Data are also available to indicate that classification for developmental toxicity may be justified. In rabbits, in a dose-range finding study, increased post-implantation loss and a decreased number of viable foetuses were evident at 50 mg/kg, a dose at which 1 maternal death occurred. No developmental toxicity was seen in the main study at lower doses. In a rat developmental toxicity study, there was evidence of developmental toxicity (increased post-implantation loss; reduced foetal weight, increased incidence of foetal malformations) but only at a maternally lethal dose of 100 mg/kg/day. Although these findings in the rat and rabbit developmental toxicity studies are not particularly informative, the rat 2-generation reproduction study showed reduced postnatal survival and pup growth at the highest dose in the F0 and F1 generations (52.8-76.4 mg/kg; dosing via the diet).

Parental body weight gain was lower than controls during the pre-mating period and increased liver weight and hepatic hypertrophy were seen in the parents at termination. Similar systemic effects were seen at the next lower dose as well. However, the Applicant has argued that the action of quizalofop-P-tefuryl to induce hepatic aromatase activity (via PPARα activation) and stimulate conversion of testosterone to oestrogen should also be taken into account. As oestrogen is a key hormone for reproduction, they argue, this might be expected to have significant adverse effect on reproduction in rats. The Applicant has suggested that such a mode of action is plausible, given the consistency of the results from repeated dose and reproductive studies with quizalofop-P-tefuryl, and that it would not be of relevance for human hazard assessment. See Annexes I and II for a detailed analysis by the Applicant.

Further to the general effect on pup development, an increased incidence of hydrocephaly was observed in the rat 2-generation study at the top dose in F1B and F2B litters. Although this malformation could indicate developmental toxicity of quizalofop-P-tefuryl, and cannot readily be related to hepatic aromatase activation, it is significant that comparable lesions were not reported for the F1A or F2A litters. This inconsistency suggests that the occurrence of hydrocephaly in this study may have been incidental and not treatment-related. This possibility is supported by the absence of hydrocephaly in the rat prenatal developmental toxicity, where severe maternal toxicity and other foetal malformations were observed.

Also of relevance is the absence of detail for the method of examination used to confirm the presence of hydrocephaly in the two generation study. Typically, hydrocephaly in foetuses and neonates is detected by free-hand sectioning of the head following fixation; it is not usually done on dead neonates where autolysis may already be underway rendering the brain tissue unsuitable for sectioning and for evaluation. Whether appropriate examination of the pups was undertaken and whether the diagnosis was correct cannot be confirmed, and for this reason the Applicant judged the data to be unreliable.

The UK CLP Competent Authority considers that this re-analysis of the available data does cast some doubt on the appropriateness of the current classification in Repr. 1B for developmental toxicity. The Applicant has argued that no classification might be an option. However, as it has not been established that the various developmental findings observed in the 2-generation study did actually occur by chance or by a mode of action that is not relevant for humans, Repr Cat 2 would seem a more appropriate classification.

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification:	Muta.2; H341
	Repr. 1B; H360Df
	Acute Tox. 4*; H302
	STOT RE 2*; H373**
	Aquatic Acute 1; H400
	Aquatic Chronic 1; H410
Labelling:	Hazard Statement Code: H341, H360Df, H302, H373**, H410
	Signal word: Danger
	Hazard Pictogram: GSH08, GSH07, GSH09
	Supplemental hazard statement code: None

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Classification:	Muta. Cat. 3: R68
	Repr. Cat. 2; R61
	Repr. Cat. 3; R62
	Xn; R22-48/22
	N; R50-53
Labelling:	Risk Phrases: R61, R22, R48/22, R62, R68, R50/53
	Safety Phrases: S53, S45, S60, S61
	Indication of Danger: T; N

2.4 Current self-classification and labelling

2.4.1 Current self-classification and labelling based on the CLP Regulation criteria

Classification and labelling of quizalofop-P-tefuryl is according to its current entry in Annex VI to CLP.

2.4.2 Current self-classification and labelling

Classification and labelling of quizalofop-P-tefuryl is according to its current entry in Annex VI to CLP.

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Quizalofop-P-tefuryl was notified in the UK under Dir 67/548/EEC (94-06-0565). It is a herbicide, which has subsequently been included in Annex I to Council Directive 91/414/EEC by means of Commission Directive 2009/37/EC of 23 April 2009. Finland was the Rapporteur Member State. The proposed classification following review under Directive 91/414/EEC differs from the current Annex VI classification because additional data were considered which were not included in the original notification which led to the classification included in the 28th ATP of Directive 67/548/EEC (2001/59/EC) (agreed at ECB C&L meeting in October 1998).

In accordance with Article 36(2) of the CLP Regulation, it is proposed that a revision to the classification and labelling of quizalofop-P-tefuryl in Annex VI of the CLP Regulation should be considered. As the substance is already listed in Annex VI of CLP this proposal only addresses those hazard classes for which an amendment to the classification is proposed; supporting information is also included where relevant.

The dossier has been prepared by Chemtura Corporation in accordance with Article 37(6) of CLP and submitted by the UK CA.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

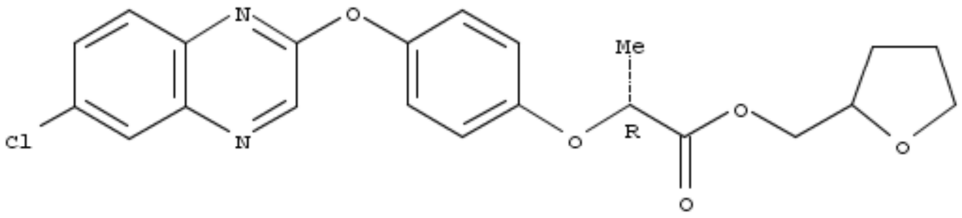
1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	414-200-4
EC name:	(±) tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate
CAS number (EC inventory):	119738-06-6 *
CAS number:	200509-41-7
CAS name:	Propanoic acid, 2-[4-[(6-chloro-2-quinoxalinyl)oxy]phenoxy]-, (tetrahydro-2-furanyl)methyl ester, (*2R*)-
IUPAC name:	(*RS*)-Tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate
CLP Annex VI Index number:	607-373-00-4
Molecular formula:	$C_{22}H_{21}ClN_2O_5$
Molecular weight range:	428.9

* Note, this is the CAS number that is currently included in Annex VI of CLP for the substance with EC 414-200-4, (±) tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate. However, this does not reflect the stereochemistry.

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Quizalofop-P-tefuryl	≥ 79.5% 50:50 SR:RR isomer ratio	-	Minimum purity of the active substance as manufactured

SR = (*S*)-Tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate

RR = (*R*)-Tetrahydrofurfuryl (*R*)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate

Note that the current Annex VI entry refers to the CAS number 119738-06-6. However, this does not reflect the stereochemistry and it is proposed to amend the entry to include 200509-41-7.

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
Confidential	-	-	-

There are 12 impurities in quizalofop-P-tefuryl. The impurities have been taken into consideration in the classification of this substance. Details on the impurities are considered to be confidential and further information is provided in the technical dossier.

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
-	-	-	-	Not relevant

1.2.1 Composition of test material

The purity of quizalofop-p-terfuryl tested in the studies ranged from 88.79% to 95.6%. Information on the actual composition used is provided in the relevant tables of this report and also in associated IUCLID summaries (where provided). The tested material in all cases is considered to be equivalent to and representative of that specified above.

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	**Value** (% purity of test material)	**Reference**	**Comment (e.g. measured or estimated)**
State of the substance at 20°C and 101,3 kPa	Pure: White solid powder Technical: Orange waxy solid	Riggs 1996b Riggs 1991b	Visual assessment Purity: Pure: 99.96 % Purity: Technical: 89.2 %
Melting/freezing point	58.3°C	White & Mullee 2002	EEC A.1, GLP, DSC method Purity: 99.0 %
Boiling point	Decomposes before boiling at 213 °C.	Hogg et al. 1994	EEC A.2, GLP, distillation method; Purity: 96.9%
Relative density	1.34 at 20.5°C	White and Mullee 2002	EEC A.3, GLP, Gas comparison pyknometer Purity: 99%
Vapour pressure	$< 7.9 \times 10^{-6}$ Pa at 25°C	Thomson 1989a	EPA Guidelines Subdivision D, 63-9,GLP gas saturation method Purity: 97.43 %
Surface tension	69.3 mN/m at 21ºC, 1.73 mg/l aqueous solution	Tremain 2002a	EEC A.5 Ring method; GLP Purity: 95.8%
Water solubility	3.15 mg/l at 25 °C, pH 4.37 3.13 mg/l at 25 °C, pH 7.00	Riggs 1989a	Flask method, EPA, GLP Purity: 97.43 %
Partition coefficient n-octanol/water	log Pow = 4.32 at 25°C (Milli-Q™ water)	Archer & Korsch 1989	EPA Guideline 63-11 Shaking method; GLP Purity: 99.5 %
Flash point	132ºC.	Tremain 2002a	EEC A 9 Closed cup, Setaflash tester, GLP Purity: 95.8%
Flammability	Not flammable.	Tremain 2002a	EEC A 10, Flammability (solids), GLP Purity: 95.8%
Explosive properties	Not explosive.	Tremain 2002a	EEC A 14, GLP Purity: 95.8 %
Self-ignition temperature	Auto-ignition temperature >400°C.	Tremain & Bartlett 1994	EEC A 15, auto-ignition temperature, GLP Purity: 96.9%
Oxidising properties	Not oxidizing. (Expert statement)	Tremain 2002b	EEC A 17
Granulometry	Not relevant		
Stability in organic solvents and identity of relevant degradation products	Not relevant		
Dissociation constant	pKa = -1.25 at 25ºC	Thomson 1989b	OECD 112, Spectrophotometric method, GLP; Purity: 97.7 %

Viscosity	Not relevant	-	-

2 MANUFACTURE AND USES

2.1 Manufacture

The active substance is manufactured outside of the EU.

2.2 Identified uses

Quizalofop-P-tefuryl is used in the EU to control a range of annual and perennial grass weeds in a range of broad-leaved field crops.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Table 10: Summary table for relevant physico-chemical studies

Method	Results	Remarks	Reference
Not applicable			

3.1 Physico Chemical Properties

3.1.1 Summary and discussion of physical-chemical properties

The physical-chemical properties are summarised in Table 9 above.

Quizalofop-P-tefuryl (pure) is a white solid powder with no detectable odour, low water solubility and rapid degradation under alkaline conditions. Its vapour pressure is very low and it has a log Pow of >4 (4.32 at 25°C) which is likely to affect its behaviour in the environment, specifically its potential to bioaccumulate. On heating quizalofop-P-tefuryl decomposes before boiling at 213°C.

It is not flammable, the auto-ignition temperature is greater than 400°C and the flash point is 132°C. Quizalofop-P-tefuryl is not flammable, explosive or oxidising.

3.1.2 Comparison with criteria

As detailed in Table 9, quizalofop-P-tefuryl does not meet the criteria for classification for physico-chemical properties.

3.1.3 Conclusions on classification and labelling

No classification

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

The following text is extracted from the DAR (EVIRA, 2007) and EFSA (2008) conclusion documents.

Toxicokinetics (absorption, distribution, excretion and metabolism) of quizalofop-P-tefuryl in rats was studied in four oral studies (Doolittle, 1991a&b; Gay *et al*., 1992; Bates, 1995). In all studies, quizalofop-P-tefuryl was uniformly radiolabelled with ^{14}C in the phenyl group of the quinoxaline ring. In the first study (Doolittle, 1991a; DAR B.6.1.2), excretion and residues of radioactivity following administration of a single low and a single high dose level of quizalofop-P-tefuryl were studied. The second study (Doolittle, 1991b; DAR B.6.1.1) was a repeated low dose study with excretion and residue analysis. In addition, a high dose level was administered to collect samples for metabolite characterization. In the third study (Gay *et al*., 1992; DAR B.6.1.3), metabolites were identified from samples collected in the previous studies. In the fourth study (Bates, 1995; DAR B.6.1.4), residue levels were measured after a high dose level to confirm the results after the first study. The results of all studies are essentially in line with each other. Based on the results of these studies, oral absorption, distribution, residues, elimination, and metabolism of quizalofop-P-tefuryl show a relatively rapid partial absorption, distribution and elimination mainly in faeces.

Absorption

Based on the distribution and excretion of the radioactivity, absorption was relatively rapid. Following a single oral dose, radioactivity was present in the urine within four hours after dosing. Absorption was higher in animals that were not fasting prior to treatment. Based on the amount of radioactivity excreted in the urine, the amount excreted 24 hours after dosing in the faeces and residue levels in the tissue, the minimum amount of absorption was estimated to be between 57-80% of the administered dose in the first experiment (after a single dose, with fasting) and 75% in another experiment (after repeated dose, very short fasting periods). Based on the results of the third experiment (after a single high dose, without fasting) and using the same principles in evaluation, the amount of absorption allows estimation of about 87%.

Distribution and radioactive residues in tissues and their derivates

The radioactivity was relatively rapidly distributed after single and multiple doses. The total residue levels were <3% of the administered dose in females and <9% of the administered dose in males eight days after dosing. Tissue residues were higher in males than in females. The highest tissue residues were found in fat, whole blood, kidneys and liver in males, and in fat, ovary, whole blood and kidneys in females. Distribution was similar after multiple doses of 50 mg/kg/day; the highest levels were in whole blood, fat, liver and kidney. The total mean residues in the tissues seven days after dosing accounted for 1.7 and 4.8% of the administered repeated low dose in females and males, respectively. Residue levels in tissues of rats dosed once with 700 mg/kg were much higher. The total mean residues in the tissues and carcass accounted for 6.7 and 51.8% of the administered dose in females and males. The very high dose levels in males were considered to have arisen due to toxic response and subsequent early death in these animals.

Excretion

Elimination of radioactivity was relatively rapid with total elimination half-lives less than 24 hours in females and slightly longer than 24 hours in males. A negligible quantity of radioactivity was eliminated as carbon dioxide indicating that pulmonary route of elimination is not important. Although the overall elimination of the total dose was similar in both sexes, there is a sex difference in the route of excretion, with females excreting more in the urine and males excreting more in the faeces. Over 90% of the radioactivity was eliminated in females within 96 hours and in males within 144 hours. 83-94% of the administered radioactivity was eliminated within 96 hours after a single or repeated low dose administration.

After a single dose, over 68% of radioactivity was eliminated within 48 hours; 61 and 53% of dose was found in faeces and 7 and 29% in urine in males and females, respectively. Males excreted in urine less than 2/3 of the amount of radioactivity that was excreted by females. After a single low dose administration, males excreted only 1/3 of the amount of radioactivity that was excreted by females. In line with this, the

amount of radioactivity found in faeces was higher in males than in females. After repeated administration, excretion in urine increased significantly in both males and females (from 12.3% to 26.6% in males at 168 hours, and from 36.0% to 53.5% in females at 168 hours).

The total excretion in urine and faeces at 168 hours was similar after a single dose or repeated dose administration. The rate of elimination was only slightly less than after a single dose within 48 hours, but the urinary excretion was significantly higher after repeated dose compared with a single dose. At 48 hours, total elimination in males was 68% after a single low dose and 62% after repeated low dose administration. In females, the respective values were 82% and 85%. After multiple doses, 37-44% of dose was found in faeces and 19-47% in urine within 48 hours. The administration of higher dose increased the excretion of the radioactivity in urine in males during the 7-day collection period but decreased the excretion of the radioactivity in urine in females during the first two days. The cumulative excretion of radioactivity into urine after a high dose administration reached the plateau at about 144 hours in females and at 168 hours in males. The cumulative urinary excretion was 20-41% in males and 35-48% in females during 168 hours after a high dose administration. The majority of the high dose (over 80%) was eliminated within six days in females and within eight days in males.

Metabolism

The major initial route of metabolism/degradation is via hydrolysis of the ester linkage. The metabolism of quizalofop-P-tefuryl is rapid and extensive in rats. The main metabolic pathway in rats is hydrolysis to quizalofop-acid (2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionic acid; QUIZ) and tetrahydrofurfuryl alcohol (THFA) in the stomach or gastrointestinal tract. The relevance of both these metabolites to the toxicological profile of quizalofop-P-tefuryl is further discussed in Annex II of this report.

QUIZ, the acid form of quizalofop-P-tefuryl, can either be hydroxylated giving rise to 2-[4-(3-hydroxy-6-chloroquinoxalin-2-yloxy)phenoxy]propionic acid (QUIZ-OH), which can be further hydrolysed to 4-(3-hydroxy-6-chloroquinoxalin-2-yloxy)phenol (CHQOP) and CHHQ or hydrolysed directly or sequentially to 4-(6-chloroquinoxalin-2-yloxy)phenol (CQOP) and 6-chloro-2-hydroxyquinoxaline (CHQ). CQOP and CHQ can in turn be hydroxylated to CHQOP and CHHQ, respectively. A possible metabolite arising from the formation of CHQ by ether cleavage of QUIZ is 2-(4-hydroxyphenoxy)propionic acid (PPA).

There was a clear sex difference in the metabolic profile in the urine. The major metabolite in the urine excreted by female was QUIZ, accounting for up to 44.7% of the administered dose (26.2-44.7%). In male rats, the proportion of QUIZ in the urine was much lower (6.7-14.4% of the administered dose). Females also excreted higher levels of CHQ in their urine than males after a single dose. Following a high dose, a relatively lower level of CHQ was excreted by animals than after a low dose level. The major metabolite excreted in the urine by males was QUIZ-OH after a dose of 500 mg/kg, accounting for 8.66% of the administered dose. No individual polar or unidentified metabolite accounted for more than 5.5% of the administered dose. No conjugated metabolites were observed in rat urine. In contrast to the metabolic profile in urine, there was no clear sex difference in the faecal metabolite profile. After a single dose, 10-15% of the administered dose was eliminated unchanged in the faeces. However, no unchanged parent material was eliminated in the faeces of rats receiving multiple doses. The major metabolite in the faeces of both sexes was QUIZ accounting for 23.2-41.7% of the administered dose. CQOP was verified as a metabolite only in the faeces of males receiving multiple doses. QUIZ-OH was present in all samples examined after administration of a single dose. The level of QUIZ-OH in faeces was higher in males than in females (10.6-12.3% vs. 2.29-2.30% of administered dose) after a single dose, but not after a repeated dose. More than 63% of the administered dose was identified. No single unknown metabolite or unextractable residue exceeded 8.3% of dose.

4.1.2 Human information

[14C]-Quizalofop-P-tefuryl was applied topically to human skin *in vitro* at two concentrations (Roper & Stupart, 2005); the undiluted commercial formulation (40 g/L) and an in-use spray dilution (0.5 g/L). The dermal delivery of the undiluted formulation and in-use spray dilution for human skin were 12.19% (49.19 µg equiv./cm^2) and 25.09% (1.31 µg equiv./cm^2), respectively.

4.1.3 Summary and discussion on toxicokinetics

Based on the results of toxicokinetics studies, quizalofop-P-tefuryl shows a relatively rapid absorption, distribution and elimination mainly in faeces. Following a single oral dose, radioactivity was present in the urine within four hours after dosing. Based on the amount of radioactivity excreted in the urine, faeces and residue levels in the tissue, the absorption was estimated to be between 57 – 87% of the administered dose. Although it could be considered that quizalofop-P-tefuryl is almost completely absorbed after oral administration, since no bile cannulated studies are available, it has been agreed to use the low dose figure of 60% (rounded up from 58%) for oral absorption. Quizalofop-P-tefuryl is rapidly distributed after single and multiple doses, with the highest tissue residues in fat, ovary, whole blood, kidneys and liver. No accumulation is observed. About 68 and 82% of the radioactivity is eliminated in males and females, respectively, within 48 hours. Quizalofop-P-tefuryl is extensively metabolised: the major route of metabolism is hydrolysis of the ester linkage to form quizalofop acid and tetrahydrofurfuryl alcohol (THFA) (also see Annex II). Further metabolism occurs via hydroxylation and cleavage of the ether linkage yielding 6-chloro-2-hydroxyquinoxaline (CHQ) and the corresponding phenol (2-(4-hydroxyphenoxy)propionic acid (PPA). After a single dose, 10 – 15% of the administered dose was eliminated unchanged in the faeces.

4.2 Acute toxicity

Table 11: Summary table of relevant acute toxicity studies

Method	LD(C)50	Remarks	Reference
rat (Crl:CD®BR) male/female 5/sex/dose oral: gavage (vehicle 1% Methocel) Test material purity: 88.95% doses: 888, 1154, 1500 mg/kg EPA OPP 81-1 (Acute Oral Toxicity) TSCA Health Effects Test Guidelines, 40 CFR, Section 798.1175 Klimisch 1 (GLP, reliable without restriction)	LD50: > 888 — < 1154 mg/kg bw (male) based on: test mat. LD50: 1010 mg/kg bw (female) based on: test mat. LD50: 1012 mg/kg bw (male/female) based on: test mat.	1500 mg/kg: Mortality 5/5 males, 5/5 females. Clinical signs included hypoactivity (10/10), lachrymation (7/10), clear wet staining around mouth (2/10), wet yellow staining around mouth (4/10), dry red material around mouth (3/10), dry red material around nose (3/10), typical agonal changes seen at necropsy 1154 mg/kg: Mortality 5/5 males, 4/5 females. Clinical signs included hypoactivity (10/10), lachrymation (7/10), clear wet staining around mouth (2/10), wet yellow staining around mouth (1/10), dry red material around mouth (1/10), dry red material around nose (1/10), typical agonal changes seen at necropsy 888 mg/kg: Mortality 0/5 males, 1/5 females. Clinical signs included hypoactivity (10/10), lachrymation (2/10), clear wet staining around mouth (1/10), wet yellow staining around mouth (1/10), dry red material around mouth (3/10), dry red material around nose (3/10). No compound-related	Naas (1991) (DAR B.6.2.1.1)

Method	LD(C)50	Remarks	Reference
		changes observed at terminal necropsy.	
rabbit (New Zealand White) male/female 5/sex/dose Single dose: 2000 mg/kg Test material purity: 93.24% Coverage: semiocclusive FIFRA Guidelines, 40 CFR, Part 158, 1982 Klimisch 1 (GLP, reliable without restriction)	LD50: > 2000 mg/kg bw (male/female) based on: test mat. (no effects)	Following a single 2000 mg/kg bw 24-hour application to the skin of adult male and female New Zealand White rabbits was assessed. None of the animals died. No evidence of toxicity was observed. C4874 technical was defined as non-toxic. LD50 greater than 2000 mg/kg.	Lilja (1988) (DAR B.6.2.2.1)
rat (Sprague-Dawley) male/female 5/sex/dose liquid aerosol (nose only) Test material: Pantera 60% TK Technical (purity 60.7%) 1.4, 4.7, 21, 22 mg/L (nominal concentration) 0.53, 1.6, 4.6, 6.5 mg/L (analytical concentration) EPA OPP 81-3 (Acute inhalation toxicity) Klimisch 1 (GLP, reliable without restriction)	LC50 (4 h): >6.5 mg/L air (analytical) (male/female) based on: test mat. (no mortality) (Corresponding to 3.9 mg/L Quizalofop-p-terfuryl)	No mortality. No clinical signs during exposure. Respiratory (rales and laboured breathing) and secretory (nasal discharge and excess lacrimation) responses and slight body weight loss during first week after exposure with recovery thereafter. Necropsy findings unremarkable.	Hoffman (1993) (DAR B.6.2.3.1)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Quizalofop-P-tefuryl had a moderate acute oral toxicity to rats with an LD50 of 1012 mg/kg (Naas, 1991).

4.2.1.2 Acute toxicity: inhalation

The four-hour LC50 of Pantera 60% TK Technical (Hoffman, 1993) was greater than 6.5 mg/L via nose-only exposure (corresponding to 3.9 mg/L for quizalofop-P-tefuryl). It was not stated whether higher concentrations could have been attained, but because the respirable fraction was less at higher concentrations than at lower concentrations the highest concentration used in this study was considered acceptable.

4.2.1.3 Acute toxicity: dermal

Quizalofop-P-tefuryl had a low (LD50 >2000 mg/kg) acute dermal toxicity to rabbits (Lilja, 1988).

4.2.1.4 Acute toxicity: other routes

No information

4.2.2 Human information

No information

4.2.3 Summary and discussion of acute toxicity

Quizalofop-P-tefuryl had a moderate acute oral toxicity to rats with an LD50 of 1012 mg/kg and low acute dermal toxicity to rabbits. The four-hour LC50 via inhalation of quizalofop-P-tefuryl to rats was >3.9 mg/L.

4.2.4 Comparison with criteria

With an oral LD50 of 1012 mg/kg bw, quizalofop-P-tefuryl warrants classification as Acute Tox. 4; H302 according to the CLP Regulation.

It has low dermal and inhalation toxicity (LD50 >2000 mg/kg bw and LC50 >3.9 mg/L, respectively) and therefore does not warrant classification.

4.2.5 Conclusions on classification and labelling

Acute Tox. 4; H302

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

All clinical signs observed in the acute toxicity studies via the oral, dermal and inhalation routes (see Table 11) were considered to be non-specific signs of general acute toxicity.

4.3.2 Comparison with criteria

Substances that have produced significant non-lethal toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant non-lethal toxicity in humans following single exposure, are classified as STOT-SE 1 or 2. Classification is supported by evidence associating single exposure to the substance with a constant and identifiable effect.

Classification in STOT-SE 3 is reserved for transient target organ effects and is limited to substances that have narcotic effects or cause respiratory tract infection.

The signs that were apparent after single oral exposure (no adverse effects were observed after dermal and inhalation exposure) to quizalofop-P-tefuryl were indicative of nonspecific, general acute toxicity. As there was no clear evidence of specific target effects on a target organ or tissue that were independent of mortalities, and no definitive signs of respiratory tract irritation or narcotic effects, no classification for specific target organ toxicity (single exposure) is required.

4.3.3 Conclusions on classification and labelling

No classification

4.4 Irritation

Irritation data are provided as supportive information only.

4.4.1 Skin irritation

Table 12: Summary table of relevant skin irritation studies

Method	Results	Reference
Rabbit (New Zealand White) Male/Female 3/sex/dose (total 6) 500 mg technical quizalofop-P-tefuryl Purity: 93.24% Vehicle: none OECD 404, GLP	Mean Scores over 24-72 hours for six rabbits: Erythema: 0-0-0-0-0-0 (mean: 0) Oedema: 0-0-0-0-0-0 (mean: 0)	Lilja, 1988b (DAR B.6.2.4.1)

4.4.1.1 Non-human information

See Table 12.

4.4.1.2 Human information

No information

4.4.1.3 Summary and discussion of skin irritation

No signs of dermal irritation were observed in any rabbit during the study period. There were no deaths or overt signs of toxicity during the study. Quizalofop-P-tefuryl did not irritate the skin of rabbits.

4.4.1.4 Comparison with criteria

No signs of erythema or oedema were observed, therefore, quizalofop-P-tefuryl does not meet the criteria for classification.

4.4.1.5 Conclusions on classification and labelling

No classification

4.4.2 Eye irritation

Table 13: Summary table of relevant eye irritation studies

Method	Results	Reference
Rabbit (New Zealand White) Male/Female 3/sex/dose (total 6) 200 mg of a 1:1 w/w solution of technical quizalofop-P-tefuryl in cotton seed oil Purity: 93.24% OECD 405, GLP	Mean scored over 24-72 hours for 6 rabbits: Cornea: 0-0-0-0-0-0 (mean: 0) Iris: 0-0-0-0-0-0 (mean: 0) Conjunctivae – redness: 0-0-0-0-0-0.3 (mean: 0.06) Conjunctivae-chemosis: 0-0-0-0-0-0 (mean: 0)	Lilja, 1988c (DAR B.6.2.5.1)

4.4.2.1 Non-human information

See Table 13

4.4.2.2 Human information

No information

4.4.2.3 Summary and discussion of eye irritation

Slight conjunctival redness (score: 0.3; 24-72 hours) was observed in one rabbit, however, all other rabbits showed no signs of irritation.

4.4.2.4 Comparison with criteria

No effects were observed on the cornea or the iris. All average eye irritation scores were <2, therefore, no classification is required.

4.4.2.5 Conclusions on classification and labelling

No classification

4.4.3 Respiratory tract irritation

4.4.3.1 Non-human information

See 4.3 above (STOT-SE).

No repeated dose toxicity studies via the inhalation route have been conducted.

4.4.3.2 Human information

No information.

4.4.3.3 Summary and discussion of respiratory tract irritation

Quizalofop-P-tefuryl is not a respiratory irritant.

4.4.3.4 Comparison with criteria

Quizalofop-P-tefuryl is not a respiratory irritant therefore, no classification is warranted.

4.4.3.5 Conclusions on classification and labelling

No classification

4.5 Corrosivity

Table 14: Summary table of relevant corrosivity studies

Method	Results	Remarks	Reference
Not relevant			

4.5.1 Non-human information

No signs of corrosion were observed in the available irritation studies conducted with quizalofop-P-tefuryl (see section 4.4 above).

4.5.2 Human information

No information.

4.5.3 Summary and discussion of corrosivity

No signs of corrosion were observed in the available irritation studies, therefore, quizalofop-P-tefuryl is not considered to be corrosive.

4.5.4 Comparison with criteria

Quizalofop-P-tefuryl was not corrosive in the available irritation studies and does not have a pH of ≤2 or ≥11.5. Therefore, quizalofop-P-tefuryl is not considered to meet the criteria for classification.

4.5.5 Conclusions on classification and labelling

No classification

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 15: Summary table of relevant skin sensitisation studies

Species	Method	Doses	Number of animals responding	Result
Guinea Pig (Dunkin Hartley) 20 females/test group 10 females/ control group	OECD 406 GPMT GLP (Denton 1998)	Induction Intradermal: 20% Topical: 20% Challenges 1st: 25% and 50% in Alembicol D 2nd: 20% in Alembicol D Purity: 95.6% Occlusive exposure	**1st Challenge** 0%*: 13/20 and 5/20 at 24 and 48 hours 25%: 13/20 and 10/20 at 24 and 48 hours 50%: 15/20 and 12/20 at 24 and 48 hours Negative Control 0%* :1/10 and 0/10 at 24 and 48 hours 25%: 1/10 and 0/10 at 24 and 48 hours. 50%: 1/10 and 0/10 at 24 and 48 hours **2nd Challenge** 0%*: 12/20 and 1/20 at 24 and 48 hours 20%: 14/20 and 13/20 at 24 and 48 hours Negative Control (note naïve controls were not used). 0%*: 5/10 and 1/10 at 24 and 48 hours 20%: 9/10 and 6/10 at 24 and 48 hours	Positive
Guinea Pig 10/sex/test group 2/sex/control group	FIFRA and OECD (with some deviations) guideline Buehler GLP (Lilja 1989)	Induction 100% Challenge 100% Purity: 93.24%	Test 100%: 0/20 and 0/20 at 24 and 48 hours Negative Control 0/4 and 0/4 at 24 and 48 hours	Negative

* 0% relates to vehicle alone i.e., Alembicol D

4.6.1.1 Non-human information

Two sensitisation studies are available. Quizalofop-P-tefuryl was considered to have sensitising properties in a Maximisation test (Denton, 1998; DAR B.6.2.6.2), but not in a Buehler test (Lilja 1989; DAR B.6.2.6.1).

In relation to the Maximisation test (Denton, 1998), it was concluded in the study report that the responses for five animals were equivocal, but no animals gave a clearly positive sensitisation response following two challenge applications. The authors considered the responses after challenge and re-challenge indicate positive responses, but not in 30% of animals (6/20) (criteria for classification).

The dermal reactions observed after challenge and re-challenge are detailed in Tables 16 and 17 below, and are summarised in Table 18.

Table 16: Dermal reactions observed after challenge and re-challenge– test animals.

Animal	Score											
	Challenge						Re-challenge					
	AA		P		C		A		C		Results	
	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	R	RR
1	0	0	1	0	0	0	0	0	0	0	-	neg
2	0	0	0	0	1	0	0	0	1Q	0	-	neg
3	1	0	0	0	1	0	1	0Q	0	0	-	neg
4	1	1Q	0	0	0	0	0	0	1	0	-	neg
5	0	1Q	0	1Q	2Q	1Q	2Q	2Qs	1	0		neg
6	1	0	1	0	1	0	3Q	1Q	1	0	-	neg
7	1	0	1	0	1	0	0Q	1	1	1	-	neg
8	1	1	1	0	2	1	3	1	1	0	-	neg
9	1	1Q	0	0	1	0Q	3	2s	1	0	±	Pos?
10	1	1	1	1	1	0	3	2s	1	0	±	POS
11	1	1	1	1	2	0	0	0Q	0	0	-	neg
12	2	1	1	2	2	0	3Q	2s	1	0	±	POS
13	1	0	1	1	0	0	2Q	1	0	0	-	POS
14	0	0	0	0	1	0	2	1Qs	1	0	-	neg
15	1Q	2Q	1	1	0	1Q	3s	2s	1	0	±	POS
16[a]	0	0	0	0	0	0	0	0	0	0	-	(neg)
17	1	1	1	1	2	2	2Q	2Q	1	0	-	neg
18	1	1Q	1	1Q	0	0	2	1Qs	0	0	-	POS
19	1	1	1	2	0	0	1Q	0	0	0	-	POS
20	1	1Q	1	1Q	2	1Q	1	2s	0	0	±	neg

AA = Anterior site exposed to technical quizalofop-P-tefuryl, 50% m/m in Alembicol D
A = Anterior site exposed to technical quizalofop-P-tefuryl, 20% m/m in Alembicol D
P = Posterior site exposed to technical quizalofop-P-tefuryl, 25% m/m in Alembicol D
C = Control site exposed to Alembicol D
0 = No erythema, 1 = Slight erythema, 2 = Well defined erythema, 3 = Moderate erythema
Q = Desquamation, S = Scabbing
R = Data in the study report, RR = evaluation by RMS in DAR
a The dressing applied to this animal was found removed at the beginning of Day 30.

Table 17: Dermal reactions observed after challenge and re-challenge– control animals.

Animal	Score											
	Challenge						Re-challenge					
	AA		P		C		A		C		Results	
	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	R	RR
C1	0	0	0	0	0	0	1Q	0	1	0	-	neg
C2	0	0	0	0	1Q	0Q	3	2S	1Q	0	-	pos
C3	0	0	0	0	0	0	3cb	0s	0	0	-	pos?
C4	0	0	0	0	0	0	2Q	2Q	0	0	-	pos

Animal	Score											
	Challenge						Re-challenge					
	AA		P		C		A		C		Results	
	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	24 h	48 h	R	RR
C5	0	0	1	0	0	0Q	1Q	2Q	1	0		pos?
C6	1	0	0	0	0	0	1	0	1	0	-	neg
C7	0	0	0	0	0	0Q	1	1Q	0	1Q	-	neg
C8	0	0	0	0	0	0	2Q	1s	0	0	-	pos
C9	0	0	0	0	0	0	2Q	1s	1s	0s	-	pos
C10	0	0	0	0	0	0	0	0	0	0	-	neg

AA = Anterior site exposed to technical quizalofop-P-tefuryl, 50% m/m in Alembicol D
A = Anterior site exposed to technical quizalofop-P-tefuryl, 20% m/m in Alembicol D
P = Posterior site exposed to technical quizalofop-P-tefuryl, 25% m/m in Alembicol D
C = Control site exposed to Alembicol D
0 = No erythema, 1 = Slight erythema, 2 = Well defined erythema, 3 = Moderate erythema
Q = Desquamation, S = Scabbing, cb = chemical burn
R = Data in the study report, RR = evaluation by RMS in DAR

Table 18: Summary of dermal reactions observed after challenge and re-challenge– control animals

Challenge – Number of positive reactions	**24 hours Test**	**48 hours Test**	**24 hours Control**	**48 hours Control**
50% m/m in Alembicol D	15/20	12/20	1/10	0/10
25% m/m in Alembicol D	13/20	10/20	1/10	0/10
Alembicol D Vehicle alone	13/20	5/20	1/10	0/10
Re-challenge – Number of positive reactions 20% m/m in Alembicol D	14/20	13/20	9/10a	6/10a
Alembicol D Vehicle alone	12/20	1/20	5/10a	1/10a

a The study did not used naive controls at re-challenge

The re-challenge procedure did not use naive controls. The EFSA review considered the procedure of evaluation of the results from re-challenge invalid since several control animals showed a positive reaction to quizalofop-P-tefuryl application. As this was a re-challenge, it was a second application of quizalofop-P-tefuryl in vehicle for the control animals and therefore sensitisation is possible.

The data from the first challenge indicates quizalofop-P-tefuryl in Alembicol D has sensitisation potential (Table 18). However, interpretation is compromised by the skin reactions to the vehicle alone in the test animal group. Overall the number of animals responding to quizalofop-P-tefuryl in vehicle is not dissimilar to vehicle alone, although the persistence at 48 hours with vehicle alone is less. This makes the data difficult to interpret with respect to classification criteria.

However, the DAR (EVIRA, 2007) considered the study to be acceptable and valid for assessing the responses after the first challenge on the basis that after the first challenge, control animals did not show

remarkable erythema. Based on the initial challenge they considered there were 7 animals with overall positive reactions out of 20 (Table 16). Furthermore, were the re-challenge data to be taken into account to confirm the positive reactions, the DAR considered there were at least 6 animals with positive reactions after both challenges and that the re-challenge may be considered confirmatory to the sensitising properties of quizalofop-P-tefuryl.

4.6.1.2 Human information

No information. No reports of sensitisation.

4.6.1.3 Summary and discussion of skin sensitisation

Quizalofop-P-tefuryl had sensitising properties in a Maximisation test, but not in a Buehler test.

4.6.1.4 Comparison with criteria

In the Maximisation study, 7/20 animals gave a positive reaction at the first challenge (Table16). If the results of the second challenge are used to confirm the positive reactions after the first challenge, at least 6 test animals with positive reaction after both challenges are found. This scale of positive reaction justifies classification for sensitising potential. Given that this response was relatively weak, and that the intra-dermal induction dose was high (20%), classification as Skin Sens. 1B; H317 is proposed.

This classification differs from the current Annex VI classification. This is due to the fact that the Maximisation study (Denton, 1998) was not reviewed in the context of the classification decision included in the 28th ATP of Dir. 67/548/EEC.

4.6.1.5 Conclusions on classification and labelling

Skin Sens. 1B; H317

4.6.2 Respiratory sensitisation

4.6.2.1 Non-human information

There is no evidence that quizalofop-P-tefuryl is a respiratory sensitiser. In relation to any assessment of respiratory sensitisation from repeat dose studies, there are no relevant data.

4.6.2.2 Human information

No information

4.6.2.3 Summary and discussion of respiratory sensitisation

There is no evidence that quizalofop-P-tefuryl is a respiratory sensitiser.

4.6.2.4 Comparison with criteria

There is no evidence that quizalofop-P-tefuryl is a respiratory sensitiser and therefore no classification is warranted.

4.6.2.5 Conclusions on classification and labelling

No classification

4.7 Repeated dose toxicity

Table 19: Summary table of relevant repeated dose toxicity studies

Method	Results (effects of major toxicological significance)	Reference
Studies in Rats		
Rat (Charles River CD) male/female 28 day study 10/sex/dose Subchronic (oral: feed) Test material purity: not reported 0, 250, 500, 1000, 5000 ppm (nominal in diet) 0/0, 19.7/21.6, 40.3/43.9, 79.2/84.2, 319.9/361.1 mg/kg bw/day (males/females) (actual ingested) Exposure: 28 days (Continuous administration in the diet) following guideline EPA OPP 82-1 Essentially compliant with OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) GLP	<u>5000 ppm (319.9/361.1 mg/kg bw/day)</u>: *Body weight*: ↓28-38% (males), 18-24% (females) *Food consumption*: ↓ 33-70% (males), 23-48% (females). *Organ weights*: Kidney ↓ 28% (males), 19% (females) actual, no effect on adjusted. Liver ↑ 21% (females only) actual; ↑ 54% (males), 56% (females) adjusted to body weight. Testis ↓ 23.1% actual, ↑ 23.0% adjusted to body weight. <u>1000 ppm (79.2/84.2 mg/kg be/day)</u> *Organ weights*: Liver ↑51% (males), 36% (females) actual and 57% (males), 33% (females) adjusted to body weight. <u>500 ppm (40.3/43.9 mg/kg bw/day)</u> *Organ weights*: Liver ↑ 31% (males), 17% (females) actual and 19% (males only) adjusted to body weight. NOEL was 250 ppm in both sexes based on increased liver weight at 500 ppm (approximately 40.3 and 43.9 mg/kg/day for males and females respectively).	Goldenthal (1989) (DAR B.6.3.1.1)
Rat (Charles River CD VAF/Plus) male/female 90-day study 13/sex/dose Subchronic (oral: feed) Test material purity: 94.7% 0, 25, 500, 2500 ppm (nominal in diet) 0, 1.69, 33.4, 134 mg/kg bw/day (males) and 0, 2.0, 41.6 and 145 mg/kg bw/day (females) (actual ingested)	<u>2500 ppm (134/145 mg/kg bw/day)</u> *Body weight*: ↓ 31.3% (males), 20.3% (females). *Food consumption*: ↓ 28.7% (males), 28.2% (females). *Food efficiency*: Generally ↑ in males and ↓ in females. *Haematology*: ↓erythrocyte 12%, haemoglobin 11% and haematocrit 13% values in males. ↑ platelet counts 19% and MCHC index 3% in males. ↓ haemoglobin 8% and haematocrit values 6% in females. *Clinical chemistry*: ↑ALP (139%, 98%), AST (104%, 29%), ALT (45%, 53%), urea nitrogen (46%, 41%) and albumin (16%, 14%); ↓Globulin (39%, 18%) (males, females). ↓Calcium 7% and total protein 11% in males. ↑Glucose 5% in females. *Organ weights*: ↑Liver (30%, 47% actual and 93%, 81% adjusted for body weight in males, females). ↓Testes (50% actual, 24% adjusted for body weight) *Gross pathology*: Soft testes seen in 2/10 males and accentuated	Goldenthal (1990) (DAR 6.3.2.1)

Method	Results (effects of major toxicological significance)	Reference
Exposure: 90 days (Continuous administration in the diet) EPA OPP 82-1 (90-Day Oral Toxicity) GLP	lobulation of the liver seen in 5/10 males. *Histopathology*: Treatment-related findings were seen in the adrenal cortex, liver and testis and secondary effects were seen in the epididymis and pituitary. Testicular degeneration characterized by tubular atrophy, loss of normal maturation pattern of spermatocytes, formation of dystrophic syncytical cells, aspermatogenesis and hypospermatogenesis was seen in all animals (10/10 males) and corresponded with the macroscopic observation of soft testes and also to the reduced testes weights. Changes seen secondary to testicular degeneration were accumulation of intralumenal cellular debris in the epididymis and increased numbers of "castration cells" in the anterior pituitary. Vacuolar change was also seen in the zona glomerulosa of the adrenal cortex of both sexes but was more prominent in males (9/10 males and 4/10 females). Hepatocellular hypertrophy was seen in all animals (10/10 males and 10/10 females), which correspond to the macroscopic observation of accentuated lobular pattern and to increased liver weights. The testicular effects, and in particular the presence of "castration cells" (LH/FSH secreting cells) in the pituitary, are consistent with decreased circulating testosterone following increased aromatase conversion of testosterone to oestrogen following hepatic induction of the enzyme via PPARα activation. <u>500 ppm (33.4/41.6 mg/kg bw/day)</u> *Haematology*: ↓ haematocrit 7%, ↑ platelet count 20% and MCHC 3% in males. *Clinical chemistry*: ↑ albumin 23% /9% (males/ females). ↑ALP 57%, ↓ globulin 13% in males. *Organ weights*: ↑Liver weights (47%, 34% actual and 47%, 33% adjusted for body weight in males, females). *Gross pathology*: Accentuated lobulation of the liver seen in one male. The NOAEL was 25 ppm (corresponding to 1.7 mg/kg bw/day in males and 2 mg/kg bw/day in females), based on haematological and clinical chemistry findings and increased liver weight at 500 ppm.	
Studies in Mice		
28-day study mouse (CD-1) male/female 5/sex/dose subacute (oral: feed) Test material purity: 91.18% 0, 250, 1000, 2500 or 5000 ppm (nominal in diet) corresponding to 0, 48-56, 164-209 and 285-452 mg/kg bw/day for males and	<u>5000 ppm:</u> 100% mortality by day 7. Pathological findings; hepatocellular hypertrophy and necrosis (all animals), myocardial degeneration (3 males and 3 females), adrenal cortical hypertrophy (all males and 3 females), lymphoid cell depletion and atrophy of the spleen (2 males and 1 female), necrosis of the germinal epithelium of the testes (all 5 males). <u>2500 ppm: (285-452/213-472 mg/kg bw/day) (</u> 100% mortality by day 28. ↓ body weight. ↓ food consumption. Pathological findings; hepatocellular hypertrophy and necrosis (all animals), myocardial degeneration (all animals), adrenal cortical hypertrophy (all animals) and lymphoid cell depletion and atrophy of the spleen (2 males).	Mitchell (1991a) (DAR B.6.3.1.2)

Method	Results (effects of major toxicological significance)	Reference
0, 54-75, 254-280 and 213-472 mg/kg bw/day for females Exposure: 4 weeks (Continuous administration in the diet) OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) GLP	<u>1000 ppm: (164-209/254-280 mg/kg bw/day)</u> ↑ 13%/8% body weight (males/females). ↑ 664%/433% SGPT and 30%/19% albumin (males/females). ↑ 192% /220% liver, 73%/62% adrenal weights (absolute/ relative to body weight) in males; 49%/48% liver, 12%/12% kidney weights (absolute/ relative to body weight) in females. Hepatocellular hypertrophy and necrosis (all animals). <u>250 ppm: (48-56/54-75 mg/kg bw/day)</u> ↑ 4% body weight (females). ↑ organ weights in females 49%/48% liver, 12%/12% kidney (actual/relative to body weight)). Hepatocellular hypertrophy and necrosis (5 males and 2 females). No NO(A)EL achieved.	
95-96 day study Mouse (CD-1) male/female 10/sex/dose Subchronic (oral: feed) Test material purity: 89.8% 0, 50, 125 or 250 ppm (nominal in diet) corresponding to 0, 7-11, 18- 28 and 36-58 mg/kg bw/day for males and 0, 9-16, 22-40 and 43-79 mg/kg bw/day for females Exposure: 95 or 96 days (Continuous administration in the diet) EPA OPP 82-1 (90-Day Oral Toxicity) GLP	<u>250 ppm: (36-58/43-79 mg/kg bw/day)</u> *Body weights*: ↑ 18% in males at all time points. *Clinical chemistry*: ↑ 52% alkaline phosphatase, 43% glucose and 11% albumin in males. ↑ 31% BUN and 29% glucose in females. *Kidney weight:* ↑ 15%/12% (absolute/relative to body weight) in females. *Liver effects*: ↑ approx 2 fold liver weight (absolute and relative to body weight) in both sexes. Liver enlargement (5 males, 1 female) and discolouration (4 males). Hepatocellular hypertrophy (10 male, 7 female), necrosis (4 males and 2 females) and vesiculation and/or vacuolation (2 males and 3 females). <u>125 ppm: (18-28/22-40 mg/kg bw/day)</u> *Body weights*: ↑ 10% in males at most time points. *Clinical chemistry*: ↑ 27% glucose and 3% albumin in males. ↑ 18% glucose in females. *Kidney weight:* ↑ 18%/14% (absolute/relative to body weight) in females. *Liver effects*: ↑ 40%/33% (absolute) and 37%/29% (relative to body weight) liver weight in males/females. Liver enlargement (1 male and 1 female) and discolouration (1 female). Hepatocellular hypertrophy (9 males and 5 females) and vesiculation and/or vacuolation (2 males). <u>50 ppm: (7-11/9-16 mg/kg bw/day)</u> No effects of toxicological significance. The NOAEL was 50 ppm (7-11 mg/kg bw/day for males and 9-16 mg/kg bw/day for females).	Mitchell (1991b) (DAR B.6.3.2.2)
Studies in Dogs		
28-day study Dog (Beagle) male/female	<u>5000 ppm</u>: *Mortality*: All males and females killed in extremis on day 19. *Clinical signs*: 3/4 animals had red and swollen lips, other	Crosby Tompkins (1991b) (DAR

Method	Results (effects of major toxicological significance)	Reference
2/sex/dose Subacute (oral: feed) Test material purity: 89.8% 0, 1000, 5000, 10000/2250 (10000 ppm days 0-4, 0 ppm days 4-6, 2250 ppm day 7 and thereafter) (nominal in diet); 1000 ppm equivalent to approximately 40 mg/kg bw/d. Exposure: 28 days (Continuous in the diet) equivalent or similar to EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral)) GLP	findings included white ocular discharge, lachrymation and decreased defecation. *Body weights*: All animals lost weight prior to being killed in extremis in week 2. *Food consumption*: ↓ >50% males and females throughout study, consequently killed in extremis in week 2. *Haematology*: ↓ 24%/17% haemoglobin, 27%/19% haematocrit, 14%/9% MCV, 63%/72% platelets (males/females) and ↑ 44% APTT (males) and 200%/66% absolute and 43%/43% relative numbers of segmented neutrophils (males/females). *Clinical chemistry*: 5-16 fold ↑ ALT and bilirubin (males and females), AST (females). *Organ weights*: ↓ absolute (70% males and 82.3% females) and relative (63.7% males, 76.3% females) thymus weight, considered to be secondary effects of dosing; ↓ 28.1% absolute and 14.0% relative testis weight. *Gross pathology*: Grey streaks, dark red areas and contents of GI tract (males and females) possibly reflective of body weight loss and reduced food consumption. Haemorrhagic thymus glands in males. *Histopathology*: Interstitial lymphoid infiltrate of the kidneys (males and females) <u>10000/2250 ppm</u> Due to excessive toxicity (severely reduced body weights and food consumption) present in all dogs in the 10000 ppm group, the dogs were given control diet only on days 4-6 and 2250 ppm from day 7. *Clinical signs*: White ocular discharge (1 male, 1 female), lachrymation (1 male) and decreased defecation (2 males, 1 female). *Body weights*: Body weight loss (8%/2%) week 0-1 (males/females) before the dose level was lowered. These animals never gained weight at a rate comparable to the control group throughout the remainder of the study and was ↓ 10%/12% at termination (males/females). *Food consumption*: ↓ ~70% (males and females) during first week of the study. (Initial 5 days the dose level was 10000 ppm. Because of inappetence, control diet given for 3 days before the dose level lowered to 2250 ppm. After receiving 2250 ppm food consumption means (g/animal/day) for the females were ↓ ~ 40% for all weeks and for males were ↓ 45% during weeks 3-4. *Haematology*: ↓ 18%/13% haemoglobin, 19%/14% haematocrit, 80%/65% platelets (males/females) and ↑ 63%/33% absolute and 38%/24% relative numbers of segmented neutrophils (males/females). *Clinical chemistry*: ↑ 2-3fold bilirubin (males and females) and one male ↑ 8 fold ALT and 2fold urea nitrogen. *Organ weights*: ↓ ~65% thymus (males and females), considered to be secondary effects of dosing. ↓ 38.5% absolute and 31.6% relative testis weight. *Histopathology*: Interstitial lymphoid infiltrate of the kidneys (males only).	B.6.3.1.3) Crosby Tompkins (1992)

Method	Results (effects of major toxicological significance)	Reference
	1000 ppm: (40 mg/kg bw/day) *Organ weights*: ↓ 46-64% thymus (one male and one female), toxicological significance of this, if any, unknown. Definite signs of systemic toxicity were apparent at dose levels of 2250, 5000 and 10000 ppm. The NOAEL was 1000 ppm (40 mg/kg bw/day). Based on the results of this study dose levels of 50, 900 and 1800 ppm were selected for the definitive 90-day study.	
90-day study Dog (Beagle) male/female 4/sex/dose subchronic (oral: feed) Test material purity: 88.95% 0, 50, 900, 1800 ppm (nominal in diet) 0, 2, 32-40 and 51-64 mg/kg bw/day for males and 0, 2, 27-34 and 68-77 mg/kg bw/day for females (actual ingested) Exposure: 90 days (Continuous administration in the diet) EPA OPP 82-1 (90-Day Oral Toxicity) GLP	1800 ppm: (51-64/68-77 mg/kg bw/day) *Clinical signs and mortality*: One male was killed during week 13. All other animals survived. Clinical signs observed included black faeces, diarrhoea or soft stool with wet red material and lachrymation. *Body weight and weight gain*: Body weight gain ↓ beginning second week of dosing in males and continued throughout the study. Mean body weights ↓ 5-17% in males compared to controls from weeks 5-13 (not statistically significant). *Food consumption*: ↓ ~40% in males from week 3 onwards. *Haematology*: ↓Mean red blood cell (26%/7% males/females week 12), haemoglobin (30%/9% males/females week 12) and haematocrit (27%/6% males/females week 12) in both sexes at weeks 5 and 12 (males more strongly affected). Segmented neutrophils ↑ (27-31%) and lymphocytes ↓ (46-78%) in males at weeks 5 and 12 and lymphocytes reduced (35%) in females at week 12. *Clinical chemistry*: ↑Mean bilirubin (2x), urea nitrogen (61%) and creatinine (29%) at week 5 (males). Calcium ↓ at weeks 5 (6%) and 12 (11%) (males). Total protein ↓ at weeks 5(13% females) and 12 (20% males, 11% females). *Organ weights*: Relative liver weights ↑ 27% in males. Decreased (not statistically significantly) absolute (26%) and relative (20%) testes/epididymides weights. *Gross pathology*: The male dog that was prematurely killed had a duodenal ulcer. One male at week 13 had dark red areas in the caecum. All seven animals at scheduled termination had reddened mesenteric lymph nodes compared to 1, 3 and 3 in the control, 50 and 900 ppm groups (sexes combined). *Histopathology*: non-neoplastic: All males had aspermatogenesis in the testes and aspermia in the epididymides. A review of the testes, epididymis and prostate from all of the dogs in this study, by the original conducting laboratory, has shown that two of the four dogs had normal testes although all four had immature prostate. Males and females had skin lesions (hyperkeratosis, acute inflammation or lymphoid infiltration into the dermis) 900 ppm: (32-40/27-34 mg/kg bw/day) No effects of toxicological significance. The NOAEL was 900 ppm (corresponding to 32-40 (males), 27-34 (females) mg/kg bw/day), based on clinical signs, lower body weight and food consumption, haematology and clinical	Crosby Tompkins (1991a) (DAR B.6.3.2.3) Lambert (2015)

Method	Results (effects of major toxicological significance)	Reference
	chemistry findings, reduced testis/epididymides weight, maturation failure of spermatocytes, liver weight increase and increased incidence of reddened mesenteric lymph nodes at 1800 ppm.	
1 –year study Dog (Beagle) male/female 6/sex/dose chronic (oral: feed) test material purity: 93.8% 0, 50, 750, 1500 ppm (nominal in diet) 0, 2, 24-32 and 41-56 mg/kg bw/day for males and 0, 1-2, 27-36 and 30-58 mg/kg bw/day for females (actual ingested) Exposure: 52 weeks (Continuous administration in the diet) EPA OPP 83-1 (Chronic Toxicity) GLP	<u>1500 ppm: (41-56/30-58 mg/kg bw/day)</u> *Clinical signs and mortality*: Two females killed in extremis. One dog showed liver necrosis and had markedly reduced red blood cell parameters (killed week 43), the other death (week 19) was considered to be due to enteritis of the intestines and not treatment-related. Treatment-related diarrhoea in males. *Body weight and weight gain*: ↓ body weight gain from week 2 onwards (males) (8.5% ↓ than controls by week 7). *Food consumption*: Slightly ↓ throughout the study (males and females). *Haematology*: Mean red blood cell count, haemoglobin and haematocrit ↓ at weeks 12, 25 and 51. Mean MCHC ↓ at week 12 in both sexes and all time points in females. Segmented neutrophils ↑ at weeks 25 and 51 in males and weeks 12 and 51 in females. APTT ↑ in females at weeks 12 and 25, (but lower than the pre-treatment values). *Clinical chemistry*: ↑ ALP and phosphorus at weeks 12, 25 and 51 (males and females), ↓ calcium at weeks 12 (females), 25 and 51 (males and females). (Values within the historical control range). *Organ weights*: ↓ spleen weights (32-36% males, 43-45% females, compared to control), ↓ adrenal weights in both sexes (15-27%), ↑ liver weights relative to final body weight (23%) in males. *Gross pathology*: Pale mucosal surface in intestines, enlarged stomach, multiple red foci on lung lobes, fibrinous exudates in trachea and main stem bronchi and red pancreatic lymph node (dog killed week 19). Yellowing of all mucous membranes and blood vessels, enlarged liver with dark red centrilobular areas, enlarged left ventricle and hepatic lymph node and enlarged left ventricle, yellow fluid in pericardial sac and multiple white foci on endocardium (dog killed week 38). No treatment-related findings at terminal kill. *Histopathology*: Mild centrilobular necrosis in liver, severe necrosis of caecal mucosa, supparative inflammation in trachea, lungs and intestines (female killed week 19). Severe centrilobular necrosis in liver, non-suppurative inflammation of bile ducts with hyperplasia, suppurative inflammation in lungs, fibrous osteodystrophy in femur and splenic extramedullary haematopoiesis (female killed week 43). No treatment-related findings at terminal kill. <u>750 ppm: (24-32/27-36 mg/kg bw/day)</u> No effects of toxicological significance. The NOAEL was 750 ppm (equivalent to 24-32 mg/kg bw/day for males and 27-36 mg/kg bw/day for females) based on morbidity, clinical signs, haematological and clinical chemistry findings, decreased spleen and adrenal weights at 1500 ppm.	Crosby Tompkins (1993) (DAR B.6.3.2.4)

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

Short-term toxicity of quizalofop-P-tefuryl was studied in rats, mice and dogs (Table 19).

Rats

In both a 28-day (Goldenthal, 1989) and a subchronic (90-day) toxicity study (Goldenthal, 1990) treatment related effects were seen at doses of 500 ppm (33.4-43.9 mg/kg bw/day) and higher. Effects at 500 ppm (28 and 90 day studies) were limited to haematology and clinical chemistry findings, increased liver weights and accentuated lobulation of the liver of males. At 1000 ppm (80-84 mg/kg bw/day) only increased liver weight was seen (28 day study). At 2500 ppm (134-145 mg/kg bw/day; 90-day study) the following effects were seen: changes in haematology and clinical chemistry parameters (small decrease in haemoglobin, increase in platelets, liver enzymes, urea nitrogen, albumin, and globulin); markedly reduced food consumption and body weights; decreased kidney and testis weights; increased liver weight; histopathological changes in the adrenal cortex (vacuolar changes in the zona glomerulosa), liver (hepatocellular hypertrophy) and testes (testicular degeneration). Secondary effects were seen in the epididymis and pituitary. The Applicant has proposed that the effects in the testes, epididymis and pituitary are consistent with the proposed mode of action being dependent upon decreased circulating testosterone, through increased conversion of testosterone to oestrogen, secondary to induction of hepatic aromatase through activation of PPARα in the liver. Further, the 30% reduction in mean body weight seen in males at this dose level may have a direct impact the testes and spermatogenesis and should be considered when interpreting the testicular effects seen in this study (Rehm *et al*., 2008).

No treatment related findings were seen at 250 ppm (20-22 mg/kg bw/day) in the 28 day study or at 25 ppm (1.7-2 mg/kg bw/day) in the subchronic study.

Mice

In mice, treatment related findings were seen at doses of 125 ppm (18-22 mg/kg bw/day) and above in 28 day (Mitchell, 1991a) and subchronic (95-96 day; Mitchell 1991b) studies. Effects at 125 ppm (95-96-day study) and 250 ppm (28-day and 95-96-day studies) (36-54 mg/kg bw/day) were similar and comprised increased body weight and increased liver and kidney weights with associated effects on clinical chemistry parameters and histopathological findings in the liver (hepatocellular hypertrophy and necrosis). At 1000 ppm (164-280 mg/kg bw/day; 28-day study) adrenal weights were also increased. All mice receiving diet containing 2500 ppm (164-280 mg/kg bw/day; 28-day study) or more quizalofop-P-tefuryl, died before the end of the study. In addition to the effects seen at lower doses, myocardial degeneration, adrenal cortical hypertrophy and lymphoid depletion and atrophy of the spleen were seen. Minimal necrosis of the germinal epithelium of testes was seen in males at 5000 ppm (285-452 mg/kg bw/day) but all mice at this dose level had died between day 5-7, and these had shown dramatic weight loss throughout the study. It is clear that this dose level had exceeded any tolerated dose, and the Applicant has proposed that the testicular effects were secondary to the extreme stress that these animals were under during the duration of the study. This conclusion is supported by findings of lymphoid atrophy and adrenal hypertrophy in the same animals (Everds *et al*., 2013) and the findings in the testes should not be interpreted as quizalofop-P-tefuryl-induced toxicity.

No effects were seen at 50 ppm (7-16 mg.kg bw/day) in the 95-96-day study.

Dogs

In a 4-week range-finding toxicity study (Crosby Tompkins, 1991b & 1992) dogs fed 5000 ppm were sacrificed in extremis. Thymus and thyroid weights decreased at ≥ 2250 ppm, clinical chemistry findings were observed at ≥ 2500 ppm and haematological findings at 5000 ppm.

At 1800 ppm (51-77 mg/kg bw/day) in the subchronic study (Crosby Tompkins, 1991a) adverse clinical signs, reduced body weight gain and food consumption in males, changes in haematological and serum chemistry parameters, increased liver weight and decreased testes/epididymides weights and macroscopic and microscopic tissue changes were seen. Relative, but not absolute, liver weights were increased in males and there were marked changes in the testes/epididymides. The testicular seminiferous tubules contained

few mature sperm and the tubules were lined with a few supporting or Sertoli cells but spermatogenic cells were absent. A targeted pathology review of the dog testes, epididymis and prostate by the conducting laboratory has concluded that the observed changes are consistent with histological changes seen accompanying large weight loss, such as that endured by dogs on the high dose, and support the subsequent known effect that weight loss has on the maturation of the reproductive organs. Further, due to the age of the animals in this study, there are anticipated effects of sexual maturation on reproductive organs, and these effects are consistent with pathology findings in the targeted review (Goedken *et al*., 2008). The Applicant concluded that the effects were secondary to the weight loss and age and were not a direct effect of quizalofop-P-tefuryl. The lymph nodes of two males and all females at 1800 ppm contained areas of haemorrhagic, hyperaemia or inflammation.

In a one-year dog study (Crosby Tompkins, 1993) death of one female, clinical signs (diarrhoea in males), slight reduction of body weight gain (males) and food consumption (males and females), changes in haematological and serum chemistry parameters, decreased spleen and adrenal weights and slightly increased liver weights in males were seen at 1500 ppm (30-58 mg/kg bw/day). There were no treatment-related effects in the testes or associated organs suggesting that the changes seen in the 90 day study were not treatment related.

No treatment related effects were seen at 1000 ppm (approximately 40 mg/kg bw/day) in the 28 day study, 900 ppm (32-40 mg/kg bw/day) in the 90 day study, or at 750 ppm (24-36 mg/kg bw/day) in the 1 year study.

4.7.1.2 Repeated dose toxicity: inhalation

No data available.

4.7.1.3 Repeated dose toxicity: dermal

No data available.

4.7.1.4 Repeated dose toxicity: other routes

No data available.

4.7.1.5 Human information

No information available.

4.7.1.6 Other relevant information

No other relevant information available.

4.7.1.7 Summary and discussion of repeated dose toxicity

Repeated dose toxicity of quizalofop-P-tefuryl administered orally was studied in rats, mice and dogs and treatment related effects were seen in the adrenals, kidney liver and testes. The following summary focuses on the effects that appear of greatest relevance for classification.

Adrenals

Vacuolar change in the zona glomerulosa of the adrenal cortex was seen in rats of both genders at the highest dose in the 90 day study (2500 ppm: 134/145 mg/kg; males/females). Increased adrenal weight was seen in mice after 28 days at 1000 ppm (164/209 mg/kg; males/females) but not in the longer term studies. There was a slightly decreased adrenal weight seen at the highest dose (1500 ppm: approx 50 mg/kg) in the 1 year

dog study. Histopathological changes were only seen in the rat at a maximum tolerated dose and are considered to be secondary to the significant systemic toxicity. Overall these findings provide no evidence of organ dysfunction and do not warrant consideration for classification.

Heart

Myocardial degeneration was seen in the 28-day mouse study in animals that died prior to scheduled termination at doses of 2500 and 5000 ppm. There was no dose response relationship (incidence 0/0, 0/0, 0/0, 5/5 and 3/3 in males/females at 0, 250, 1000, 2500 and 5000 ppm, respectively) and no evidence of any cardiac lesion in 90-day or 2 year studies. Consequently these are considered to reflect agonal changes and not of relevance for classification purposes.

Liver

Increased liver weight was seen in all species and liver histopathology was seen in rats at the LOAEL. Liver hypertrophy and necrosis were seen in both rats and mice. In the rat vesiculation and/or vacuolation was also noted. These effects are considered to be of toxicological significance and relevant for consideration in the context of a "peroxisome proliferator" (PPARα) mode of action (Annex I).

Kidney

Effects on kidney were inconsistent and confined to differences in kidney weight (decreases in rat, increases in mice) at dose levels associated with body weight effects. The differences were unaccompanied by any histopathological change and, as such, provide no evidence of organ dysfunction and do not warrant classification.

Spleen

Atrophy of the spleen was seen in the 28-day mouse study in 2 males and 1 female at 5000 ppm. These animals died following less than 7 doses and no evidence of any spleen effects were seen in 90-day or 2 year studies. Consequently these are considered to reflect agonal changes and not of relevance for classification purposes.

Testis

Decreased testes weight and testicular degeneration, aspermatogenesis and aspermia were reported in the dog 90 day study at the highest and systemically toxic dose level (1800 ppm). A subsequent targeted pathology review of all of the testes, epididymis and prostate from the dogs on this study has concluded that the effects seen are consistent with an inhibition of maturity in the affected dogs, consistent with effects secondary to the large weight loss that these dogs showed and are not a direct effect of quizalofop-P-tefuryl. These effects were absent in the 1 year study (top dose 1500 ppm) and since this lesion is commonly seen in control dogs as a spontaneous finding and was not repeated in the 1 year study, it is considered not to be of toxicological significance.

Decreased testes weight and testicular degeneration, aspermatogenesis and aspermia were reported in the rat 90 day studies. These effects are considered to be of toxicological significance in the rat, but are considered secondary to the hepatic effects of PPARα compounds, which are widely considered to be not relevant to humans.

Thymus

Decreased thymus weight was seen in the 28-day dog study at all dose levels. In this study excessive toxicity was seen at doses of 2250 ppm and above and the effects on the thymus are considered to represent a stress response in seriously compromised animals. At 1000 ppm (40 mg/kg bw/day) thymus weight was considered to be low in one of two animals of each sex. In the absence of any effects on thymus weight in any animals on the 90-day and 1 year dog studies at similar dose levels (41-77 mg/kg bw/day) the difference in thymus weight in the 28-day study is considered to be incidental to treatment with quizalofop-P-terfuryl.

4.7.1.8 Summary and discussion of repeated dose toxicity findings relevant for classification according to DSD

Not applicable: DSD classification no longer relevant.

4.7.1.9 Comparison with criteria of repeated dose toxicity findings relevant for classification according to DSD

Not applicable: DSD classification no longer relevant.

4.7.1.10 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification according to DSD

Not applicable

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to CLP Regulation

See Section 4.7.1.7.

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT RE

There was a consideration of the evidence available to support classification for repeated dose toxicity at EFSA's PRAPeR Expert Meeting 54 Sub-group1 (07 – 11 July 2008). Aside from the effects on testes observed in rats and dogs, for which the classification endpoint of reproductive toxicity is more relevant, it was concluded that there was no toxicity in the available studies to support classification.

Repeated dose, specific target organ toxicity applies where significant health effects are reported which are considered to impair function, both reversible and irreversible. There is a guidance value of 10 mg/kg/day (rat; oral 90-day study), such that effects occurring below this would justify classification with STOT RE1. Similarly, there is a guidance value of 100 mg/kg/day for STOT RE2. For data derived from 28-day studies, these values are multiplied by 3 (to give 30 and 300 mg/kg bw/day). For a 1-year study, it is possible to divide by a factor of 4 (to give 2.5 and 25 mg/kg bw/day).

Significant hepatic effects (increased weight and histopathology) were observed at 134 mg/kg bw/day in the rat 90-day and at 18-22 mg/kg bw/day in the mouse 90-day study. There were no effects at ≤ 100 mg/kg bw/day to justify classification. Effects seen in the mouse are considered to be adaptive changes, consistent with PPARα activation induced by quizalofop-P-tefuryl (Annex I). Classification is not applicable where species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification. This is the case for liver effects resulting from peroxisome proliferation, as discussed under 4.10.5 below.

There were also findings of significance in the adrenals, heart, kidneys, spleen and thymus of rats, mice and/or dogs. However, as discussed in Section 4.7.1.7, there was a lack of consistency across studies of different duration with the same species and between species. Generally, the findings were isolated and did not form a coherent profile of repeated dose toxicity. The testicular effects in rats and dogs are considered under Reproductive Toxicity (Section 4.11).

Overall, it is concluded that no classification for specific target organ toxicity is required

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT RE

No classification

4.9 Germ cell mutagenicity (Mutagenicity)

Table 20: Summary table of relevant *in vitro* and *in vivo* mutagenicity studies

Method	Results	Remarks	Reference
in vitro			
Bacterial gene mutation assay (Ames test) S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) S. typhimurium TA 1538 (met. act.: with and without) Doses: 0, 667, 1000, 3333, 6667, 10,000 µg/plate (main assay) equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay) Klimisch 2 (reliable with restrictions)	**Negative** with and without metabolic activation	**Negative** for all strains tested, both with and without metabolic activation. A vehicle (DMSO) control and positive controls were used in both experiments. Results valid.	San & Springfield (1990) (DAR B.6.4.1.1)
Bacterial gene mutation assay E. coli WP2 uvr A (met. act.: with and without) Doses: 0, 1.5, 5.0, 15, 50, 150, 500, 1500 and 5000 µg/plate (initial toxicity / mutagenicity assay) 0, 15, 50, 150, 500, 1500 and 5000 µg/plate (confirmatory mutagenicity assay) OECD Guideline 471 (Bacterial Reverse Mutation Assay) Klimisch 1 (reliable without restriction)	**Negative** with and without metabolic activation	**Negative** for E. coli WP2 uvr Aboth with and without metabolic activation. Tested up to precipitating concentrations; no cytotoxicity. Vehicle control and positive controls were used in both assays. Results valid.	Wagner & Hines (2004) (DAR B.6.4.1.2)
Mammalian cell gene mutation assay mouse lymphoma L5178Y cells (met. act.: with and without) Doses: Initial assay: 32, 42, 56, 75, 100, 133, 178, 237, 422 µg/mL (without activation); 24, 32, 42, 56, 75, 100, 133, 178, 237, 316 µg/mL (with activation) Second assay: 50, 100, 125, 174, 200, 249, 274, 301, 324, 352 µg/mL (with and without activation) Confirmatory assay: 50, 100, 200, 298, 323, 374 µg/mL (without activation), 200, 251, 298, 323, 349 µg/mL (with activation) equivalent or similar to OECD	**Negative** with and without metabolic activation	**Negative** with metabolic activation. Top dose limited by cytotoxicity. **Equivocal** without metabolic activation - one experiment out of three met the criteria for a dose-response doubling in mutant frequency. Top dose was limited by cytotoxicity. EMS was used as the positive control without metabolic activation and 7,12-DMBA was used as the positive control with activation. Results valid.	Bigger & Clarke (1991) (DAR B.6.4.1.3)

Method	Results	Remarks	Reference
Guideline 476 (*In vitro* Mammalian Cell Gene Mutation Test); EPA OPP 84-2 Klimisch 1 (reliable without restriction)			
In vitro Rat hepatocytes UDS test Doses: Preliminary cytotoxicity study: 0.15, 0.5, 1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/mL UDS assay: 1.5, 5.0, 15, 50, 150, 500 µg/mL EPA OPP 84-2 Klimisch 1 (reliable without restriction)	**Negative**	**Negative** 7,12-DMBA was used as the positive control. DMSO was used as the solvent control. Results valid.	Curren (1990) (DAR B.6.4.1.5)
In vitro mammalian chromosome aberration test Chinese hamster Ovary (CHO) (with and without metabolic activation) Doses: 313, 625, 1250 and 2500 µg/mL (with and without activation) 25, 50, 100, 200 and 400 µg/mL (repeat study without activation) Equivalent or similar to OECD Guideline 473 (*In vitro* Mammalian Chromosome Aberration Test), but see remark in column 3.	**Negative** with metabolic activation Result without metabolic activation was not interpretable given weaknesses in study design.	This study had several methodological flaws compared to the standard expected today and, during review by EFSA it was judged to be essentially "not acceptable". Notably only 100 (not 200) metaphases were analysed per dose. In the context of this classification proposal, the study is of limited value, given the availability of an *in vivo* bone marrow micronucleus study with a clear negative result.	Putman & Morris (1990) (DAR B.6.4.1.4)
in vivo			
Mouse bone marrow micronucleus assay Mouse (ICR) male/female Intraperitoneal dosing 24h sampling time: 0, 100, 200, 400 mg/kg (in corn oil) 48 h sampling time: 0, 400 mg/kg OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) EPA OPPTS 870.5395 (*In vivo* Mammalian Cytogenics Tests: Erythrocyte Micronucleus Assay) Klimisch 1 (reliable without restriction)	**Negative**	Groups of 5 male and 5 female mice were given a single i.p. dose of test substance or control. There were no increases in micronucleus frequency in treated animals. All mice at 400 mg/kg exhibited lethargy and piloerection. In the 24h experiment, P/N ratios were reduced by up to 21% and 28% of controls in males and females, respectively. Smaller reductions were seen in the 48h study. Note that 5/10 animals had died in a range-finder at 550 mg/kg. Cyclophospamide was used as the positive control: valid result.	Krsmanovic & Huston (2007) (DAR B.6.4.2.3)
In vivo UDS assay	**Negative**	None of the test substance doses caused a significant increase in	San & Reece (2003)

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male oral: gavage 0, 250, 500 and 1000 mg/kg bw (nominal conc.) equivalent or similar to OECD Guideline 486 (Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells *in vivo*) Klimisch 1 (reliable without restriction)		mean net nuclear grain count at either 2-4 or 12-16 hours post-exposure. DMN was used as a positive control substance and corn oil as a negative (vehicle) control. Results valid.	(DAR B.6.4.2.2)
Mouse bone marrow micronucleus assay mouse (ICR) male/female intraperitoneal doses: 138, 275, 550 mg/kg (in corn oil) 5 male and 5 female mice per dose; sampling at 24, 48 and 72 hours EPA OPP 84-2	Negative	At 550 mg/kg: 6/10 mice were found dead within 3 days of treatment; other toxic signs included ruffled fur, lethargy, tremors and paralysis. There were no significant increases in micronucleus frequency in any dose group. *Note: During the EFSA review,* this *study was considered unacceptable as it did not fulfil the requirements in the OECD Test Guideline No. 474 of testing a chemical for the ability to cause micronuclei in vivo. Only 1000 polychromatic erythrocytes per animal were scored for the presence of micronuclei. According to the current OECD test guideline, analysis of 2000 PCEs for micronuclei is required.*	Putman & Morris (1991) (DAR B.6.4.2.1)

4.9.1 Non-human information

4.9.1.1 *In vitro* data

In an Ames test (San & Springfield, 1990) quizalofop-P-tefuryl was not cytotoxic or mutagenic up to the highest dose tested (10 mg/plate). A subsequent study demonstrated that quizalofop-P-tefuryl was not cytotoxic or mutagenic with the tester strain E. coli WP2 uvrA (Wagner and Hines, 2004).

In a mammalian cell gene mutation study (Bigger & Clarke, 1991), quizalofop-P-tefuryl was negative in the presence of exogenous metabolic activation. In the absence of metabolic activation, one experiment out of three met the criteria of a dose responsive doubling in mutant frequency. Hence, the result is equivocal in the absence of metabolic activation.

Quizalofop-P-tefuryl caused no significant increase in the UDS assay (Curren, 1990) as measured by the mean number of net nuclear grain counts at any dose level. The result was not confirmed in an independent experiment but the study was performed in triplicate cultures (at least two cell cultures required by the guideline). In addition, the result of the study was clearly negative and therefore was concluded to be acceptable.

4.9.1.2 *In vivo* data

Quizalofop-P-tefuryl caused no significant increase in the mean number of net nuclear grain counts at any dose level in rat liver cells *in vivo* (San & Reece, 2003).

Quizalofop-P-tefuryl was negative in a well conducted, robust mouse bone marrow micronucleus assay (Krsmanovic & Huston, 2007).

4.9.2 Human information

No information

4.9.3 Other relevant information

No other relevant information.

4.9.4 Summary and discussion of mutagenicity

Genotoxicity of quizalofop-P-tefuryl was tested in five *in vitro* and three *in vivo* tests. At EFSA, the meeting of PRAPeR experts agreed that the overall profile does not indicate genotoxic concerns.

4.9.5 Comparison with criteria

Genotoxicity of quizalofop-P-tefuryl was tested in five *in vitro* and three *in vivo* tests (Table 20). There were two bacterial mutagenicity tests, both with negative results. The *in vitro* mammalian cell gene mutation test gave a negative result in the presence of exogenous metabolic activation but in the absence of metabolic activation, the result was equivocal. The *in vitro* chromosome aberration test gave an equivocal result overall, but does not meet the current regulatory standard. A clear negative result was obtained in an *in vitro* rat hepatocyte UDS assay.

Significantly, quizalofop-P-tefuryl has been tested adequately *in vivo*, giving clear negative results in both a mouse bone marrow micronucleus test and a liver UDS test. As such, no classification is warranted for this endpoint.

It is unclear why Annex VI of the CLP Regulation currently includes a mutagenicity classification for quizalofop-P-tefuryl. Although the original records for the relevant meeting(s) and basis for the eventual classification have not been obtained, it seems most likely that an administrative error was made. The substance should have been classified as a suspect carcinogen (Carc Cat 3: R40) not a suspect mutagen (Muta Cat 3; R40, later Muta Cat 3; R68).

4.9.6 Conclusions on classification and labelling

No classification

4.10 Carcinogenicity

Table 21: Summary table of relevant carcinogenicity studies

Method	Results	Reference
2-year study rat (Charles River CD) male/female 50/sex/dose (main study) plus 15/sex/dos (satellite groups to provide data at a 1 year interim kill) oral: feed test material purity: 89.2% 0, 25, 750 and 1500 ppm (initially), 1500 ppm dose reduced for males to 1250 ppm at start of week 11 (nominal in diet) , equivalent to approximately 1.3, 39.5 and 72.2 mg/kg bw/d in males and 1.7, 48.7 and 101.5 mg/kg bw/d in females. Exposure: 2 years (Continuous administration in the diet) EPA OPP 83-5 (Combined Chronic Toxicity / Carcinogenicity) GLP	**Non-neoplastic findings** 1500/1250 ppm (72.2/101.5 mg/kg bw/day) *Body weight and weight gain*: Body weights ↓ males and females throughout the study (↓20% at week 10). Dose level consequently reduced from 1500 to 1250 ppm during week 10. The relative difference compared to controls was reduced after dose reduction (males ↓16.3-16.4%, 13.3%, 7.6% weeks 52, 80 and 104 respectively; females ↓10-15%, 14.3%, 16.1% weeks 52, 80 and 104 respectively). *Food consumption*: ↓ males and females throughout study. The relative difference compared to controls was reduced after dose reduction. *Haematology*: Erythrocytes ↓ at 6 months (males), haematocrit ↓ at 6 months (males) and at 12 months (males and females), MCV ↓ at 6, 12 and 18 months (females) and at 24 months (male s and females), MCH ↓ at 6 months (females) , at 18 and 24 months (males and females), MCHC ↑ at 6 months (males, ↓ at 18 and 24 months (males and females). *Clinical chemistry*:ALP ↑, albumin ↑, globulin ↓ and cholesterol ↓ at all intervals (males). Phospholipids and total lipids ↓ at 18 months (males). ALP ↑ at 24 months, albumin ↑ at 12, 18 and 24 months (females). ↓ free fatty acids and triglycerides at 18 and 24 months(females) *Gross pathology*: Liver ↑ incidence of tan foci, nodules and masses. Testis ↑ incidences small and soft testis, white/tan foci or enlargement. *Organ weights*: ↑ absolute (47-53%) and relative liver weights (58-74%) (males and females) at 12 and 24 months. ↓ absolute (40%) and relative (32%) testis weights at 12 months only. *Histopathology*: Non-neoplastic: Liver ↑ incidences of hypertrophy (26/26 males, 34/35 females), hyperplasia of hepatocytes (6/26 males, 4/35 females) and bile stasis (26/26 males, 12/35 females) at terminal kill. Thyroid gland ↑ incidence of follicular epithelial hypertrophy (25/26 males) at terminal kill. It is considered that the thyroid changes are secondary to the hepatic changes. Testis ↑ incidences of degeneration of the seminiferous tubules with secondary aspermia in the epididymis (19/26) at terminal kill. *Electron microscopy*: ↑ number of peroxisomes (males and females), ↑ mean peroxisomal areas (females). 750 ppm: (39.5/48.7 mg/kg bw/day) Body weight and weight gain: ↓ body weight gain during 1st year only (males). *Food consumption*: ↓ during early part of the study (males and females) - possibly due to C4874 palatability. *Haematology*: Erythrocytes ↓ at 6 months and ↑ at 18 months in males, haematocrit ↓ at 6 months in males and at 12 months in females, MCV ↓ at 12 months in males and females and at 18 months in females, MCH ↓ at 18 months	Goldenthal (1993) (DAR B.6.5.1.1)

<table>
<tr><th>Method</th><th>Results</th><th>Reference</th></tr>
<tr><td></td><td>
males and females and at 24 months in males, MCHC ↑ at 6 months and ↓ at 18 months in males.
Clinical chemistry: ALP ↑, albumin ↑, globulin ↓ and cholesterol ↓ at all intervals in males. Phospholipids and total lipids ↓ at 18 months (males). Albumin ↑ at 12 and 18 months (females).
Gross pathology:Liver ↑ incidence of tan foci, nodules and masses. Testis ↑ incidences small and soft testis, white/tan foci or enlargement.
Organ weights: ↑ absolute (30-40%) and relative (30-40%) liver weights (males and females) at 12 and 24 months.
Histopathology: Non-neoplastic: Liver ↑ incidences of hypertrophy (30/30 males, 34/37 females), hyperplasia of hepatocytes (7/30 males, 2/37 females) and bile stasis (6/30 males, 8/37 females) at terminal kill. Thyroid gland ↑ incidence follicular epithelial hypertrophy (30/30 males) at terminal kill.
Electron microscopy: ↑ number of peroxisomes (males and females).
<u>25 ppm: (1.3/1.7 mg/kg bw/day)</u>
No effects

Neoplastic findings
Histopathology: Neoplastic: Increased incidences of hepatocellular adenomas and carcinomas, Leydig cell tumours and kidney squamous cell carcinoma.
Overall tumour incidence
<table>
<tr><td></td><td colspan="5">Dietary concentration C4874 (ppm)</td></tr>
<tr><td>Finding</td><td>Sex</td><td>0</td><td>25</td><td>750</td><td>1500/ 1250</td></tr>
<tr><td>Liver – hepatocellular adenoma</td><td>M
F</td><td>1/50
0/50</td><td>0/50
0/50</td><td>16/50
14/50</td><td>29/50
15/50</td></tr>
<tr><td>Liver - hepatocellular carcinoma</td><td>M
F</td><td>0/50
0/50</td><td>0/50
0/50</td><td>5/50
1/50</td><td>15/50
2/50</td></tr>
<tr><td>Testis – Leydig cell tumour</td><td>M</td><td>3/50</td><td>1/50</td><td>19/50</td><td>22/50</td></tr>
<tr><td>Kidney – squamous cell carcinoma</td><td>M
F</td><td>0/50
0/50</td><td>0/50
0/50</td><td>0/50
0/50</td><td>1/50
2/50</td></tr>
</table>

The NOEL and NOAEL for carcinogenicity was 25 ppm (corresponding to 1.3 mg/kg bw/day for males and 1.7 mg/kg bw/day for females) based on slightly increased liver weights, liver histopathology (hepatocellular hypertrophy, hyperplasia, bile stasis), thyroid histopathology, liver tumours, Leydig cell tumours at ≥750 ppm and rare renal tumours at 1250/1500 ppm. Quizalofop-P-tefuryl was shown to increase the number of peroxisomes in liver at ≥750 ppm and the area of peroxisomes at 1250 ppm.
</td><td></td></tr>
</table>

Method	Results	Reference
18-month study mouse (CD-1) male/female 50/sex/dose oral: feed Test material purity 94% 0, 10, 60, 125, 250 ppm (nominal conc.) 0, 1.7, 10.2, 21.7, 42.6 mg/kg/day (males); 0, 2.0, 13.0, 26.2, 55.2 mg/kg/day (females) (actual ingested) Exposure: 18 months (Continuous in the diet) EPA OPP 83-2 (Carcinogenicity) OECD Guideline 451 (Carcinogenicity Studies) JMAFF Oncogenicity studies (1985) Klimisch 1 (reliable without restriction) GLP	**Non-neoplastic findings** 250 ppm: (42.6/55.2 mg/kg bw/day) *Mortality*: Percentage survival at 18 months ↓ (32% / 44% for males / females compared to 64% / 60% for control males / females). *Body weight*: ↑ throughout study (more pronounced in males than females). At end of study mean body weights were 44.4 g and 38.6 g for males and females respectively compared to 41.9 g and 37.6 g for control males and females. *Food consumption*: ↓ throughout study, calculated as g/food consumed/unit body weight. These differences suggest that total food consumption was similar for control and high-dose animals but that relative food consumption was slightly ↓ at 250 ppm group due to higher body weights. *Macroscopic findings*: Slightly ↑ incidence of enlarged livers. *Organ weights*: Increased mean liver weights (88% and 46%), liver/body (80% and 41%), liver/brain weight ratios (88% and 45%) (males and females). Increased mean kidney weights (10% and 22%) and kidney/body (5% and 17%) and/or kidney/brain weight ratios (9% and 21%) (males and females). *Microscopic findings*: ↑ incidence in the accumulation of diffuse hepatic pigment present in either Kupffer cells or bile caniculi (pigment present in 35 males and 29 females compared to 3 males and 7 female controls). 125 ppm: (21.7/26.2 mg/kg bw/day) *Mortality*: Percentage survival at 18 months ↓ (42% / 53% for males / females compared to 64% / 60% for control males / females). *Organ weights*: Increased mean liver weights (17% and 16%), liver/body (22% and 18%) and liver/brain weight ratios (17% and 17%)↑ (males and females). Mean kidney/body weight ratio 11% ↑ (females only). *Microscopic findings*: ↑ incidence in the accumulation of diffuse hepatic pigment present in either Kupffer cells or bile caniculi (pigment present in 26 males and 21 females compared to 3 males and 7 female controls). 60 ppm: (10.2/13 mg/kg bw/day) Organ weights: Mean liver weight (17%) and liver/body weight ratios (18%) ↑ (males only). **Neoplastic findings** C4874 was not carcinogenic at any dose level in this study. The NOEL of C4874 for carcinogenicity is 250 ppm (equivalent to 42.6 and 55.2 mg/kg/day for males and females respectively) and the NOEL for toxicity is 10 ppm (equivalent to 1.7 and 2.0 mg/kg/day for males and females respectively).	Mitchell (1993) (DAR B.6.5.2.1)

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

The chronic toxicity and oncogenicity of quizalofop-P-tefuryl was studied in rats and mice (see Table 21).

Rats

In rats, there were no signs of overt toxicity and no changes in survival rate, ophthalmoscopy, or urinalysis related to the administration of quizalofop-P-tefuryl in the diet at 25, 750 and 1500/1250 ppm (Goldenthal, 1983). Mean body weights and food consumption were decreased compared to controls in the high dosage levels and also slightly in mid dose males during the first year of the study. The dosage level of 1500 ppm was reduced to 1250 ppm due to an excessive reduction in mean body weight. In haematology, decreased number of erythrocytes, haematocrit, MCV, MCH and MCHC was observed in mid/high dose males. Decreased MCV, MCH and MCHC were observed also in mid/high dose females. Alkaline phosphatase and albumin values were increased and globulin values decreased in mid/high dose animals. Cholesterol, phospholipids, triglyceride, total lipid and free fatty acid levels were decreased in mid/high dose males. In females, free fatty acid values were decreased at high dose level and triglyceride values at mid and high dose levels.

Liver

The liver was the main target organ. Liver weights (absolute and relative) were increased >30% in mid and high dose animals. An increased incidence of tan foci, nodules and masses were observed in the liver at mid and high dose levels. Microscopic examination of liver revealed hypertrophy, hyperplasia of hepatocytes, bile stasis and hepatocellular adenomas and carcinomas in both males and females at mid and high dose level. The incidence of hepatocellular adenoma was significantly increased in mid and high dose animals (2%, 0%. 32%, 58% in males and 0%, 0%, 28% and 30% in females at 0, 25, 750 and 1250/1500 ppm, respectively). There was also clear treatment-related increased incidence of hepatocellular carcinoma in male rats (0%, 0%. 10%, 30% at 0, 25, 750 and 1250/1500 ppm, respectively). In females, there was a less clear-cut dose-response relationship for hepatocellular carcinoma (0%, 0%, 2%, 4%).

Electron microscopy (EM) indicated that quizalofop-P-tefuryl produced an increase in the number of hepatic peroxisomes which was considered to have been related to the increased incidence of liver tumours. Substances classed as “peroxisome proliferators” are well known non-genotoxic hepatocarcinogens in rats. The occurrence of hepatocellular hypertrophy, hyperplasia, adenomas and carcinomas in the mid and high dose groups correlated well with the EM findings and support conclusion that the mechanism of hepatocellular tumour induction involved peroxisome proliferation and the resulting oxidative stress. There is a clear no-effect level for this effect and the mechanism is usually considered irrelevant for humans (see Annex I to this report for more detail).

Following an analysis of several quizalofop-based substances, it has been noted by the Applicant that the incidence of comparable hepatic findings among them suggests that a common metabolite (quizalofop acid) may be the active species. The Applicant asserts that quizalofop acid is a peroxisome proliferator (PPARα agonist). See Annex II for a detailed discussion.

Testis

Testis weights were reduced at the high dosage level by 40% at 12 months. An increased incidence of small and soft testis, white/tan foci or enlargement was evident at mid and high dose levels. Treatment related microscopic changes were noted in the testis of the high dose males (also in satellite group at 12 months). These changes consisted of degeneration of the seminiferous tubules with secondary aspermia in the epididymis. Increased incidence of Leydig cell tumours was observed at mid and high dose levels (6%, 2%. 38%, 44% in males at 0, 25, 750 and 1250/1500 ppm, respectively).

High incidence of Leydig cell tumours were observed at the same dose levels as hepatocellular tumours. As discussed in Annex I, peroxisome proliferators have been reported to induce Leydig cell tumours in CD rats.

A postulated mechanism of action for the Leydig cell tumours revolves around the reported induction of hepatic aromatase in the rat which accelerates conversion of testosterone to oestrogen, resulting in chronically reduced plasma testosterone levels. In the rat, this would trigger the pituitary gland to release luteinising hormone. Increased levels of luteinising hormone would provide a chronic, mitogenic drive to the Leydig cells of the testes. Since chronic cell proliferation is an accepted risk factor for cancer this hypothesis provide a plausible mechanism of action which would be secondary to the hepatic effects of peroxisome proliferators in rats that would not be relevant to human hazard assessment (also see Annex I). The Applicant has further noted that the incidence of comparable testicular findings reported for other quizalofop acid generators is consistent with this hypothesis (Annex II).

Thyroid

The thyroid gland showed follicular epithelial hypertrophy in the mid and high dosage levels in both males and females. In rats, it is a well-known phenomenon that hepatocellular hypertrophy of the enzyme induction type causes secondary thyroid changes. The thyroid changes were considered to be secondary to the hepatic changes.

Kidney

In rats there was low incidence of rare renal squamous cell carcinoma at 1250/1500 ppm (1/50 male and 2/50 females). No similar tumours were seen in control animals or the lower dose groups. The Applicant has acknowledged these tumours to have been treatment-related. A mechanistic explanation for the increased tumours is not available; they are considered relevant for human hazard assessment of quizalofop-P-tefuryl.

Mice

There was no evidence of carcinogenicity as a result of test article administration (Mitchell, 1993). Mortality was increased in males receiving 125 ppm and in both males and females receiving 250 ppm. There was no treatment-related effect in physical observations, food consumption or white blood cell data. The body weights in the 250 ppm dose group were greater than control weights. In mice hepatocellular or testicular tumours were not observed. Note that in the PRAPeR Expert meeting, Member State experts discussed whether the low survival rate in mice at 125 ppm could have an impact on the assessment of carcinogenic potential of quizalofop-P-tefuryl, but it was agreed that the animals survived long enough to develop tumours.

Liver & kidney

In mice, liver was the main target organ. Absolute and relative liver (>80% in males, >40% in females) and kidney weights (<10% in males, ~20% in females) were increased at and above 125 ppm and enlarged livers were evident in several high dose animals at necropsy. Absolute and relative liver weights were increased (17% and 18%) in males but not females at 60 ppm. There was a dose and treatment-related increase in diffuse hepatic pigment accumulation (in Kupffer cells or in bile canaliculi) at and above 125 ppm dose levels.

4.10.1.2 Carcinogenicity: inhalation

No information.

4.10.1.3 Carcinogenicity: dermal

No information.

4.10.2 Human information

No information.

4.10.3 Other relevant information

4.10.4 Summary and discussion of carcinogenicity

The carcinogenicity of quizalofop-P-tefuryl was studied in rats and mice. There was no evidence of carcinogenicity in the mouse. In the rat increased incidences of tumours were observed in the liver, testis and kidney.

Liver

In rats, increased hepatocellular adenomas and carcinomas were observed at doses ≥ 39.5 (males) ≥ and 48.7 (females) mg/kg bodyweight quizaofiop-P-tefuryl (i.e. ≥ 750 ppm in the diet). However, as discussed in Annex I to this report, these findings are considered not to be relevant to humans as they appear to occur as a consequence of peroxisome proliferation (i.e. PPARα activation)[1].

Testes

An increased incidence of Leydig cell tumours was observed at mid and high dose levels i.e. the same dose levels as hepatocellular tumours. Since other PPARα agonists have been shown to induce hepatic aromatase in the rat that results in increased Leydig cell tumours (see Annex I), this mechanism has been proposed for quizalofop-P-tefuryl. An investigative study with quizalofop-P-tefuryl in the rat (Sequani, 2015; ongoing) has shown increased conversion of testosterone to oestrogen, and increased secretion of LH, consistent with the proposed MOA and the data shown for other PPARα agonists. Full information on this study is not currently available. As the effects are secondary to the altered hepatic metabolism of testosterone, through the pleiotropic effects of PPARα agonism, they are considered not to be relevant to humans (Annex I). It is also noted that the incidence of comparable testicular findings reported for other quizalofop acid generators is consistent with this hypothesis (Annex II).

Kidney

The relevance of the increased incidence of rare renal squamous cell carcinoma in rats was considered and although only 3 animals were involved, the incidences were outside the historical control range (0% in males, 0-1.4% in females). It was agreed that the tumours may be treatment related and potentially relevant for human hazard assessment.

4.10.5 Comparison with criteria

It is unclear why quizalofop-P-tefuryl was not previously classified as a suspect carcinogen (Carc Cat 3; R40). As discussed in the Section 4.9.5, it seems that an administrative error may have resulted in a classification being introduced for mutagenicity instead.

EFSA has previously concluded that a carcinogenicity classification may be justified, given both the clear treatment-related increases of Leydig cell tumours and a low incidence of renal carcinomas seen in treated rats. The Applicant has subsequently developed a plausible hypothesis that they believe may explain the formation of Leydig cell tumours. They have argued that the weight of available evidence indicates that testicular effects are secondary to the hepatic effects induced by quizalofop-P-tefuryl acting as a PPARα agonist in rats. However, even accounting for this, it is still considered that classification is warranted because of the renal carcinomas seen in rats; they are considered of relevance to humans. See Annex I for a more detailed discussion.

In accordance with the CLP criteria, classification in category 1A for carcinogenicity is not justified as there is no evidence of quizalofop-P-tefuryl having caused cancer in humans. Given the observation of increased renal cancers in rats treated with this substance, it is therefore necessary to decide whether to classify quizalofop-P-tefuryl in Category 1B or 2.

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[1] See ECHA (2011) Guidance on the Application of the CLP Criteria, Section 3.9.2.5.3 Mechanisms not relevant to humans (CLP Annex I, 3.9.2.8.1. (e))

As there is evidence of increased tumours in only one species (rats) and there is the lack of genotoxicity seen with quizalofop-P-tefuryl in *vitro* and *in vivo* studies (see section 4.9 above), classification in Category 2 is considered more appropriate than Category 1B.

In view of these considerations, the available evidence is considered to match the criteria for classification as a Category 2 carcinogen. There are no grounds to identify a particular route of exposure on the label.

4.10.6 Conclusions on classification and labelling

Carc. Cat. 2 H351

4.11 Toxicity for reproduction

4.11.1 Effects on fertility

Table 22: Summary table of relevant reproductive toxicity studies

Method	Results	Reference
OECD Guideline 416 (Two-Generation Reproduction Toxicity Study) (adopted May 1983). GLP Rat (Sprague-Dawley) 26 males / 26 females / dose oral: feed 0, 25, 300, 900 ppm (nominal in diet). Purity of test material 93.8% Equivalent to: 1.4, 16.9, 52.8 mg/kg/day F0 males; 2.1, 24.5, 68.1 mg/kg/day F0 females; 1.7, 20.5, 68.8 mg/kg/day F1 males; 2.3, 25.7, 76.4 mg/kg/day F1 females. Exposure: 53 weeks (continuous in diet). At least 11week pre-mating period; 21 day mating period; offspring reared to weaning; selection of F1 from F1a. Two litters per generation. Klimisch 2 (reliable with restrictions)	*Parental toxicity* <u>900 ppm</u> F0: Males 10% ↓ body weight pre-mating period. ↑serum phospholipids 24% and ↑ total lipids 18% females. ↑ liver weight 54% males, 40% females. ↑ incidence diffuse hepatocyte hypertrophy. Vacuolar change in the cells of the pars distalis of the pituitary gland in males. F1: Males 33% ↓ body weight at start of pre-mating period 12% ↓ at end; females 28% ↓ at start 7% ↓ at end. ↓ food consumption during early pre-mating period. ↑ liver weight 42% males, 32% females. ↑ incidence diffuse hepatocyte hypertrophy. Vacuolar change in the cells of the pars distalis of the pituitary gland in males. <u>300 ppm</u> F0: No effects on body weight. ↑serum phospholipids 26% and ↑ total lipids 23% females. ↑ liver weight 27% males, 25% females. ↑ incidence diffuse hepatocyte hypertrophy. Vacuolar change in the cells of the pars distalis of the pituitary gland in males. F1: Males 14% ↓ body weight at start of pre-mating period no effect at end; females 11% ↓ at start; no effect at end. ↑ liver weight 29% males, 30% females. ↑ incidence diffuse hepatocyte hypertrophy. Vacuolar change in the cells of the pars distalis of the pituitary gland in males. NOEL 25 ppm (F0: 1.4 mg/kg bw/day males and 2.1 mg/kg/bw/day females; F1: 1.7 mg/kg bw/day males and 2.3 mg/kg/bw/day females) *Reproductive parameters* 900 ppm reduced fertility of F1 animals F2a mating fertility index 50.0%, 69.2%, 69.2%, 45.8% (0, 25, 300 and 900 ppm groups respectively) F2a conception rate 56.5%, 72.0%, 81.8%, 52.4% (0, 25, 300 and 900 ppm groups	York (1993a) (DAR B.6.6.1.2)

Method	Results	Reference
	respectively) F2b mating fertility index 80.0%, 69.2%, 61.5%, 41.7% (0, 25, 300 and 900 ppm groups respectively) F2b conception rate 90.9%, 75.0%, 69.6%, 47.6% (0, 25, 300 and 900 ppm groups respectively) Testes weights were recorded for suspect infertile males only (3, 2, 5 and 11 in the 0, 25, 300 and 900 ppm groups respectively). Testis/Epididymis/body weight %x10 - 9.07%, 8.23%, 7.94% and 8.90% respectively. Two males 900 ppm with aspermia / seminiferous tubule degeneration. NOEL 300 ppm (F0: 16.9 mg/kg bw/day males and 24.5 mg/kg/bw/day females; F1: 20.5 mg/kg bw/day males and 25.7 mg/kg/bw/day females) *Offspring toxicity* <u>900 ppm</u> ↓ pup viability. ↓ pup growth from days 4-7 F1 and F2 litters (approx. ↓ 30% day 21) Hydrocephaly observed in dead pups: 0 F1a, 10 F1b, 0 F2a, 5 F2b. Control incidence of 1 F1a pup only. Kidney hydronephrosis observed in 12.5% F1a pups, 6.8% F2a pups. Control incidence of 0% F1a and 4.2% F2a. Details are included in Table 26. <u>300 ppm</u> ↓ pup growth F1a, F1b, F2a litters (approx. ↓ 12% day 21) NOEL 25 ppm (F0: 1.4 mg/kg bw/day males and 2.1 mg/kg/bw/day females; F1: 1.7 mg/kg bw/day males and 2.3 mg/kg/bw/day females)	
Preliminary dose range finding study for a subsequent two generation reproduction study. Study design based on guideline EPA OPP 83-4 reproduction and fertility effects, with fewer animals and limited assessments. GLP Rat (Sprague-Dawley) 12 males / 12 females / dose oral: feed 0, 25, 625, 1250 ppm (nominal in diet). Purity of test material 93.8% Equivalent to 1.9, 46, 71 mg/kg/day in males and 2.1, 54, 81 mg/kg/day in females.	*Parental toxicity* <u>1250 ppm</u>: decreased body weight (males ↓11%, females ↓ 4%) and food consumption (males ↓12%, females ↓6% - greater difference for week 1) for the pre-mating period. Lower body weight of females gestation day 20 (↓ 6%) and lactation day 4 (↓ 10%). Possible testicular effects: 2 males with small testes, 3 males with degeneration of the seminiferous tubule of the testis (bilateral and moderate in 2 males and trace in 1 male). Also, two males had cellular luminal debris in the epididymis. One of the 2 males failing to sire a litter had morphologically abnormal and non-motile sperm. NOEL 625 ppm (46 mg/kg bw/day males and 54 mg/kg/bw/day females) *Reproductive parameters* No effect on reproduction at highest dose level of 1250 ppm. NOEL 1250 ppm (71 mg/kg bw/day males and	York (1991a) (DAR B.6.6.1.1)

Method	Results	Reference
Exposure: 12-13 weeks (continuous in diet) 34 day pre-mating period; 21 day mating period; offspring reared to weaning Klimisch 2 (reliable with restrictions)	81 mg/kg/bw/day females) *Offspring toxicity* 1250 ppm: ↓ pup viability to lactation day 4 (one litter 100% mortality by lactation day 1). ↓ pup growth (approx. 38% day 21). Discolouration of various body areas in several offspring mostly on lactation day 1. Red clotted material and/or red fluid present in abdominal cavity and/or intestine of a few pups that died, with yellow or purple discolouration visible externally. 625 ppm: ↓ pup growth (approx. 19% day 21) NOEL 25 ppm (1.9 mg/kg bw/day males and 2.1 mg/kg/bw/day females)	

4.11.1.1 Non-human information

A two-generation reproduction study (York, 1993a) was preceded by a preliminary range-finding study (York, 1991a). In the preliminary study, groups of 12 male and 12 female rats were given quizalofop–P-tefuryl continuously in the diet at concentrations of 0, 25, 625 or 1250 ppm (corresponding to 1.9-2.1, 46-54 or 71-81 mg/kg bw/day for males and females). The rats were allowed a 34 day pre-mating period, a 21 day mating period and then allowed to rear their offspring to weaning. At 1250 ppm, decreased parental body weights and food consumption were observed in addition to reduced pup growth through to lactation day 21 and reduced pup survival in the early postnatal period i.e. to lactation day 4. Reduced pup growth at 625 ppm was also observed. There was no parental or pup toxicity at 25 ppm and no effect on reproduction at any dose level.

For the two-generation reproduction study (York, 1993a), groups of 26 male and 26 female rats were given quizalofop–P-tefuryl continuously in the diet at concentrations of 0, 25, 300 or 900 ppm (corresponding to 0, 1.4-1.7, 16.9-20.5 or 52.8-68.8 mg/kg bw/day for males (F0-F1) and 0, 2.1-2.3, 24.5-25.7 or 68.1-76.4 mg/kg bw/day for females (F0-F1)). For the F0 and F1 generations, the rats were allowed to rear two litters of offspring to weaning. The F1 parental generation was selected from the F1a litter.

No treatment-related mortalities or clinical signs were observed during the F0 or F1 generations. Significant reductions in weekly pre-mating body weights were observed in males at 900 ppm (10%) for the F0 generation. At selection of the F1 generation, the difference in body weight from controls was 14% and 33% respectively for 300 and 900 ppm males and 11% and 28 % respectively 300 and 900 ppm females. At the end of the pre-mating period for the F1 generation, the difference in body weight from controls was reduced to 12% for males and to 7% for females at 900 ppm; the body weights of the 300 ppm animals were comparable with the controls. In addition, slight reductions in pre-mating period food consumption were observed at 900 ppm for the F1 generation.

Serum phospholipids and total lipids were increased in F0 females at 300 and 900 ppm and were considered treatment-related since they correlated with hepatic changes seen macroscopically and microscopically and with increases in liver weight. The microscopic changes included an increase in diffuse hepatocyte hypertrophy. An increased incidence in the clear cell foci of the liver was also observed in F1 males at 900 ppm.

Vacuolar change in cells of the pars distalis in the pituitary gland was observed in F0 and F1 male rats at 300 and 900 ppm. This vacuolar change appears in the LH/FSH secreting cells of the pituitary and indicates increased secretion of the peptides by these cells as a consequence of decreased circulating testosterone. This is consistent with the proposed MOA for production of the testicular effects seen, and is secondary to the hepatocyte hypertrophy and aromatase induced hormonal effects rather than a direct effect on the pituitary gland.

Dilatation of the renal pelvis (hydronephrosis) was seen macroscopically at necropsy of the F1 males and females at 900 ppm. Microscopic examination of the kidney was not undertaken and the significance of this finding is unknown.

For the F0 generation, there was no evidence of any effect due to quizalofop-P-tefuryl on the number of males impregnating a female or on the number of females conceiving. For the F1 generation, there appeared to be an increase in the number of pairings failing to produce an F2b litter in the 900 ppm group.

Table 23: Mating performance

F1 Generation	0 ppm	25 ppm	300 ppm	900 ppm
% / Number pairs failing to conceive – F2a mating	50.0% 13/26	30.8% 8/26	30.8% 8/26	54.2% 13/24
Male fertility index – F2a mating	50.0%	72.0%	72.0%	45.8%
Female fertility index – F2a mating	50.0%	69.2%	69.2%	45.8%
% / Number pairs failing to conceive – F2b mating	19.2% 5/26	30.8% 8/26	38.5% 10/26	58.3% 14/24
Male fertility index – F2b mating	80.0%	68.0%	60.0%	41.7%*
Female fertility index – F2b mating	80.0%	69.2%	61.5%	41.7%*

* Statistically significant difference from control p< 0.05

Total litter size at birth (F1a, F1b and F2a) was reduced at 900 ppm (by 8%, 14% and 38% respectively with a higher incidence of dead pups and a lower number of live pups. In addition, there was reduced pup viability at birth for the F1a, F1b and F2a litters in the 900 ppm group. The F2b litter did not show the same response to 900 ppm quizalofop-P-tefuryl as a marked reduction in pup viability was observed between days 0 and 4, greater than seen with the previous litters. There were no similar effects at 300 ppm.

Table 24: Pup viability (%) days 0 and 4 (pre-cull)

Pup viability (%)	Day	0 ppm	25 ppm	300 ppm	900 ppm
F1a	0	96.6	97.5	97.3	75.4**
	4	97.6	98.2	96.2	75.6*
F1b	0	97.0	90.6	96.5	80.2
	4	95.6	98.4	94.1	90.8
F2a	0	100.0	98.0	96.0	79.3
	4	98.0	99.2	98.3	86.4
F2b	0	89.8	96.8	89.1	88.4
	4	86.3	93.7	92.0	51.5

* Statistically significant difference from control p< 0.05
** Statistically significant difference from control p< 0.01

Review of the reported individual animal data showed discrepancies in the numbers of pups live and dead at birth such that the total litter size (number of live plus dead pups) could not be verified. It was not possible to establish if pups were born dead or if they were born live and died shortly after.

The body weight of the live pups at birth was comparable for all groups including the control. Pup body weight at 900 ppm was lower than control from day 7 (at 21 days of age, approximately 31%, 29%, 29% and 32% lower than control for the F1a, F1b, F2a and F2b pups respectively). At 300 ppm, pup body weight was lower than controls from day 14 (at 21 days of age, approximately 14%, 10%, 11% and 3% lower than control for the F1a, F1b, F2a and F2b pups respectively). Since the pups were considered to be eating the diet during the last 2 weeks of lactation, the reduced pup body weights were considered indicative of systemic toxicity at 300 ppm.

Malformations and necropsy findings are shown in Table 25 (variations have not been included). None of the observations are considered to be clearly treatment-related due to their inconsistent incidence of occurrence across the generations.

Table 25: Summary of malformations and necropsy findings in pups

Observation / Generation		0 ppm	25 ppm	300 ppm	900 ppm
Malformations F1a dead offspring	No. litters/pups examined: affected	6/13 0	6/8 1/1	10/12 0	15/77 0
Anasarca & pulmonary hyperplasia	No. litters/pups affected	0	1/1	0	0
Malformations F1a offspring day 21	No. litters/pups examined: affected	21/110 1/1	20/102 0	22/120 0	17/72 0
Hydrocephaly & anophthalmia	No. litters/pups affected	1/1	0	0	0
Necropsy observations F1a offspring day 21	No. litters/pups examined	21/110	20/102	22/120	17/72
Kidney hydronephrosis	No. /% pups affected	0	0	1/120 0.8%	9/72 12.5%
F1b dead offspring	No. litters/pups examined: affected	7/10 0	5/20 1/3	10/16 0	9/56 4/11
Malformation of hydrocephaly	No. litters/pups affected	0	1/3	0	3/10
Malformation of micrognathia, malformed oral opening, cleft palate, anophthalmia, only 3 facial papillae present	No. litters/pups affected	0	0	0	1/1
Necropsy observation of kidney contained red material	No. /% pups affected	0	0	0	1/56 1.8%
F1b offspring day 21 External examination only		No findings reported			
Malformations F2a dead offspring	No. litters/pups examined: affected	1/1 0	3/4 0	7/12 0	5/24 0
Malformations F2a offspring day 21	No. litters/pups examined: affected	12/96 0	18/142 0	18/137 0	10/59 1/1
Testis small in size	No. litters/pups affected	0	0	0	1/1
Necropsy observations F2a offspring day 21	No. litters/pups examined	12/96	18/142	18/137	10/59
Lung hemorrhagic	No. /% pups affected	0	1/142 0.7%	0	0
Kidney hydronephrosis	No. /% pups affected	4/96 4.2%	1/142 0.7%	2/137 1.5%	4/59 6.8%
Ureter distended	No. /% pups affected	1/96 1.0%	1/142 0.7%	0	1/59 1.7%

Observation / Generation		0 ppm	25 ppm	300 ppm	900 ppm
Testis hemorrhagic	No. /% pups affected	1/96 1.0%	0	0	0
F2b dead offspring	No. litters/pups examined: affected	8/46 0	4/26 1/2	9/31 0	9/57 3/5
Malformation of hydrocephaly	No. litters/pups affected	0	1/2	0	3/5
Necropsy observation of kidney hydronephrosis	No. /% pups affected	3/46 6.5%	3/26 11.5%	0	1/57 1.8%
Necropsy observation of ureters distended	No. /% pups affected	0	1/26 3.8%	0	0
F2b offspring day 21 External examination only		No findings reported			

Kidney hydronephrosis was of increased incidence in F1a pups at 900ppm with 9 (12.5%) of pups being affected at necropsy on day 21. For the F2a pups 4 (6.8%) of pups at 900ppm were similarly affected and 4 (4.2%) control pups were also affected. As the incidence of occurrence was inconsistent across the generations, there was considered to be no conclusive evidence for an effect of treatment.

Hydrocephaly was observed in some dead pups (F1b and F2b only) at 900 ppm. The pups with hydrocephaly occurred in litters where most if not all pups were dead at birth or by day 4. The significance of this finding is further discussed below.

In conclusion, the NOEL for parental toxicity was 25 ppm (reduced body weights, increased liver weight, liver hypertrophy and vacuolar change in the pituitary in parental animals at 300 and 900 ppm). The NOEL for reproduction was 300 ppm based on a possible reduction in the fertility of the F1 generation at 900 ppm and the NOEL for offspring toxicity was 25 ppm (reduced pup viability at 900 ppm and reduced pup growth at 300 and 900 ppm).

4.11.1.2 Human information

No information

4.11.2 Developmental toxicity

Table 26: Summary table of relevant developmental toxicity studies

Method	Results	Reference
OECD Guideline 414 (Prenatal Developmental Toxicity Study) (adopted May 1981). GLP Rat (Sprague-Dawley) 25 females (time-mated) /dose oral: gavage 0, 10, 30 and 100 mg/kg/day (nominal conc. in corn oil). Purity of test material 91.5%	*Maternal toxicity* 100 mg/kg/day: 40% mortality. Clinical findings prior to death included anogenital staining, body surface staining, pale colour, decreased defecation, hair loss, material around eye, emaciated, coldness to touch and moribundity. No cause of death could be determined for these animals. Body weight losses in surviving animals occurred during the treatment period and continued thereafter; body weight gain was lower than controls (by approx. 28% days 6-16, 48% days 0-20). At necropsy of the 15 females surviving to day 20, 3 had total litter resorption, 1 had vaginal mucous material and 1 had a spleen half the normal size. 30 mg/kg/day: Only clinical signs of toxicity (anogenital	York (1990a) (DAR B.6.6.2.1.2)

Method	Results	Reference
Exposure: 10 days; days 6 to 15 of gestation (once daily) Study duration: days 0 to 20 of gestation Klimisch 1 (reliable without restriction)	staining) seen. NOEL 10 mg/kg bw/day *Developmental toxicity* <u>100 mg/kg/day</u>: ↑ post-implantation loss in surviving animals (30% vs. 8% in controls); mean foetal weight ↓ 29% (2.4 g vs. 3.4g in controls); increased incidence of foetal malformations and variations. Refer to tables 27 and 28 for malformations and variations observed. NOEL 30 mg/kg bw/day	
Preliminary dose range finding study for a subsequent developmental toxicity study. Study design based on guideline EPA OPP 83-3 prenatal developmental toxicity study, with fewer animals and limited uterine assessment. GLP Rat (Sprague-Dawley) 5 females (time-mated) /dose oral: gavage 0, 25, 100, 200, 400 and 600 mg/kg/day (nominal conc. of technical grade material in corn oil) Exposure: 10 days; days 6 to 15 of gestation (once daily) Study duration: days 0 to 20 of gestation Klimisch 2 (reliable with restrictions)	*Maternal toxicity* 100% mortality at 200 mg/kg/day and higher between days 9 and 13 of gestation. At 600 mg/kg/day, laboured breathing, excessive salivation, reduced motor activities and dams cold-to-the-touch were observed after dosing. At 100, 200 and 400 mg/kg/day, these observations also were noted but not necessarily after treatment administration. These findings were either a direct result of treatment, or were indicative of the dying process as all the dams died within one-to-two days following the observation. Stomach irritation including erosions, inflammatory foci or both, was noted at necropsy examination at 100 mg/kg/day and higher; heart and thymus haemorrhaging were noted at 400 and 600 mg/kg/day. At 100, 200 and400 mg/kg/day, body weight losses or reduced weight gains occurred from gestation days 6 to 9. One death at 100 mg/kg/day (day 17): no clinical observations or necropsy findings in 4 surviving animals although body weight gain was lower than controls by approx. 50% days 6-16, 12% days 0-20. NOEL 25 mg/kg bw/day *Developmental toxicity* NOEL 100 mg/kg bw/day based on foetal viability only – no other foetal endpoints evaluated.	Schardein (1989) (DAR B.6.6.2.1.1)
OECD Guideline 414 (Prenatal Developmental Toxicity Study) (adopted May 1981). GLP Rabbit (New Zealand White) 16 females (time-mated) /dose oral: gavage 0, 5, 10 and 20 mg/kg/day (nominal conc. in corn oil). Purity of test material	*Maternal toxicity* No maternal toxicity at highest dose level. NOEL > 20 mg/kg bw/day *Developmental Toxicity* No developmental toxicity at highest dose level. NOEL > 20 mg/kg bw/day	York (1991b) (DAR B.6.6.2.2.2)

Method	Results	Reference
88.95% Exposure: 13 days; days 7 to 19 of gestation (once daily) Study duration: days 0 to 29 of gestation Klimisch 1 (reliable without restriction)		
Preliminary dose range finding study for a subsequent developmental toxicity study. Study design based on guideline EPA OPP 83-3 prenatal developmental toxicity study, with fewer animals and limited uterine assessment. GLP Rabbit (New Zealand White) 5 females (time-mated) /dose oral: gavage 0, 2.5, 10, 25, 50 and 100 mg/kg/day (nominal conc. in corn oil). Purity of test material 93.81% Exposure: 13 days; days 7 to 19 of gestation (once daily) Study duration: days 0 to 29 of gestation Klimisch 2 (reliable with restrictions)	*Maternal toxicity* At 100 mg/kg/day two abortions and two deaths; one abortion and one death at 50 mg/kg/day. Body weight loss at 25 mg/kg/day and higher. NOEL 10 mg/kg bw/day *Developmental toxicity* Increased post-implantation loss and decreased number of viable foetuses at 50 mg/kg/day NOEL 25 mg/kg bw/day (foetal viability, body weight external and soft tissues were evaluated)	York (1990b) (DAR B.6.6.2.2.1)

4.11.2.1 Non-human information

For the preliminary to the rat prenatal developmental toxicity study (Schardein, 1989), groups of 5 time-mated female rats were dosed by oral gavage with 0, 25, 100, 200, 400 or 600 mg/kg bw/day on gestation days 6 through to 15 and terminated on day 20 for evaluation of maternal and developmental effects. Maternal lethality was observed at 200 mg/kg bw/day and higher with all rats failing to survive the dosing period. At 100 mg/kg/day, one rat died on day 17 following body weight loss and changes in clinical condition; reduced body weight gain was observed in the surviving rats. Despite these treatment-related effects, 100 mg/kg/day was selected as the highest dose level for the subsequent prenatal developmental toxicity study. No maternal toxicity was observed at 25 mg/kg bw/day. Developmental toxicity was not evident at 25 or 100 mg/kg/day based on a very limited evaluation of the foetuses (the counting of live and dead implantations only).

For the prenatal developmental toxicity study (York, 1990a), groups of 25 time-mated female rats were dosed by oral gavage with 0, 10, 30 or 100 mg/kg bw/day on gestation days 6 through to 15 and terminated on day 20 for evaluation of maternal and developmental effects. At 100 mg/kg/bw/day, 10 rats died between days 15 and 18. A marked effect on body weight was seen in the rats at this dose level including body weight loss together with coat staining particularly in the anogenital area. Three of the 15 surviving rats had no live foetuses at termination, only resorptions (mostly early resorptions). Despite the severity of the maternal toxicity and consequential effects on the litters, a full evaluation of the foetuses was made. The conclusions of the evaluation were that post-implantation loss was increased (30% at 100 mg/kg/day and 8%

in controls), the number of viable foetuses was decreased (10 at 100 mg/kg/day and 13 in controls) and mean foetal body was lower than controls by 29%. Malformed foetuses were observed in 9/12 litters and variations associated with retarded ossification were observed in others. The malformations and variations are listed in the subsequent tables together with the historical control incidence.

Table 27: Foetal Malformations

Foetal malformation	**100 mg/kg bw/day**[a] No. foetuses (litters)	**Historical control incidence**[b] No. foetuses (litters)/studies
Anasarca	22 (2)	0
Encephalocoele	2 (2)	2 (2) / 2
Folded retina	1 (1)	0
Skull malformation	1 (1)	Not listed
Dome shaped head	1 (1)	Not listed
Cleft palate	6 (6)	3 (3) / 3
Micrognathia	1 (1)	2 (2) / 2
Malpositioned oesophagus	2 (2)	Not listed
Diaphragmatic hernia	3 (3)	1 (1) / 1
Interventricular septal defect	2 (2)	0
Gastroschisis	2 (2)	0
Omphalocoele	4 (4)	1 (1) / 1
Vertebral and rib malformations	2 (2)	9 (9) / 8
Ectrodactyly	1 (1)	Not listed
Anal atresia/small anal opening	4 (4)	5 (5) / 5
Tail malformation	7 (7)	Not listed

[a] 12 litters examined (excludes litter from dam which died on day 19)
Concurrent control incidence is 0 for all malformations listed
Incidence is also 0 for all malformations listed at 10 and 30 mg/kg/day except for micrognathia with a single incidence at 30 mg/kg/day
[b] data from 34 studies (1978-1984) each with between 20 and 25 control litters

Although the incidence of most of the malformations seen in the 100 mg/kg/day group exceeded that of the concurrent and historical control groups the foetuses were from litters severely compromised by excessive maternal toxicity and therefore no clear association between quizalofop-P-tefuryl and teratogenicity can be made.

Table 28: Foetal Variations

Foetal variation	**100 mg/kg bw/day**[a] No. foetuses (litters)	**30 mg/kg bw/day** No. foetuses (litters)	**10 mg/kg bw/day** No. foetuses (litters)	**Concurrent Control Incidence** No. foetuses (litters)	**Historical Control Incidence**[b] No. foetuses (litters)/studies
Oedema – ventral neck	2 (2)	0	0	0	Not listed
Renal papillae not developed	5 (4)	2 (2)	1 (1)	0	136 (96) / 33
Ureter(s) distended	2 (2)	0	1 (1)	0	
Skull bones reduction ossification	39 (8)	0	4 (1)	1 (1)	33 (27) / 15

Foetal variation	**100 mg/kg bw/day**[a] No. foetuses (litters)	**30 mg/kg bw/day** No. foetuses (litters)	**10 mg/kg bw/day** No. foetuses (litters)	**Concurrent Control Incidence** No. foetuses (litters)	**Historical Control Incidence**[b] No. foetuses (litters)/studies
Hyoid unossified	6 (4)	1 (1)	2 (2)	1 (1)	76 (51) / 23
Skull bones unossified	6 (2)	0	0	0	Not listed
Skull bones misshapen	1 (1)	0	0	0	4 (3) /3
27 presacral vertebrae	1 (1)	0	0	0	[c]34 (26) / 15
Vertebral arches bent	2 (1)	0	0	0	Not listed
Vertebral arches reduced in ossification	41 (9)	0	0	0	12 (11) / 10
Vertebral arches unossified	8 (2)	0	0	0	Not listed
Vertebrae reduced in ossification	3 (1)	0	0	0	Not listed
Vertebrae unossified	1 (1)	0	0	0	Not listed
Centra bipartite	3 (1)	0	0	0	Not listed
Less than 13 pairs of full ribs	7 (1)	4 (2)	4 (4)	5 (4)	16 (14) / 11
4th rudimentary rib	25 (7)	5 (5)	4 (4)	2 (1)	Not listed
7th cervical rib	4 (3)	3 (3)	1 (1)	1 (1)	17 (14) / 12
Sternebra 5 and/or 6 unossified	23 (7)	10 (5)	7 (7)	6 (4)	897 (398) / 33
Misaligned sternebra	2 (2)	11 (8)	6 (4)	2 (2)	[d]18 (17) / 11
Other sternebra unossified	9 (3)	1 (1)	0	0	44 (37) / 23
Entire sternum unossified	13 (3)	0	0	0	2 (2) / 2
Pectoral bones reduced in ossification	7 (1)	0	0	0	Not listed
Pelvic bones reduced in ossification	26 (5)	1 (1)	1 (1)	0	Not listed
Pelvic bones unossified	22 (5)	0	0	0	Not listed
Metacarpals and phalanges unossified	1 (1)	0	0	0	6 (5) / 4
Metatarsals and phalanges unossified	1 (1)	0	0	0	
Tarsal flexure	2 (2)	0	0	0	[e]2 (2) / 2

[a] 12 litters examined (excludes litter from dam which died on day 19)
[b] data from 34 studies (1978-1984) each with between 20 and 25 control litters
[c] listed as greater than 26 presacral vertebrae
[d] listed as fused and/or misaligned
[e] listed as carpal/tarsal flexure

The foetuses in the 100 mg/kg bw/day group were lower in body weight in comparison with the controls (by 29%) and therefore variations in ossification (particularly reduced ossification and non-ossification) are to be expected. The magnitude of the reduction in foetal weight makes any comparison of the incidence of the variations with historical control animals of 'normal' size inappropriate. The marked reduction in foetal weight is clearly a consequence of the excessive maternal toxicity and therefore no association between quizalofop-P-tefuryl and developmental toxicity can be made.

The intermediate dose of 30 mg/kg bw/day showed some maternal toxicity; 8/25 females had staining of the coat in the anogenital area on at least one occasion but there was no effect of treatment on maternal body weight. The NOEL for maternal toxicity is therefore 10 mg/kg bw/day. No developmental toxicity was seen at either 30 or 10 mg/kg bw/day; the NOEL for developmental toxicity was therefore 30 mg/kg bw/day.

For the preliminary to the rabbit prenatal developmental toxicity study (York, 1990b), groups of 5 time-mated female New Zealand White rabbits were dosed by oral gavage with 0, 2.5, 10, 25, 50 or 100 mg/kg bw/day on gestation days 7 through to 19 and terminated on day 29 for evaluation of maternal and developmental effects. At the highest dose level of 100 mg/kg bw/day, 2 rabbits died (days 13 & 19), 2 aborted (days 23 & 27) and the other had no live foetuses on day 29 (total resorption). These treatment-related events were accompanied by severe body weight loss (up to 25% in individuals). At 50 mg/kg bw/day, 1 rabbit died (day 19), 1 aborted (day 21) and 3 survived to day 29 with marked body weight loss. The 3 surviving rabbits did have live foetuses in utero but in the presence of increased post-implantation loss (up to 90% in individuals). At 25 mg/kg bw/day, 1 rabbit aborted (day 29) and the cause of death was attributed to gastritis. The remaining 4 rabbits survived to day 29 with moderate body weight loss but only 2 were pregnant; increased post-implantation loss was not observed. Although 1 rabbit given 10 mg/kg bw/day aborted (day 26) this was not ascribed to treatment. There was no clear effect of this dose on maternal body weight. Of the 4 remaining rabbits, 1 was not pregnant and 3 had live foetuses in utero on day 29. All rabbits given 2.5 mg/kg bw/day survived the duration of the study and showed no signs of maternal toxicity; 1 was not pregnant.

The reported conclusions of this study are that maternal toxicity was evident at doses of 25 mg/kg/day and greater as evidenced by body weight loss, abortion and/or death. Developmental toxicity was evident at the 50 and 100 mg/kg/day levels. There was no evidence of teratogenicity at any dose level tested. Based on these findings, dose levels of 0, 2.5, 10 and 20 mg/kg/day were selected for the subsequent prenatal developmental toxicity study in rabbits.

For the prenatal developmental toxicity study (York, 1991b), groups of 16 time-mated female New Zealand White rabbits were dosed by oral gavage with 0, 2.5, 10 or 20 mg/kg bw/day on gestation days 7 through to 19 and terminated on day 29 for evaluation of maternal and developmental effects. There was no maternal toxicity at highest dose level of 20 mg/kg/day and no developmental toxicity.

4.11.2.2 Human information

No information

4.11.3 Other relevant information

No information

4.11.4 Summary and discussion of reproductive toxicity

The reproductive toxicity of quizalofop-P-tefuryl was investigated in a two generation reproduction study (preceded by a dose range finding single generation study) and in two prenatal developmental toxicity studies, one in rats and one in rabbits. Additionally, effects on the testes were observed in repeated dose toxicity studies with rats and dogs.

Fertility and reproductive function

Testicular effects (decreased testes weight, testicular degeneration, aspermatogenesis and aspermia) were seen at doses 134 mg/kg bw/day in the rat 90-day study. The conclusion that the testicular effects in the dog were not treatment-related is based upon the fact that no similar effects were seen in the 1 year study at similar dose levels (1500 ppm (41-56 mg/kg bw/day). In addition, in the 90 day study the dogs were only 6 months old at the start of the study, and hence were sexually immature. The effects in the rat testes are considered to be a result of a rat-specific PPARα induction of hepatic aromatase resulting in decreased testosterone and perturbation of the hypothalamic/pituitary/testicular axis (Annex I) with effects consistent with those reported for other quizalofop acid generators (Annex II).

In the two generation study, the parental NOEL for systemic toxicity was 25 ppm (corresponding to 1.4 -1.7 mg/kg bw/day for F0-F1 males and 2.1 -2.3 mg/kg bw/day for F0-F1 females). The effects of treatment at higher dose levels included reduced body weight of F0 males during the pre-mating period at 900 ppm and reduced body weight during the pre-mating period for the F1 males and females at 300 and 900 ppm. Serum phospholipids and total lipids were increased in F0 females at 300 and 900 ppm. Liver weight was increased in F0 and F1 animals at 300 and 900 ppm and correlated with hepatic changes seen microscopically as an increase incidence of diffuse hepatocyte hypertrophy. An increased incidence in the clear cell foci of the liver was also observed in F1 males at 900 ppm. Vacuolar change in cells of the *pars distalis* in the pituitary gland was observed in F0 and F1 male rats at 300 and 900 ppm and considered to be secondary to the hepatocyte hypertrophy and not a direct effect on the pituitary gland. These cells are the LH secreting cells of the pituitary (castration cells) and indicate a perturbation of testosterone, consistent with the proposed mode of action (MOA) for the activation of hepatic PPARα and the induction of aromatase leading to reductions in circulating testosterone.

The NOEL for reproduction was 300 ppm (corresponding to 16.9-20.5 mg/kg bw/day for F0-F1 males and 24.5-25.7 mg/kg bw/day for F0-F1 females). For the F0 generation there was no evidence for any effect due to quizalofop-P-tefuryl on fertility. For the F1 generation, there appeared to be an increase in the number of pairings failing to achieve pregnancy at 900 ppm. However, the high number of unsuccessful pairings in the control group (50% for the mating to produce the F2a litters) is of concern in a reproduction study such that the reliability of the study to detect treatment-related effects on fertility is questioned. In the absence of data on oestrus cyclicity, sperm evaluation, organ weights and comprehensive histopathological examination of the reproductive tract, the capability of this two generation reproduction study to demonstrate any effect of quizalofop-P-tefuryl on reproduction is considered less than adequate. On the basis of the limited information available, it is concluded that the NOEL of quizalofop-P-tefuryl on reproduction in the rat is at least 300 ppm.

The two generation reproduction study showed an inconsistent pattern of response to 900 ppm quizalofop-P-tefuryl with respect to pup viability in each generation. Pup viability on day 0 ranged from 75.4% to 88.4% over the four litters in the 900 ppm group. Although variable, these values were consistently lower than the concurrent control range of 89.8% to 100%. However, it is noted that even for the control animals, the pup viability for the F2b litter is inconsistent with that seen in the previous litters (89.8% versus 96.6 to 100%). Pup viability to day 4 was variable and ranged from 51.5% to 90.8% over the four litters in the 900 ppm group (control range 86.3% to 98.0%).

Review of the reported individual animal data showed discrepancies in the numbers of pups live or dead at birth such that the total litter size (number of live plus dead pups) in each litter could not be determined and whether or not pups were born dead or born live and died shortly after could not be established. These data are therefore judged to be unreliable. Furthermore, the likely cause of the effect of 900 ppm on pup viability cannot be determined. It could be that the offspring were adversely affected by *in utero* exposure to quizalofop-P-tefuryl such that their development was impaired becoming incompatible with post natal survival. Typically, this would result in high pup mortality around the time of birth.

An investigative study on quizalofop-P-tefuryl in the rat (Sequani Ltd study number CXE0001, ongoing) has shown treatment-related increases in circulating oestrogen and serum luteinizing hormone. Further information on this study is not yet available. The increases in circulating oestrogen, as a consequence of the PPARα mediated induction of hepatic aromatase, would be expected to affect reproductive parameters in a

variety of ways and while in the female rat there would be no luteinizing hormone effect, the increased oestrogen alone would be expected to perturb the tightly controlled process of reproduction. Once again this MOA, being mediated via increased activity of aromatase following activation of the hepatic PPARα receptor, would be expected to be a 'rat only' phenomenon of no relevance to human hazard assessment (also see Annex I).

Developmental toxicity

Consideration of the data from the preliminary dose range finding study showed an effect of 1250 ppm on neonatal viability of the F1a generation with pup viability on day 0 being 96.4% and on day 4 being 55.6%. These data would suggest that the pups were not compromised in utero; there is no reported data on the presence or absence of milk in the stomachs of the pups that died to investigate the possibility of maternal neglect.

It is therefore concluded that 900 ppm quizalofop-P-tefuryl reduces pup viability, but the cause of the effect cannot be determined due to the unreliability of the data presented in the report of the two generation reproduction study and the limited data reported for the preliminary study. Although these studies clearly have deficiencies, reported findings in the exposed animals were not inconsistent with the proposed hypothesis of perturbation of the hormonal milieu, by a PPARα MOA that would be expected to be rat-specific with no relevance to humans (Annex I).

Hydrocephaly was observed in some of the dead F1b and F2b pups in the 900 ppm group and occurred where most if not all littermates were dead at birth or dead by day 4. As the pup deaths were treatment-related, it is possible that the occurrence of hydrocephaly is also treatment-related. However, pup death in the 900 ppm group occurred in both of the two litters produced per generation but hydrocephaly was observed in only the second litter of each generation; there was no reported occurrence of hydrocephaly in the F1a or F2a litter. This inconsistency suggests that the occurrence of hydrocephaly in this study may be incidental and not treatment-related. This possibility is supported by the absence of hydrocephaly in the rat prenatal developmental toxicity where severe maternal toxicity did cause foetal malformation.

Also of relevance is the absence of detail for the method of examination used to confirm the presence of hydrocephaly in the two generation study. Typically, hydrocephaly in foetuses and neonates is detected by free-hand sectioning of the head following fixation; it is not usually done on dead neonates where autolysis may already be underway rendering the brain tissue unsuitable for sectioning and for evaluation. Whether appropriate examination of the pups was undertaken and whether the diagnosis was correct cannot be confirmed and for this reason the data are judged to be unreliable. It is therefore concluded that the occurrence of hydrocephaly in the two generation study is most likely incidental to the administration of quizalofop-P-tefuryl.

Assessment of prenatal developmental toxicity in the rat was conducted using dose levels of 0, 10, 30 and 100 mg/kg bw/day administered on gestation days 6 through to 15. The highest dose level of 100 mg/kg bw/day was found to be lethal to 40% of the animals with deaths occurring between days 15 and 18. There was a marked effect on maternal body weight at this dose level with body weight gain between days 6 and 16 being only 17% in comparison with the controls (i.e. 47g was gained by controls and only 8 g by rats given 100 mg/kg bw/day - based on those animals surviving to term with live foetuses in utero).

The maternal toxicity seen at 100 mg/kg bw/day was extremely severe and is believed to be responsible for the adverse effects seen on the litters including increased post-implantation loss, a decreased number of viable foetuses and foetuses with a mean body weight lower than controls by approximately 30% (the control mean body weight was 3.4 g and the test group mean was 2.4 g). In addition, 3 of the 15 surviving rats given 100 mg/kg bw/day had no live foetuses at termination having totally resorbed their litters. The foetuses were not only compromised in their viability and growth but in their development with various malformations (including anasarca, cleft palate, diaphragmatic hernia, gastroschisis, omphalocoele, interventricular septal cleft, anal atresia and tail malformation) and variations (essentially reduced or absent ossification) being observed. This prenatal developmental toxicity study in the rat has generated adverse results for developmental effects at a maternally lethal dose of quizalofop-P-tefuryl. Although reported as teratogenicity and developmental toxicity the effects seen in the offspring are considered attributable to the

severe maternal toxicity at the time of major organogenesis; they are therefore consequential and not a direct effect of quizalofop-P-tefuryl on the embryo/foetus.

For a prenatal developmental toxicity study, the highest dose level tested should induce some developmental and/or maternal toxicity (clinical signs or a decrease in body weight) but not death or severe suffering (OECD Test Guideline 414). The maternal effects of the highest dose level of 100 mg quizalofop-P-tefuryl/kg bw/day clearly exceed these criteria and the results cannot be considered appropriate for the determination of developmental effects. The intermediate dose level of 30 mg quizalofop-P-tefuryl/kg bw/day induced clinical signs (anogenital staining) in the pregnant females and, in line with the test guideline criteria, should be regarded as an appropriate highest dose level for the prenatal developmental toxicity evaluation. On this basis, the NOEL for maternal toxicity is 10 mg/kg bw/day and the NOEL for developmental toxicity is 30 mg/kg bw/day. There was no evidence of teratogenicity at 30 mg/kg bw/day.

Assessment of prenatal developmental toxicity in the rabbit was conducted using dose levels of 0, 2.5, 10 and 20 mg/kg bw/day administered on gestation days 7 through to 19. These dose levels were selected on the basis of the results of a preliminary study which assessed 0, 2.5, 10, 25, 50 and 100 mg/kg bw/day. Interpretation of the results of the preliminary study was limited by the high proportion of animals failing to survive to termination with live foetuses in utero. However, the effects of 50 and 100 mg/kg bw/day were clear with maternal death and body weight loss being observed. The effects of 25 mg/kg bw/day were less conclusive, with there being only 2 pregnant rabbits at termination and with the pattern of body weight reduction being inconsistent with that seen at the higher dose level of 50 mg/kg/day. However, the reported conclusions of the study were that maternal toxicity was evident at doses of 25 mg/kg/day and greater and thus the highest dose level selected for the definitive study was 20 mg/kg bw/day. No maternal toxicity was seen at this dose level in the definitive study.

The maternal toxicity seen in the rat and rabbit studies displays a steep dose response to quizalofop-P-tefuryl in both species. For the rabbit, an appropriate highest dose level for the prenatal developmental toxicity, in line with the OCED criteria, is greater than 20 mg/kg bw/day but less than 50 mg/kg bw/day i.e. within a narrow window.

4.11.5 Comparison with criteria

Assessments made previously

When the harmonised classification of quizalofop-P-tefuryl was first considered, leading to the current entry in Annex VI of the CLP Regulation, the rat 2-generation study was the only reproductive toxicity study that had been submitted by the Applicant. The rat and rabbit developmental studies were not considered at that time.

More recently, taking into account also the developmental toxicity studies, an EFSA peer review group concluded in 2008 that classification for developmental toxicity (equivalent to Repr 2 under CLP) was a possible option. However they did not reach a firm conclusion. In the peer review report for quizalofop-P-tefuryl dated December 2008, the discussion of the PRAPeR Expert Meeting 54 Sub-group1 (07 – 11 July 2008) Mammalian Toxicology is documented on page 5 of 18 as follows:

In the DAR the RMS considered the rabbit study not acceptable because it only went up to 20 mg/kg bw/day where no effects were observed. Therefore it can only be concluded that the active is not teratogenic up to this dose level. Based on this limited dose range the validity of this study was questioned (it was noted that a further study had been proposed as a data requirement in the DAR). There was a range finding study but only a very limited number of animals were tested. It was noted however, that in rats a lot of major malformations were observed at a dose level that resulted in maternal mortality (100 mg/kg bw/day). The dosing regime of this study also had limitations. In the rat two generation study there was a number of malformations observed at 50 mg/kg bw/day. On balance it was agreed that the rabbit was not adequately tested and there was a requirement for a further rabbit study done to the current guidelines (i.e. up to maternal toxicity). However, it was considered that this did not preclude concluding on the risk assessment of this substance, as there were clear no effect levels and margins of safety would be sufficient, and the study

would not be used for setting reference values, but experts agreed that the R63? should be proposed to ECHA, because of the limitations of the studies.

In this extract, the term "R63?" is assumed to be equivalent to "the possibility of classification for developmental toxicity in Repr Cat 3; R63 (according to 67/548/EEC)".

Further to this, the Rapporteur Member State (Finland) commented on the main data submitter/applicant comments with respect to classification and labelling is documented (on page 15) as follows:

RMS 04.06.08: The following classification is proposed by DE: T, R22, R48/22, R40, R61, R62. RMS has proposed Xn; R22, R40, R43 and R48/22. R40 is based on Leydig cell tumours (and white tan foci) at and above doses of 39.2 mg/kg bw/day and renal squamous cell carcinoma. R48/22 is based on testicular effects observed in subchronic and chronic studies; testicular degeneration, aspermatogenesis and aspermia at doses of 51-134 mg/kg bw/day and decreased fertility at 52.8-68.8 mg/kg bw/day. The lowest dose levels are slightly above 50 mg/kg bw/day, but considering that the dietary dosing is not very accurate due to spillage, the level is about 50 mg/kg bw/day. R48/22 or R62 should be considered due to testicular effects. R48/22 is preferred because the fertility effects were observed at dose levels toxic to parents and may be considered secondary to parental toxicity and R62 is not justified. RMS does not agree with R61 based on the present studies.

The proposed classification following this review was therefore: Xn; R22, Carc Cat 3; R40, R43 and (as an additional option, but there being no agreement) Repr Cat 3; R63.

The EFSA Scientific Report (2008) 205, 1-216 conclusion of the peer review of quizalofop-P states, for quizalofop-P-tefuryl, that:

In the two-generation rat study, the NOAEL for parental and offspring was 1.4 mg/kg bw/day based on increased liver weight and liver hypertrophy in adult males and females, vacuolar changes in pituitary in adult males, decreased body weights during lactation in F1 generation and decreased viability during early lactation. The NOAEL for reproduction was 16.9 mg/kg bw/day. In developmental toxicity studies in rats the maternal NOAEL was set at 10 mg/kg bw/day, whereas the developmental NOAEL was 30 mg/kg bw/day based on increased post-implantation loss per dam with concomitant lower number of viable foetuses and increased number of malformations at maternally toxic dose. In rabbits, the NOAEL was 20 mg/kg bw/day for maternal and developmental toxicity. However, the rabbit was not adequately tested but this was considered not to preclude concluding on the risk assessment. Due to the limitations of the studies, Repr. Cat. 3; R63? ("Possible risk of harm to the unborn child") was agreed for proposal to the European Chemicals Agency (ECHA).

Proposal drafted by the Applicant

Under CLP, substances are allocated to one of two categories or are regarded as requiring no classification. Category 1 includes substances known or presumed to be human reproductive toxicants and category 2 includes substances suspected to be human reproductive toxicants.

Substance are classified in Category 1 when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).

There are no human data available on the potential reproductive toxicity of quizalofop-P-tefuryl. As such, a classification in Repr 1A cannot be supported.

Whilst the data from the two generation study provide evidence for an effect on fertility, as discussed above, there is insufficient evidence to consider quizalofop-P-tefuryl to be a presumed human reproductive toxicant and to place it in Category 1B. The effect on fertility was determined from the mating of animals and from limited histopathology only; the study does not include determination of oestrus cyclicity, sperm motility and

morphology or weights of the reproductive organs. Despite the clear deficiencies of the two-generation reproduction study, reported results are not inconsistent with the proposed MOA which depends upon aromatase induction and consequential hormone perturbation, secondary to activation of the PPARα receptor in the liver, a widely accepted rat only phenomenon of little if any relevance to humans. This PPARα MOA and therefore its non-relevance to humans (Annex I), is also consistent with the experimental results related to testicular findings from repeat dose and carcinogenicity studies. It is concluded that there is sufficient reason to preclude the need for Category 1B classification. Category 2 classification is considered below.

Substances are classified in Category 2 when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

The influence of parental toxicity on reproductive effects is considered under CLP. *In general all findings on reproductive toxicity should be considered for classification purposes irrespective of the level of parental toxicity. A comparison between the severity of the effects on fertility/development and the severity of other toxicological findings must be performed.*

Fertility effects: Adverse effects on fertility and reproductive performance seen only at dose levels causing marked systemic toxicity (e.g. lethality, dramatic reduction in absolute body weight, coma) are not relevant for classification purposes. There is no established relationship between fertility effects and less marked systemic toxicity. Therefore it should be assumed that effects on fertility seen at dose levels causing less marked systemic toxicity are not a secondary consequence of this toxicity. However, mating behaviour can be influenced by parental effects not directly related to reproduction (e.g. sedation, paralysis), and such effects on mating behaviour may not warrant classification.

Systemic toxicity was associated with administration at the highest dose of 900 ppm. Parental body weight gain was lower than controls during the pre-mating period and increased liver weight and hepatic hypertrophy were seen in the parents at termination. Other endpoints which might clarify or confirm the effect of 900 ppm quizalofop-P-tefuryl on reproduction have not been included in this study i.e. oestrus cyclicity, sperm evaluation, reproductive organ weights and comprehensive histopathological examination of the reproductive tract. It is therefore concluded that the existing two generation reproduction study is not sufficiently robust to reliably confirm an effect of quizalofop-P-tefuryl on fertility. Although there is some evidence to suggest an effect of 900 ppm on the fertility of the F1 animals, this potential is only at systemically toxic doses and might indicate most appropriate classification for quizalofop-P-tefuryl to be Category 2 H361f.

However, the reported increased plasma concentrations of oestrogen and the decreased circulating testosterone, which have been shown for quizalofop-P-tefuryl and other PPARs, would result in an altered hormonal milieu which would be expected to result in altered reproductive parameters. Since this is expected to be a rat specific, hepatic effect of PPARs, then in the absence of the hepatic effects of PPARs any hormonal disruption would not be expected to function in man. Although the two-generation reproduction study clearly has deficiencies, some of the reported findings in the exposed animals were consistent with the proposed hypothesis of increased conversion of testosterone to oestrogen. For example, vacuolar change in cells of the *pars distalis* in the pituitary gland was observed in F0 and F1 male (only) rats at 300 and 900 ppm. This is considered secondary to the hepatocyte hypertrophy and not a direct effect on the pituitary gland, indicating the presence of so-called 'castration cells' which are LH secreting, and support the hypothesis of reduced circulating testosterone; only being seen in male rats. In consideration of a plausible PPARα hypothesis for non-human relevance (Annex I), and consistency of the experimental results related to findings from repeat dose and reproductive studies for quizalofop-P-tefuryl (despite the deficiencies of the two-generation reproduction study) and additional information from other quizalofop acid generators (Annex II) it could be considered that there is sufficient reason to preclude the need for any classification for fertility under CLP.

Developmental effects: Adverse effects on postnatal survival and growth seen only at dose levels causing maternal toxicity may be due to lack of maternal care or other causes such as adverse effects on or via lactation or developmental toxicity. In case post-natal effects are caused by lack of maternal care classification for developmental effects may not be warranted.

In the two generation reproduction study, the highest dose of 900 ppm had an effect on pup growth in the F0 and F1 generations. In addition, there was evidence to suggest that this dose level had an effect on pup viability. However, the data for each of the 2 litters produced per generation was inconsistent even for the control animals. Detailed examination of the reported individual animal data was unable to confirm the total litter size (number of live plus dead pups) in each litter at birth. It could not be determined if pups were born dead or if they were born live and died shortly after and prior to day 4. As a consequence, the data are judged to be unreliable. The preliminary dose range finding study confirmed an effect of 1250 ppm on neonatal viability of the F1a generation with pup deaths occurring between days 0 and 4 and, the absence of any effect of 625 ppm. The two generation reproduction study indicates an effect of 900 ppm on pup viability but, the reported data are such that the timing of pup death cannot be established nor the cause confirmed.

Hydrocephaly was observed in some of the dead F1b and F2b pups where most if not all littermates were dead at birth or dead by day 4. As the pup deaths were treatment-related, it is possible that the occurrence of hydrocephaly was treatment-related despite the absence of occurrence in the F1a and F2a litters. The method of examination used to confirm the presence of hydrocephaly is not reported. Whether appropriate examination of the pups was undertaken and whether the diagnosis was correct cannot be confirmed. The data are therefore judged to be unreliable. Hydrocephaly was not detected in the rat prenatal developmental toxicity where severe maternal toxicity did cause foetal malformation.

In conclusion, the two generation reproduction study forms the basis for classification because neither the rat nor rabbit prenatal developmental toxicity studies showed any developmental effects at dose levels that were not associated with maternal lethality. As such, it is concluded that classification in Category 1A or 1B are not applicable.

At the highest dose of 900 ppm, quizalofol-P-tefuryl had an effect on postnatal survival and pup growth in the F0 and F1 generations. Parental body weight gain was lower than controls during the pre-mating period and increased liver weight and hepatic hypertrophy were seen in the parents at termination. Similar systemic effects were seen at the lower dose of 300 ppm. As 900 ppm quizalofop-P-tefuryl caused neonatal deaths and impaired pup growth, the substance might be considered to warrant classification with Repr 2; H361d for developmental effects. However, a simplified hypothesis that briefly defines the key, causative, events is the activation of PPARα which leads to induction of hepatic aromatase, an enzyme that catalyses conversion of testosterone to oestrogen (also see Annex I). As a consequence there is the potential for some increase in oestrogen levels and, since it is the key hormone for reproduction, this might be expected to have significant adverse effect in rats, as a rat specific mode of action. In consideration of a plausible PPARα hypothesis for non-human relevance and consistency of the experimental results related to findings from repeat dose and reproductive studies for quizalofop-P-tefuryl (despite the deficiencies of the two-generation reproduction study) and other quizalofop acid generators (Annex II) it could be considered that there is sufficient reason to preclude the need for any classification for developmental toxicity.

Concluding comments

The detailed review of the reproductive toxicity of quizalofop-P-tefuryl undertaken by the Applicant in preparation of this CLH report (above) led them to conclude that either Repr. 2; H361fd or no classification could be supported by the available data. This would apply to both the possibility of effects on fertility/reproductive function and developmental toxicity.

However, when additionally taking into account the wider toxicological database, relating to the postulated mode of action for this substance (mediated via activation of PPARα receptors), the Applicant concluded that no classification was the most appropriate position to take. In support of this, the Applicant noted the consistency of the experimental results related to findings from repeat dose and reproductive studies for

quizalofop-P-tefuryl (despite the deficiencies of the two-generation reproduction study) and other quizalofop acid generators (Annex II).

Formally, as Dossier Submitter, the UK CLP Competent Authority view is that classification with at least Repr 2; H361fd is appropriate. It was considered that the Applicant had made a reasonable attempt to provide a critical review of the data and that the link they made to a mode of action involving activation of PPARα receptors was not unreasonable. It was also noted that the Applicant had paid due attention to the review undertaken recently by EFSA. However, significant adverse effects on both fertility/reproductive function and development had been seen in the available animal studies with quizalofop-P-tefuryl and, in such circumstances, it is appropriate to seek definitive evidence before dismissing their relevance to humans. The UK view is that this level of supporting evidence is not available for quizalofop-P-tefuryl. The adverse effects seen in animals treated with quizalofop-P-tefuryl demonstrate clearly a potential hazard to fertility/reproductive function and development. Such data is sufficient to justify classification with Repr 1B. However, it remains a matter of expert judgement whether there is sufficient uncertainty surrounding the quality of the studies, the completeness of the parameters measured, and the possibility of a mode of action that would not be relevant to humans to conclude that Repr Cat 2 is more appropriate. With due consideration for the views of the Applicant, the UK CA proposes Repr 2; H361fd for assessment by ECHA.

Repr 2; H361fd (NB. The Applicant proposed no classification for reproductive toxicity)

4.12 Other effects

4.12.1 Non-human information

4.12.1.1 Neurotoxicity

Quizalofop-P-tefuryl is not chemically or structurally related to organophosphates or other chemicals capable of inducing delayed neurotoxicity. However, a specific acute neurotoxicity study in the rat has been conducted with quizalofop-P-tefuryl (York, 1993b; DAR B.6.8.2.1) where the NOAELs were 400 mg/kg bw in males and >800 mg/kg bw in females.

4.12.1.2 Immunotoxicity

No information

4.12.1.3 Specific investigations: other studies

4.12.1.4 Human information

No information

4.12.2 Summary and discussion

Quizalofop-P-tefuryl is concluded not to be neurotoxic. There is no evidence of immunotoxicity.

4.12.3 Comparison with criteria

Quizalofop-P-tefuryl is concluded not to be neurotoxic therefore no classification is warranted. There is no information on or evidence of immunotoxicity.

4.12.4 Conclusions on classification and labelling

No classification

5 ENVIRONMENTAL HAZARD ASSESSMENT

5.6 Degradation

5.6.1 Stability

Table 28: Summary of relevant information on stability

Type of Study	DT50	Comments	Study
Hydrolysis Buffer (pH 5.1, 7.0, 9.1) + water Test material: Quizalofop-P-tefuryl Purity: 97.7% 0.4 mg/L; 22 ºC, dark Guideline: US EPA 40 CFR 160 and BBA Merkblatt No 55; equivalent or similar to OECD Guideline 111 (Hydrolysis as a Function of pH) DT50 values were calculated by regression analysis Klimisch 2 (reliable with restrictions)	pH 5.1: 8.2 d pH 7.0: 18.2 d pH 9.1: 7.2 h	Quizalofop-P-tefuryl rapidly degraded in aqueous solution under alkaline conditions but it was more stable in neutral and acidic solutions. The study mainly followed OECD guideline 111 but it was not conducted according to all its recommendations. For example hydrolysis products were not identified. In addition the performance of the test was quite shortly and incompletely reported. The test report did not include the GLP Compliance Statement. It, however, was reviewed by quality assurance and considered to accurately reflect the raw data generated during the conduct of the study.	Riggs, 1989 (DAR B.8.4.1.1 Study 1)
Hydrolysis [14C-phenylquinoxaline]-Quizalofop-P-tefuryl Purity: 99.2% Buffer (pH 5.1, 7.0, 8.9) + water 0.8-1.0 mg/L; 25°C, dark Guideline: EPA Guideline Subdivision N 161-1 (Hydrolysis); equivalent or similar to OECD Guideline 111 (Hydrolysis as a Function of pH) The rate constants and DT50 values were calculated by	pH 5.1: 277 d pH 7.0: 4.3 d pH 8.9: 8.7 h	^{14}C labelled quizalofop-P-tefuryl (purity: 99.2%) rapidly degraded in aqueous solution under alkaline conditions but it was more stable in neutral and acidic solutions. Degradation proceeded via ester hydrolysis to form quizalofop-acid. The study mainly followed OECD guideline 111 but it was not conducted according to all its recommendations. For example preliminary tests were not performed and the amounts of hydrolysis products were not reported. The GLP Compliance Statement and GLP Quality Assurance Statement were presented in same document. In addition, in that document it was informed that portions of the project were conducted before the effective date of GLP's.	Korpalski, 1990a (DAR B.8.4.1.1 Study 2)

Type of Study	DT50	Comments	Study
regression analysis. Klimisch 2 (reliable with restrictions)			
Hydrolysis Test material: [14C-phenylquinoxaline]-Quizalofop-acid Purity: 98.0% Buffer (pH 4.0, 7.0, 9.0) 1.0 mg/L; 50°C; dark Guideline: EU Method C.7 (Degradation: Abiotic Degradation: Hydrolysis as a Function of pH) Klimisch 1 (reliable without restriction)	Hydrolytically stable	Quizalofop-acid (purity: 98.0%) was stable to hydrolysis in aqueous buffer solutions (pH 4, 7 and 9).	Yu, 1999 (DAR B.8.4.1.2)
Photolysis Buffer (pH 5.0) Test material: [14C-phenylquinoxaline]-Quizalofop-P-tefuryl Purity: 99.6% 3.3 mg/L; 25°C Xenon arc lamp (699 W/m^2) Klimisch 2 (reliable with restrictions)	DT50: 25.3 hours (1.1 days) Main metabolite Quinoxaline-2-carboxylic acid (max. 11.3%)	Quizalofop-P-tefuryl was rapidly and extensively photodegraded in aqueous solution forming one major degradation product which was identified as Quinoxaline-2-carboxylic acid. The study had some deviations/deficiencies. The GLP Compliance Statement and GLP Quality Assurance Statement were presented in same document and the test temperature was 25±1ºC instead of recommended 20±3ºC. The study, however, mainly followed the recommendations of SETAC Europe. For example the pH value in the test was selected such that the hydrolysis rate of the substance in the test system was minimized.	Korpalski, 1990b (DAR B.8.4.2.1 Study 1)
Photolysis[1] Buffer (pH 5.0) Test material: [14C-phenylquinoxaline]-Quizalofop-P-tefuryl Purity: >95% 1.5 mg/L; 25°C Xenon (eq. 30 days/UK) EPA Guideline Subdivision N 161-2 (Photodegradation Studies in Water) The DT50 and DT90 values were calculated using first order reaction kinetics by	DT50: 2.4 days DT90: 8.0 days (no metabolites >10%)	Quizalofop-P-tefuryl is rapidly and very extensively photodegraded in aqueous solution at pH 5. The study had some deviations/deficiencies. The material balance of three sampling dates was less than 90 % of the applied radioactivity. These sampling occasions were, however, Days 12, 22 and 30 when one half-life of the test chemical was achieved. In addition the test temperature was 25±1ºC instead of recommended 20±3ºC. The study, however, mainly followed the recommendations of SETAC Europe. For example the pH value in the test was selected such that the hydrolysis rate of the substance in the test system was minimized. Additionally the study was conducted in compliance with GLP.	Lewis, 1999 (DAR B.8.4.2.1 Study 2)

Type of Study	DT50	Comments	Study
regression analysis. Klimisch 2 (reliable with restrictions)			

H = Hours d = Days

1 = The quantum yield calculated based on the values obtained in this study was 0.012 % (Schocken, 1999). The theoretical lifetime in upper surface water calculated based on the quantum yield value and the sunlight intensities for latitudes 40-50 degrees North was 10.4 hours (Schocken, 2000).

Quizalofop-P-tefuryl rapidly degraded in hydrolysis studies (Riggs, 1989; Korpalski, 1990a) conducted at 22 – 25ºC under alkaline conditions (DT_{50} 7.2 – 7.8 hours, pH 8.9 – 9.1). It was more stable in neutral and acidic solutions where the half-life values were 4.3 – 18.2 days (pH 7) and 8.2 – 277 days (pH 5.1). Hydrolytic degradation proceeded via ester hydrolysis to form quizalofop (the information on the amount of quizalofop formed was not reported). The metabolite quizalofop was stable under sterile hydrolysis conditions at 50ºC at pH 4, 7 and 9 (Yu, 1999).

In two photolytic degradation studies (Korpalski, 1990b; Lewis 1999), quizalofop-P-tefuryl was rapidly degraded in aqueous solutions at pH 5 with the DT_{50} values of 1.1 – 2.4 days. In one of the two studies, the photodegradation product quinoxaline-2-carboxylic acid was found up to 11.3% AR at the study end (32.2 hours).

5.6.2 Biodegradation

5.6.2.1 Biodegradation estimation

No information

5.6.2.2 Screening tests

Table 29: Summary of relevant information on screening tests (ready biodegradation)

Type of Study	Result	Comments	Study
Ready bio-degradation Act. Sludge (non-adapted) + basal med. Test material: Pantera technical Purity: 93.5% 2.0 mg/L; 20°C; Dark Guideline: OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test) (draft) Klimisch 2 (reliable with restrictions)	Biodegradation: 8% /28d	Based on the results obtained in the test quizalofop-P-tefuryl (Pantera) is not a readily biodegradable substance. The Quality Assurance Statement included in the test report was incomplete. The test report, however, included the GLP compliance statement and the study was mainly conducted according to OECD guideline 301D.	Hanstveit & Pullens, 1992 (DAR B.8.4.3.1)

d = Days

Based on the results obtained in a biodegradation test (Hanstveit & Pullens, 1992), quizalofop-P-tefuryl is not a readily biodegradable substance.

5.6.2.3 Simulation tests

Table 30: Summary of relevant information on degradation in simulation tests

Type of study	DT50	Other results including DT90	Comments	Study
Aerobic water/ sediment Test material: [14C-phenylquinoxaline]-Quizalofop-P-tefuryl Purity: 97.4% River system (Rhine) & Pond system (Swizerl.) 100g/ha 20°C, Dark Guideline: SETAC – Europe, 1995, Part 8 Klimisch 2 (reliable with restrictions)	total system: 2.5h QUIZ: 26.5 d	DT90 (tot): 8.3h CO_2: 15%/98d bound: 35%	Quizalofop-P-tefuryl disappeared quickly from both river and pond aquatic systems. Hydrolysis to the major degradate quizalofop-acid (QUIZ) was apparent initial reaction. In addition three other metabolites, 4-(6-chloroquinoxalin-2-yloxy)phenol (CQOP), 2-[4-(6-chloro-3-hydroxyquinoxalin-2-yl)oxy]phenoxypropionic acid (QUIZ-OH) and 2,3-dihydroxy-6-chloroquinoxaline (CHHQ), reached levels of 10 % of the applied radioactivity (water + sediment/sampling interval). The dissipation finally resulted in incorporation into sediment-bound residues and degradation to CO_2. The study mainly followed the recommendations of OECD guideline 308 although it was performed before this guideline was available. The sediment phase of the test systems can be regarded as anaerobic.	Seyfried, 1998 (DAR 8.4.3.2 Study 2)
	total system: 3.2 h QUIZ: 34.3 d	DT90 (tot): 10.5h CO_2: 10%/98d bound: 42%		
Aerobic water/ sediment, River system (Rhine) & Pond system (Swizerl.) Test material: [14C-phenyl]-label Purity: 96.3% 140 g/ha; 20°C, dark Guideline: OECD Guideline 308; EPA Subdivision N Pesticide Guideline 162-4 (Aerobic Aquatic Metabolism); SETAC – Europe, 1995, Part 8 Klimisch 1 (reliable without restriction)	total: <1.0 d QUIZ: 25.3 d CQOP: 40.0 d	DT90 (tot): <1.0d CO_2: 46%/102 d bound: 29%	Quizalofop-P-tefuryl was rapidly degraded to the main metabolite QUIZ with a DT50 of about 2 hours. The latter was then further metabolized to CQOP and many small fractions including QUIZ-OH and CQOP-OH which were finally mineralized to CO_2 or incorporated into the sediment bound residues.	Diehl, 2004
	total: <1.0d QUIZ: 35.1 d CQOP: 42.3 d	DT90 (tot): <1.0d CO_2: 45%/150d bound: 27%		
Aerobic water/ sediment, River system (Rhine) & Pond system (Swizerl.)	total: 0.2 days THFA: 0.3 d THFAC: 1.3 d	DT90 (tot): 0.5 d CO_2: 81%/28d bound: 11%	Quizalofop-P-tefuryl disappeared rapidly from the aquatic systems by hydrolysis to the transient metabolite tetrahydrofurfuryl alcohol (THFA), which was further	Van der Gaauw, 2004

Type of study	DT50	Other results including DT90	Comments	Study
Test material: [14C-5-furfuryl]-Quizalofop-P-tefuryl Purity: 98.0% 140 g/ha; 20°C; dark Guideline: OECD Guideline 308; EPA Subdivision N Pesticide Guideline 162-4 (Aerobic Aquatic Metabolism) Klimisch 1 (reliable without restriction)	total: 0.01 d THFA: 0.4 d THFAC: 1.6 d	DT90 (tot): 0.03d CO_2: 78%/28d bound: 11%	oxidized to tetrahydrofuroic acid (THFAC). These metabolites disappeared mainly by mineralization. A second way of their disappearance was adsorption to sediment. However, the bound residues were also shown to decrease by further mineralization. The study mainly followed the recommendations of OECD guideline 308 and it was conducted in compliance with GLP.	
Supplemental/supporting studies, not considered acceptable for risk assessment				
Metab. In pond water (Canada) [14C-phenylquinoxaline]-Quizalofop-P-tefuryl (purity 96.6 %) 0.5 mg/L; 5 & 25°C 16:8-hour light/dark Guidelines for registration of pesticides in Canada, Environmental Chemistry and Fate (T-1-255).	5ºC: 3.3-16.0 d1 25ºC: 5.5-17 h1	QUIZ was the major metabolite	Quizalofop-P-tefuryl was rapidly degraded in natural water under aerobic conditions primarily to its corresponding acid by hydrolysis. Further degradation by oxidation and hydrolysis to form Quizalofop-P-tefuryl-N-oxide, 6-chloro-2-hydroxyquinoxaline (CHQ) and CQOP also occurred. The rate of degradation was dependent on the temperature and pH of the system. The study was conducted in compliance with GLP. It was not, however, carried out according to OECD guideline 308 or the recommendations of SETAC-Europe on water/sediment studies. The main deviation was that the test system consisted only of pond water and sediment was not used. Therefore the results cannot be considered acceptable for risk assessment but they can be regarded as supporting data on the degradation pathway of quizalofop-P-tefuryl in water.	Concha, 1996a (*Due to identified issues, a robust summary not included in IUCLID. Refer to DAR B.8.4.3.2 Study 1 for additional details.*)
Anaer. Water/sediment, Pond water + sediment [14C-phenylquinoxaline]-Quizalofop-P-tefuryl (purity 98.1 %) 0.5 mg/L, 5 & 25°C, dark Guidelines for registration of pesticides in Canada (T-1-255). 1987;	5ºC: 15 d (ster.) 32 h (non-ster.)1 25ºC: 29 d (ster.), 4.5h (non-ster.)1	CO_2: <0.6 %/ 150 d bound residues: 0.53-7.4%	Quizalofop-P-tefuryl was rapidly degraded in natural water/sediment systems under anaerobic aqueous conditions primarily to its corresponding acid by hydrolysis. Further degradation by oxidation and hydrolysis to form Quizalofop-P-tefuryl-N-oxide, CHQ and CQOP also occurred. The rate of degradation was dependent on the temperature and microbial viability of the system. According to OECD guideline 308 the sediment and water are regarded as anaerobic once the redox	Concha, 1996b (*Due to identified issues, a robust summary not included in IUCLID. Refer to DAR B.8.4.3.2 Study 5 for additional details.*)

Type of study	DT50	Other results including DT90	Comments	Study
USA, EPA Pesticide Assessment Guidelines, Subdivision N, Chemistry: Environmental Fate, Section 162-3 (Anaerobic aquatic metabolism), 1982			potential (Eh) is lower than -100 mV. In this study the redox potential was in the range +333 to -100 mV. Thus the RMS considers that the water/sediment systems of this experiment cannot be regarded totally anaerobic. The results can, however, be regarded as supporting data on the degradation pathway of quizalofop-P-tefuryl.	

H = Hours d = Days
1 = These DT50 values should be considered as supporting data (deficiencies in test method).

In dark natural sediment water systems (Seyfried, 1998; Diehl, 2004; Van der Gaauw, 2004) quizalofop-P-tefuryl degraded very rapidly (DT50 and DT90 <1 day) to the metabolites quizalofop-acid (QUIZ) (max. 94% AR in water and max. 53% AR in the sediment), tetrahydrofurfuryl alcohol (THFA) (max. 16.5% AR in the water), tetrahydrofuroic acid (max. 39.1% AR in the water), 4-(6-chloroquinoxalin-2-yloxy)phenol (max. 11.6% in the sediment) and dihydroxy-quinoxaline (max. 16.4% AR in the sediment).

5.6.3 Summary and discussion of degradation

Quizalofop-P-tefuryl rapidly degraded in hydrolysis studies conducted at 22 - 25ºC under alkaline conditions (DT50 7.2 – 8.7 hours, pH 8.9 – 9.1). It was more stable in neutral and acidic solutions where the half-life values were 4.3 - 18.2 days (pH 7) and 8.2 - 277 days (pH 5.1). The main hydrolysis product quizalofop-acid (QUIZ) is considered hydrolytically stable.

Quizalofop-P-tefuryl was rapidly photodegraded in aqueous solutions at pH 5 with the DT50 values of 1.1 - 2.4 days. The major degradation product was CO_2. In one study quinoxaline-2-carboxylic acid was once found at levels of greater than 10 % of applied radioactivity (11.3 %).

Based on the results obtained in biodegradation test quizalofop-P-tefuryl is not a readily biodegradable substance.

In water sediment/systems at 20ºC quizalofop-P-tefuryl rapidly degraded (DT50 and DT90<1 day) primarily by hydrolysis to QUIZ and THFA. QUIZ then degraded with a DT50 of 25 – 35 days and DT90 of 88 – 117 days and THFA with a DT50 of 0.3 – 0.4 days and DT90 of 0.9 – 1.4 days in the total system. Further degradation by oxidation and hydrolysis to form THFAC, quizalofop-P-tefuryl-N-oxide, CHQ and CQOP and via oxidation to QUIZ-OH and CHHQ also occurred. Four of these metabolites, QUIZ-OH, CHHQ, CQOP and THFAC, reached levels of 10 % of the applied radioactivity in the total system. At the end of water/sediment studies CO_2 accounted for 10 – 81 % and unextractable residues for 11 – 42 % of the applied radioactivity.

In conclusion quizalofop-P-tefuryl undergoes rapid primary degradation (in this case fairly rapid hydrolysis) and ultimate mineralisation. It cannot, however, be considered to be readily biodegradable. Consequently, following current CLP guidance, quizalofop-P-tefuryl does not meet the criteria for “rapid degradability”.

5.7 Environmental distribution

5.7.1 Adsorption/Desorption

Due to the rapid degradation of quizalofop-P-tefuryl in soil under aerobic conditions, batch equilibrium studies with the parent compound were not performed.

5.7.2 Volatilisation

The vapour pressure of quizalofop-P-tefuryl (3.4×10^{-7} or $<7.9 \times 10^{-6}$ Pa at 25ºC) is low. Thus it is very probable that this substance will not evaporate in significant amounts. On the basis of Henry's law constant (3.9×10^{-5} or 9.0×10^{-4} Pa.m^3.mol^{-1}) quizalofop-P-tefuryl has no tendency to volatilise from aquatic solution.

The atmospheric lifetime of quizalofop-P-tefuryl was calculated to be 2.7 hours (Schocken, 2002). Thus it is not expected that the compound can be carried in the gaseous phase over long distances or can accumulate in air.

5.7.3 Distribution modelling

Not relevant to this submission

5.8 Aquatic Bioaccumulation

5.8.1 Aquatic bioaccumulation

5.8.1.1 Bioaccumulation estimation

Pesticides with high bioaccumulation potential could theoretically bear a risk of secondary poisoning for birds if contaminated prey like fish or earthworms are taken up. The log Pow of quizalofop-P-tefuryl is 4.32 and therefore is in excess of the trigger value of 4, suggesting a potential for bioaccumulation.

5.8.1.2 Measured bioaccumulation data

Table 31: Summary of relevant information on aquatic bioaccumulation

Method	Results	Reference
Lepomis macrochirus aqueous (freshwater) flow-through ^{14}C-quizalofop-P-tefuryl (radiochemical purity 99.9%) Total uptake duration: 28 d Total depuration duration: 14 d Details of method: Bioconcentration factors for the uptake period were determined by dividing the tissue concentration by the running mean concentration in water up to and including that day. The uptake rate constant (K1; mg/kg in fish/mg/L in water/day) and depuration rate (K2; day^{-1}) were determined by the Dow BIOFAC computer program. Guideline: EPA OPP 165-4 (Laboratory Studies of Pesticide Accumulation in Fish) Klimisch 1: (reliable without restriction)	Uptake reached steady state plateau after seven days exposure (time to reach 90% of steady state: 3.1±0.9 days). Depuration was very rapid with > 97% of residues present at steady state eliminated within 14 days. DT50: 0.94 d Maximum BCF in whole fish was 340 after 28 days exposure. Uptake rate constant (K1): 150 mg/kg fish/mg/L water/day Depuration (loss) rate constant (K2): 0.74 mg/kg fish/mL water/day	Burgess, 1991 (DAR B.9.2.3.1)

The log Pow of quizalofop-P-tefuryl is 4.32 and therefore triggered the need for a bioaccumulation study. In a flow-through study with bluegill sunfish *Lepomis macrochirus* the maximum bioconcentration factor (BCF) of 340 for whole fish was determined (Burgess, 1991). However, depuration is rapid, >97 % after 14

days, with an elimination half-life of less than 1 day. It can therefore be concluded that the risk of bioaccumulation in aquatic food chains is low, based on the BCF (whole fish). The metabolite, Quizalofop-acid, was considered not to bio-accumulate, with a log Pow of < 4; as were the other metabolites (EFSA, 2008).

5.8.2 Summary and discussion of aquatic bioaccumulation

Although the log Pow of quizalofop-P-tefuryl is > 4, a fish bioaccumulation study demonstrated a low risk of bioaccumulation in aquatic food chains.

5.9 Aquatic toxicity

Table 32: Summary of relevant information on aquatic toxicity

Method	Results	Reference
Bluegill sunfish *(Lepomis macrochirus)* Freshwater, flow-through Test material purity: 92.7% Nominal concentrations: 0.12, 0.23, 0.46, 0.93 and 1.9 mg/L Mean measured concentrations: 0.10, 0.14, 0.34, 0.75 and 1.4 mg/L EPA OPP 72-1 (Fish Acute Toxicity Test) Klimisch 1 (reliable without restriction)	LC50 (96 h): 0.23 mg/L test mat. (meas. (arithm. mean))	Bowman (1990a) (DAR B.9.2.1.1 Study 2)
Rainbow trout *Freshwater, flow-through* *Test material purity: 92.7 %* *USA, EPA Pesticide Assessment Guidelines, Subdivision E Guideline 72-1*	*LC50 (96 h): 0.51 mg/L*	*Bowman (1990b)* *(no robust summary included in IUCLID as this is not the lowest LC50)* (DAR B.9.2.1.1 Study 1)
Oncorhynchus mykiss: juvenile fish: growth Freshwater; flow-through Experimental result on primary metabolite, quizalofop ((RS)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy] propionic acid) Test material purity: 98.6% Nominal concentrations: 0.20, 0.62, 2.0, 6.2 and 20 mg/L. Mean measured concentration at top dose was 99% of nominal. OECD Guideline 215 (Fish, Juvenile Growth Test) Klimisch 1 (reliable without restriction)	NOEC (28 d): 20 mg/L test mat. (nominal) based on: no effects at the highest dose tested	Peither (2000) (DAR B.9.2.2.1)
Daphnia magna Freshwater; flow-through Test material purity: 92.7% Nominal test concentrations: Control, Solvent Control (Acetone), 0.12, 0.24, 0.50, 1.0 and 2.0 mg/L Mean measured test Concentrations: 0.071,	EC50 (48 h): >1.5 mg/L test mat. (nominal) based on: no effects at the highest dose tested	Burgess (1990) (DAR B.9.2.4.1)

Method	Results	Reference
0.18, 0.34, 0.66 and 1.5 mg/L EPA OPP 72-2 (Aquatic Invertebrate Acute Toxicity Test) Klimisch 1 (reliable without restriction)		
Daphnia magna Freshwater; semi-static Experimental result on primary metabolite, quizalofop ((RS)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy] propionic acid) Test material purity: 98.6% Nominal concentrations: 0.10, 0.32, 1.0, 3.2, 10 and 32 mg/L Measured concentrations at 3.2 and 10 mg/L were 90-98% of nominal values OECD Guideline 211 (*Daphnia magna* Reproduction Test) Klimisch 1 (reliable without restriction)	NOEC (21 d): 3.2 mg/L test mat. (nominal) based on: survival and reproduction LOEC (21 d): 10 mg/L test mat. (nominal) based on: reproduction EC10 (21 d): 1.8 mg/L test mat. (nominal) based on: reproduction	Bätscher (2000a) (DAR B.9.2.5.1)
Navicula pelliculosa (diatom) Freshwater; static Test material purity: 95.6% Nominal concentrations: 0.065,0.13,0.25,0.50, 1.0.2.0 and 4.0 mg/L (overall mean measured concentrations were 84-88% of nominal values) OECD Guideline 201 (Alga, Growth Inhibition Test) 1 (reliable without restriction)	EbC50 (72 h): 0.60 mg/L test mat. (nominal) ErC50 (72 h): 1.3 mg/L test mat. (nominal) NOEC biomass and growth rate (72 h): 0.13 mg/L test mat. (nominal)	Morris & Latham (1998) (DAR B.9.2.6.1 Study 2)
Pseudokirchneriella subspicata *Freshwater, static* *technical quizalofop-P-tefuryl* *USA, EPA PAG Subdiv J, , Guidelines 122-2 and 123-2*	*Biomass:* *EbC50 (72 h): >1.9 mg/L* *Growth rate:* *ErC50 (72 h): >1.9 mg/L*	*Hoberg (1992)* *(no robust summary included in IUCLID as this is not the lowest LC50)* (DAR B.9.2.6.1 Study 1)
Lemna gibba (aquatic plants) *Freshwater; static renewal* Test material purity: 95.6 % Nominal test concentrations: 0.13, 0.25, 0.50, 1.0, 2.0 and 4.0 mg/L (overall mean measured concentrations 75 to 89% of the nominal values) USA, EPA PAG Subdiv J, , Guidelines 123-2 Klimisch 1 (reliable without restriction)	Overall NOEC (14 d): 0.38 mg/L act. ingr. (meas. (arithm. mean)) based on: symptoms of toxicity (lighter frond colouration and reduced root growth) EC50 (14 d): 2.1 mg/L test mat. (meas. (arithm. mean)) based on: frond number EC50 (14 d): 2.8 mg/L test mat. (meas. (arithm. mean)) based on: biomass NOEC (14 d): 0.87 mg/L test mat. (meas. (arithm. mean)) based on: frond number NOEC (14 d): 0.87 mg/L test mat. (meas. (arithm. mean)) based on: biomass	Morris et al. (1998) (DAR 9.2.8.1)

Method	Results	Reference
Lemna gibba (aquatic plants) Freshwater, static Experimental result on primary metabolite, quizalofop ((RS)-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy] propionic acid) Test material purity: 98.6% Nominal test concentrations: 0, 0.32, 1.0, 3.2, 10 and 32 mg/mL. Measured test concentrations 92-95% of the nominal values. OECD Guideline 221 (*Lemna* sp. Growth Inhibition test) Klimisch 1 (reliable without restriction)	EC50 (7 d): 28 mg/L test mat. (nominal) based on: growth rate EC50 (7 d): 32 mg/L test mat. (nominal) based on: biomass NOEC (7 d): 3.2 mg/L test mat. (nominal)	Memmert (2000) (DAR B.9.2.8.2)

5.9.1 Fish

5.9.1.1 Short-term toxicity to fish

Quizalofop-P-tefuryl was acutely toxic to fish species with the 96 hr LC50 values for bluegill sunfish (Bowman, 1990a) and rainbow trout (Bowman 1990b) 0.23 and 0.51 mg/L, respectively.

Study 1 Bowman (1990a)

In a 96 hour acute flow-through toxicity study of quizalofop-P-tefuryl technical (purity 92.7%) to bluegill sunfish *(Lepomis macrochirus)*, twenty fish were exposed per test concentration. The nominal test concentrations were 0.12, 0.23, 0.46, 0.93 and 1.9 mg/L together with a soft blended water control and solvent (acetone) control. Analytical measurements of quizalofop-P-tefuryl in the test dilution water were made at 0 and 96 hours. The measured concentrations averaged 0.10, 0.14, 0.34, 0.75 and 1.4 mg/L. Measurements of dissolved oxygen, pH and temperature were consistent throughout the term of the experiment.

The 96 hour LC50 with 95% confidence limits of quizalofop-P-tefuryl was calculated to be 0.23 mg/L (0.14 to 0.34 mg/L) based on the mean measured concentrations. There was 100% mortality in the 0.75 and 1.4 mg/L exposure solutions and 0.34 mg/L elicited 95% mortality (Table 33).

Sublethal effects and behavioural responses (e.g., on bottom orientation, loss of equilibrium and quiescence) were elicited by the sole survivor in the 0.34 mg/L test level, with no effects at the lower test concentrations. In this study, the 96 hour no effect concentration of quizalofop-P-tefuryl to bluegill sunfish was 0.14 mg/L based on a lack of sublethal responses at and below this concentration.

Table 33: Acute toxicity to bluegill sunfish: Cumulative mortality

Mean measured test concentrations (mg/L)	Cumulative mortality			
	24 hour	48 hour	72 hour	96 hour
Control	0	0	0	0
Solvent control	0	0	0	0
0.10	0	0	0	0
0.14	0	0	0	0
0.34	0	19	19	19

0.75	20	20	20	20
1.4	20	20	20	20

Study 2 Bowman (1990b)

The 96 hour acute toxicity of quizalofop-P-tefuryl technical (purity 92.7%) to rainbow trout (*Oncorhynchus mykiss)* was determined under flow-through conditions following guideline USA, EPA Pesticide Assessment Guidelines, Subdivision E Guideline 72-1. Twenty fish were exposed to each nominal exposure concentrations of 83, 70, 76, 81 and 100 mg/L together with a dilution water and solvent (acetone) control. Based on analysis of test water samples at 0 and 96 hours, the corresponding measured concentrations were 0.10, 0.16, 0.35, 0.75 and 1.9 mg/L. Cumulative mortality results are shown in Table 34.

Based on the mean measured concentrations, the 96-hour LC50 was 0.51 mg/L. Sublethal effects included loss of equilibrium, remaining on the bottom of the test vessel, quiescence, laboured respiration and dark discolouration. The 96-hour no effect concentration based on lack of these sub-lethal effects was 0.16 mg/L. This study does not provide the critical endpoint for classification and further detail is not included.

Table 34: Acute toxicity to rainbow trout: Cumulative mortality

Mean measured test concentrations (mg/L)	**Cumulative mortality**			
	24 hour	**48 hour**	**72 hour**	**96 hour**
Control	0	0	0	0
Solvent control	0	0	0	0
0.10	0	0	0	0
0.16	0	0	0	0
0.35	0	0	0	0
0.75	1	13	19	20
1.9	20	20	20	20

Metabolites

Both the aquatic metabolites, quizalofop-acid (Latham & Morris, 1998a; DAR B.9.2.1.2 Study 1) and THFA (Bätscher, R. 2003a; DAR B.9.2.1.2 Study 1), were less toxic than the parent substance, with the 96 hr LC50 to rainbow trout of the acid metabolite, quizalofop, being >32 mg/L and for THFA, >100 mg/L.

5.9.1.2 Long-term toxicity to fish

It was considered unnecessary to conduct a chronic toxicity test on juvenile fish with quizalofop-P-tefuryl due to its quick disappearance in water/sediment systems. The major degradation product, quizalofop-acid, is stable to hydrolysis and, therefore, a 28-day chronic toxicity study on rainbow trout was conducted with this substance.

Chronic exposure of juvenile rainbow trout to quizalofop-acid resulted in a 28-day LC50 of >20 mg/L and NOEC of 20 mg/L (Peither, 2000).

Study 1 (Peither, 2000)

The toxicity of quizalofop-acid (purity 98.6%) to rainbow trout (*Oncorhynchus mykiss*) was investigated in a 28 day flow-through test. Nominal test item concentrations of 0.20, 0.62, 2.0, 6.2 and 20 mg/L were tested in parallel with solvent (N,N-dimethylformamide) and freshwater controls. At the nominal concentration of 20 mg/L, the solubility limit of the test item in test water was reached and even slightly exceeded.

Concentrations in excess of the solubility limit were not tested.

In the stock solution concentrations were analytically measured to be in the range of 106 to 109% of the nominal value and the concentration of the test item (quizalofop-acid) was demonstrated to be constant in the application solution during the longest application renewal period of 8 days. During the test period, the measured test item concentration in the analysed test medium of the highest test concentration was in the range of 64 to 146% of the nominal value. The mean measured concentration (calculated as the average over all measurements) was 20 mg/L (99% of nominal).

Based on evaluations of mortality, symptoms of intoxication, body wet weight and growth rate (Table 35), the highest concentration tested without observed effects (NOEC) was determined to be 20 mg/L. In conclusion, quizalofop-acid had no sub-lethal toxic effects on rainbow trout when tested at concentrations up to its limit of water solubility.

Table 35: Chronic toxicity to rainbow trout - mortality/symptoms of intoxication, body weight & growth rate

Nominal conconcentration of quizalofop-acid (mg/L)	**Number of affected fish**[#] (Days 0-28)	**Body weight at end of test** (g ± SD)	**Increase in mean bodyweight** (% growth)*
Control	0/0	4.3 ± 0.74	310
Solvent control	0/0	4.2 ± 0.93	300
0.20	0/0	4.2 ± 0.66	330
0.62	0/0	4.1 ± 0.47	290
2.0	0/0	4.2 ± 0.75	300
6.2	0/0	4.2 ± 0.85	310
20	0/0	3.9 ± 0.75	280

[#] number of fish dead / number of fish with intoxication symptoms
*% Growth: % increase of mean body wet weight in relation to the body wet weight at the start of the test (=100%)

5.9.2 Aquatic invertebrates

5.9.2.1 Short-term toxicity to aquatic invertebrates

Acute toxicity studies with the standard aquatic invertebrate species (*Daphnia magna*) were conducted with quizalofop-P-tefuryl. The EC50 value of quizalofop-P-tefuryl for *Daphnia magna* was >1.5 mg/L, the highest concentration tested (Burgess, 1990).

Study 1 (Burgess, 1990)

The acute toxicity of quizalofop-P-tefuryl (purity 92.7%) to *Daphnia magna* was determined in flow-through conditions at nominal concentrations of 0.12, 0.24, 0.50, 1.0 and 2.0 mg/L. Based on the results of preliminary testing 2.0 mg/L was considered to be the approximate water solubility of quizalofop-P-tefuryl in the test medium. Twenty first-instar daphnids were exposed to each of the test concentrations, solvent (acetone) and dilution water controls. The mean measured concentrations calculated from analytical sampling at 0 and 48 hours are 0.071, 0.18, 0.34, 0.66 and 1.5 mg/L.

There were no adverse effects recorded and the 48 hour EC50 was therefore >1.5 mg/L and the NOEC, 1.5 mg/L.

Metabolites

Both the aquatic metabolites, quizalofop-acid (Latham & Morris, 1998b; B.9.2.4.2 Study 1) and THFA (Bätscher, 2003b; B.9.2.4.2 Study 2) were less toxic than the parent substance.

5.9.2.2 Long-term toxicity to aquatic invertebrates

As for fish, no chronic toxicity study with active substance was submitted based on the quick disappearance of quizalofop-P-tefuryl in water/sediment system. The 21-day NOEC of the metabolite quizalofop-acid (quizalofop) to *Daphnia magna* was 3.2 mg/L based on survival and mean reproduction rates (Bätscher, 2000a).

Study 1 (Bätscher, 2000a)

The effect of the quizalofop-acid (purity 98.6%) on the reproduction rate and survival of *Daphnia magna* was investigated in a semi-static test over 21 days. The nominal concentrations of quizalofop-acid were 0.10, 0.32, 1.0, 3.2, 10, and 32 mg/L together with a dilution water control. During the test, the analytically measured test item concentrations were in the range of 90 to 98% of the nominal values. Under the test conditions, the test item concentrations were sufficiently constant during the test medium renewal periods and therefore all reported results relate to nominal concentrations.

Taking into account the survival and the reproduction rates of the test animals after the exposure period of 21 days (Table 36), the highest concentration of quizalofop-acid tested without toxic effects (NOEC) after the exposure period of 21 days was 3.2 mg/L. The lowest concentration tested with toxic effects (21 day LOEC) was determined to be 10 mg/L due to the statistically significantly reduced mean reproduction rate of *Daphnia magna* at this test concentration.

The 21 day EC10 for the reproduction rate of *Daphnia magna* was calculated to be 1.8 mg/L (95% confidence limits: 0.4 - 5.2 mg/L). However, up to and including the test concentration of 3.2 mg/L, no statistically significant reduction in mean reproduction rate was observed in this test. The 21 day EC50 could not be calculated because the inhibition of the reproduction rate was only 24% at 10 mg/L, the highest test concentration without mortality.

Table 36: Quizalofop-acid: Chronic toxicity to *Daphnia magna*

Nominal concentrations of quizalofop-acid (mg/L)	**Number of surviving *Daphnia*** (% surviving on day 21)	**Live offspring** (% of control)
Control	100	100.0
0.10	100	99.8
0.32	100	94.8
1.0	100	91.2
3.2	100	90.0
10	100	75.9*
32	0	n.a.

* significantly lower based on Dunnett-test (one sided lower, α=0.05)
n.a: not applicable

5.9.3 Algae and aquatic plants

The toxicity of quizalofop-P-tefuryl to green algae and diatoms has been assessed. The EbC50 values for *Pseudokirchneriella subspicata* (previously *Selenastrum capricornutum*) (Hoberg, 1992) and *Navicula pelliculosa* (Morris & Latham, 1998) when exposed to quizalofop-P-tefuryl were >1.9 and 0.6 mg/L respectively.

The effect of quizalofop-P-tefuryl on aquatic plants was assessed in *Lemna gibba* in a 14 day study (Morris et al., 1998). The results showed no inhibitory effect on growth at nominally 0.38 mg/L.

Study 1 (Morris & Latham, 1998)

The toxicity of the herbicide quizalofop-P-tefuryl (purity 95.6%) to the freshwater diatom *Navicula pelliculosa* was determined in a 72 hr static test, with a culture medium control and a solvent (dimethylformamide) control together with nominal concentrations of 0.065, 0.13, 0.25, 0.50, 1.0.2.0 and 4.0 mg/L. The concentrations of quizalofop-P-tefuryl were measured at the start and end of the test and overall mean measured concentrations were 84-88% of nominal values. On this basis the nominal concentrations were used to report all results.

Based on areas under the growth curve the 72 hr NOEC was 0.13 mg/L, the LOEC was 0.25 mg/L and the EbC50 was 0.60 mg/L. Based on logarithmic growth rate over the test period, the 72 hr NOEC was 0.13 mg/L, the LOEC was 0.25 mg/L and the ErC50 was 1.3 mg/L.

Table 37: Quizalofop-P-tefuryl toxicity to *Navicula pelliculosa*: Mean areas under growth curve & growth rates

Nominal conconcentrations of quizalofop-P-tefuryl (mg/L)	**Mean area under growth curve** (0-3 days)	**Percentage of solvent control**	**Mean growth rate** (0-3 days)	**Percentage of solvent control**
Culture medium control	85.6	100	1.591	100
Solvent control	85.5	-	1.586	-
0.065	99.4*	116	1.651*	104
0.13	81.0	95	1.590	100
0.25	72.2*	84	1.534*	97
0.50	51.6	60	1.428*	90
1.0	27.9*	33	1.227*	77
2.0	6.5*	8	0.766*	48
4.0	0.1*	0	0.033*	2

*Significant difference (P=0.05) from the solvent control (Dunnett's)

Study 2 (Hoberg, 1992)

An algal growth inhibition study using *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*) and following USA EPA PAG Sub-div J, Guidelines 122-2 and 123-2 is available. The toxicity of quizalofop-P-tefuryl technical (purity 93.47%) was determined in a 120 hour static test, from which 72 hr data are reported.

The nominal test concentration of quizalofop-P-tefuryl was 4 mg/L, the reported solubility limit, and the initial mean measured concentration, 1.9 mg/L. Culture medium and solvent (acetone) controls were also included.

Based on biomass the 72 hr ErC50 was >1.9 mg/L and based on growth rate the 72 hr ErC50 was >1.9 mg/L.

Table 38: Quizalofop-P-tefuryl toxicity to *Pseudokirchneriella subcapitata*: Growth rate and cell density at 72 hours

Initial measured concentrations of quizalofop-P-tefuryl (mg/L)	**Maximum mean growth rate** (0-72 hours)	**Mean cell density** ($\times 10^4$ cells/mL (SD))	
		72 hours	**120 hours**
1.9	1.043	10 (2)	97 (3)*
Solvent control	1.134	35 (8)	109 (3)
Control	1.367	29 (10)	115 (3)
Pooled control	1.251	37 (8)	112 (4)

* Significant different from pooled control data ($p \leq 0.05$; t-test) (statistical analysis for 72 hours not reported)

Study 3 (Morris *et al*., 1998)

The toxicity of quizalofop-P-tefuryl (purity 95.6%) to duckweed (*Lemna gibba*) was assessed in a static renewal test design for 14 days following US EPA Pesticide Assessment Guideline Subd.J 123-2 (Growth and Reproduction Aquatic Plants). The nominal concentrations were 0.13, 0.25, 0.50, 1.0, 2.0 and 4.0 mg/L together with solvent (dimethylformamide) and culture medium controls. Fresh ("on") and old ("off") solutions were analysed on days 0 and 2, 2 and 5 and 12 and 14, respectively. The overall mean measured concentrations ranged from 75 to 89% of the nominal values (Table 39) and on this basis all results were reported based on mean measured concentrations.

Based on the increase in number of fronds the NOEC was 0.87 mg/L, the LOEC 1.7 mg/L and the EC50 was 2.1 mg/L (95% confidence interval: 1.8 - 2.3 mg/L). Based on the increase in dry weight of the plants over the 14 day period, the NOEC was 0.87 mg/L, the LOEC 1.7 mg/L and the EC50 was 2.8 mg/L (95% confidence interval: 2.4 - 3.2 mg/L).

Symptoms of toxicity including lighter frond colouration, unnatural flotation attitudes and reduced root growth were reported at mean measured concentrations of 0.87 mg/L and above. The overall 14 day non-observed effect concentration (NOEC) was 0.38 mg/L.

Table 39: Quizalofop-P-tefuryl toxicity to *Lemna gibba*: Mean measure fronds and dry weight

Mean measured conconcentration of quizalofop-P-tefuryl (mg/L)	**Mean increase in number of fronds (Days 0-14)**[#]	**Percentage inhibition compared with solvent control**	**Mean tissue dry weight increase**[##] **(Days 0-14)** (mg)	**Percentage inhibition compared with solvent control**
Culture medium control	443	0	48.0	0
Solvent control	435	-	41.4	-
0.11	429	1	41.0	1
0.21	446	0	43.2	0
0.38	441	0	44.7	0
0.87	389	11	39.4	5
1.7	267	39*	31.2	25*
3.6	91	79*	14.7	64*

increase = No.of fronds at day 14 – No.of fronds (12) at day 0

increase = Dry weight at day 14 – estimated day 0 dry weight. Dry weight at day 0 estimated from control dry weight at day 14 (1.3 mg per 12 fronds)

* Significant difference (P= 0.05, one sided) from the solvent control

Metabolites

Further testing with the acid metabolite, quizalofop-acid, revealed significantly lower toxicity with 72-hour ErC50 to *Scenedesmus subspicatus* was >32 mg/L (Bätscher, 2000b). The metabolite THFA, with 72-hour ErC50 to *Pseudokirchneriella subcapitata* of >100 mg/L, was also considered of low toxicity (Bätscher, 2003c).

The effect of quizalofop-acid on aquatic plants was assessed in *Lemna gibba* in a 7 day study (Memmert, 2000). The results showed no inhibitory effect on growth at nominally 3.2 mg/L, an order of magnitude less toxic than the parent substance. Since this is the most sensitive endpoint for aquatic algae and plants, a short summary is provided below.

Study 4 (Memmert, 2000)

The influence of the metabolite, quizalofop-acid (purity 98.6%), on the growth of the freshwater aquatic plant *Lemna gibba* (duckweed) was investigated in a 7 day static test following the draft OECD Guideline. The nominal test concentrations were 0, 0.32, 1.0, 3.2, 10 and 32 mg/L. The analytically determined test item concentrations in the analysed test media from the start and the end of the test ranged from 92-95% of the nominal values. Consequently quizalofop-acid was stable during the test period of 7 days under the test conditions and the reported biological results are based on the nominal concentrations of the test item.

Quizalofop-acid had a statistically significant inhibitory effect on the growth of *Lemna gibba* after an exposure period of 7 days at concentrations of 10 mg/L and above (Table 40). A concentration of 10 mg/L was the lowest concentration tested with toxic effects (7day LOEC). The 7 day NOEC (highest concentration tested without toxic effects) was 3.2 mg/L, since up to this test concentration the average specific growth rate (μ), the final biomass (based on dry weight), and the mean area under the growth curve (AUC) of *Lemna gibba* were not statistically significantly different from the control. The 7-day EC50 was calculated to be 28 mg/L based on growth rate and 20 mg/L based on AUC.

Table 40: Quizalofop-acid toxicity to *Lemna gibba*: Areas under growth curve (AUC) & growth rate

Nominal conconcentrations of quizalofop-acid (mg/L)	**AUC**	**% inhibition of AUC**	**Growth rate (μ) (1/day)**	**% inhibition of growth rate**
Control	8888	0.0	0.37	0.0
0.32	8500	4.4	0.37	-0.7
1.0	8716	1.9	0.37	-0.6
3.2	9076	-2.1	0.38	-2.9
10	7140*	19.7	0.33*	9.7
32	2368*	73.4	0.16*	56.3

Negative % Inhibition: promotion in growth relative to that of control

* mean value significantly lower than in control (according to a Dunnett-test, one-sided smaller, α = 0.05)

5.9.4 Other aquatic organisms (including sediment)

No data are available.

5.10 Comparison with criteria for environmental hazards (sections 5.1 – 5.4)

Quizalofop-P-tefuryl undergoes rapid primary degradation (primarily hydrolysis to quizalofop acid) and ultimate mineralisation, however it is not readily biodegradable and therefore does not meet the current CLP criteria for being “rapidly degradable”. Although the log Pow is >4, the experimentally determined BCF is <500.

The lowest acute endpoints for technical quizalofop-P-tefuryl was observed for fish with an acute 96 hr LC50 of 0.23 mg a.s./L.

Since the lowest relevant chronic NOEC is 0.38 mg/L (*Lemna gibba*). Chronic data are not available for fish and aquatic invertebrates.

On the basis of the available data, the following classification and labelling of quizalofop-P-tefuryl is proposed:

Aquatic Acute 1 H400 (Very toxic to aquatic life) as the lowest L(E)C50 is between 0.1 and 1 mg/L. The associated M-factor is therefore 1.

Aquatic Chronic 1 H410 (Very toxic to aquatic life with long lasting effects). Adequate chronic toxicity data are not available and therefore based on the lowest L(E)C50 for fish and the overall NOEC for algae/aquatic plants being between 0.1 and 1 mg/L (M-factor is 1).

Chronic NOEC values for the aquatic metabolite, quizalofop acid, are all >1 mg/L.

Aquatic Acute 1 - H400; Very toxic to aquatic life

M factor = 1

Aquatic Chronic 1 - H410; Very toxic to aquatic life with long lasting effects

M-factor = 1

6 OTHER INFORMATION

No other information

7 REFERENCES

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8 ANNEXES

ANNEX I: Postulated Mode of Action for Rat Liver and Leydig Cell Tumours

ANNEX II: Relevance of the Tetrahydrofurfuryl Alcohol and Quizalofop Acid Metabolites to the Toxicological Profile of QUIZALOFOP-P-TEFURYL and Similar Substances

ANNEX III: Draft Assessment Report (DAR) – public version – Initial risk assessment provided by the rapporteur Member State Finland for the existing active substance - QUIZALOFOP-P-TEFURYL - Volume 3 Annex B, part 1 B.1-B.5 - November 2007

ANNEX IV: Draft Assessment Report (DAR) – public version – Initial risk assessment provided by the rapporteur Member State Finland for the existing active substance - QUIZALOFOP-P-TEFURYL - Volume 3 Annex B, part 2 B6- November 2007

ANNEX V: Draft Assessment Report (DAR) – public version – Initial risk assessment provided by the rapporteur Member State Finland for the existing active substance - QUIZALOFOP-P-TEFURYL - Volume 3 Annex B, part 4 B8- November 2007

ANNEX VI: Draft Assessment Report (DAR) – public version – Initial risk assessment provided by the rapporteur Member State Finland for the existing active substance - QUIZALOFOP-P-TEFURYL - Volume 3 Annex B, part 5 B9- November 2007