Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

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

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

CLH-O-0000001412-86-118/F

Adopted

3 June 2016

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CLH-O-0000001412-86-118/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

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

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

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

The proposal was submitted by the **United Kingdom** and received by RAC on **28 July 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

The **United Kingdom** has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **30 September 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **16 November 2015**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

Co-Rapporteur, appointed by RAC: **Lina Dunauskienė**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **3 June 2016** by **consensus.**

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-373-00-4	Quizalofop-P-tefuryl; (+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate	414-200-4	200509-41-7	Acute Tox. 4 * Muta. 2 Repr. 1B STOT RE 2 * Aquatic Acute 1 Aquatic Chronic 1	H302 H341 H360Df H373 ** H400 H410	GHS07 GHS08 GHS09 Dgr	H302 H341 H360Df H373 ** H410			
Dossier submitter's proposal	607-373-00-4	Quizalofop-P-tefuryl; (+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate	414-200-4	200509-41-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Carc. 2 Skin Sens. 1B **Modify** Acute Tox. 4 Repr. 2 **Remove** STOT RE 2 * Muta. 2	**Retain** H400 H410 **Add** H351 H317 **Modify** H302 H361fd **Remove** H373** H341	**Retain** GHS07 GHS08 GHS09 **Add** Wng **Remove** Dgr	**Retain** H410 **Add** H351 H317 **Modify** H302 H361fd **Remove** H373 ** H341		**Add** M=1 M=1	
RAC opinion	607-373-00-4	Quizalofop-P-tefuryl; (+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate	414-200-4	200509-41-7	**Retain** Aquatic Acute 1 Aquatic Chronic 1 **Add** Carc. 2 **Modify** Repr. 2 Acute Tox. 4 STOT RE 2 **Remove** Muta. 2	**Retain** H400 H410 **Add** H351 **Modify** H361fd H302 H373 **Remove** H341	**Retain** GHS07 GHS08 GHS09 **Add** Wng **Remove** Dgr	**Retain** H410 **Add** H351 **Modify** H361fd H302 H373 **Remove** H341		**Add** M=1 M=1	
Resulting Annex VI entry if agreed by COM	607-373-00-4	Quizalofop-P-tefuryl; (+/-) tetrahydrofurfuryl (R)-2-[4-(6-chloroquinoxalin-2-yloxy)phenyloxy]propionate	414-200-4	200509-41-7	Carc. 2 Repr. 2 Acute Tox. 4 STOT RE 2 Aquatic Acute 1 Aquatic Chronic 1	H351 H361fd H302 H373 H400 H410	GHS08 GHS07 GHS09 Wng	H351 H361fd H302 H373 H410		M=1 M=1	

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

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.

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 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.

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"

RAC evaluation of physical hazards

Summary of the Dossier Submitter's proposal

No classification is proposed by the Dossier Submitter (DS) for physical hazards based on the following observations Quizalofop-P-tefuryl:

- does not exhibit explosive properties based on results of testing according to EEC A14 method.
- does not exhibit oxidizing properties based on results of testing according to EEC A17 method.
- does not meet criteria for flammable solids based on results of testing according to EEC A10 method.

Comments received during public consultation

No specific comments were received.

Assessment and comparison with the classification criteria

Quizalofop-P-tefuryl does not meet the criteria for classification for physico-chemical properties. RAC supports the proposal of DS **not to classify quizalofop-P-tefuryl for physical hazards**.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

Oral

Quizalofop-P-tefuryl was tested for acute oral toxicity in male and female albino rats in a GLP-compliant study according to EPA OPP 81-1and TSCA Health Effects Test Guidelines, 40 CFR, Section 798.1175;. When administred once orally in a vehicle (1% Methocel) via gastric intubation, it caused mortality in rats: 5/5 males and 5/5 females at the highest dose of 1500 mg/kg bw, 5/5 males and 4/5 females at the midle dose of 1154 mg/kg bw, 0/5 males and 1/5 females at the lowest tested dose of 888 mg/kg bw. The LD_{50} value for male and female rats calculated by the method of Litchfield and Wilcoxon was 1012 mg/kg (with 95% confidence limit of 764-1342 mg/kg). The slope relationship between dose response and applied dose was steep.

Based on this data, the DS proposed to confirm the classification of quizalofop-P-tefuryl as Acute Tox 4; H302, and hence remove the current minimum classification.

Dermal

Quizalofop-P-tefuryl was tested for acute dermal toxicity in New Zealand White rabbits (male and female), according to a GLP-compliant study according to FIFRA Guidelines, 40 CFR, Part 158;. No deaths were observed in 5 females and 5 males at the single dose tested, 2000 mg/kg bw/d. No treatment related clinical signs of toxicity or effects on body weight were observed. No abnormalities were recorded at necropsy. No classification for acute dermal toxicity is proposed by the DS, as the LD_{50} was >2000 mg/kg bw/d for both males and females rabbits.

Inhalation

Quizalofop-P-tefuryl was tested for acute inhalation toxicity in Sprague-Dawley rats (5 male and 5 female per each concentration tested), in a GLP-compliant study according to EPA OPP 81-3 guideline;. Rats were exposed nose-only for 4 hours at concentrations of 0.53; 1.6; 4.6 and 6.5 mg/L (analytical concentration) of formulation containing 60% quizalofop-P-tefuryl formulation (corresponding to concentrations of 0.318; 0.96; 2.76 and 3.9 mg/L Quizalofop-P-terfuryl technical, respectively). No deaths were observed at any of the above doses and no clinical signs were seen during exposure. During the two-hour post-exposure observation period, signs of toxicity included: respiratory responses (rales, laboured breathing), secretory responses (nasal discharge, excess lachrymation, etc.) and staining of the fur. These symptoms indicate that a formulation containing 60% of Quizalofop-P-tefuryl is irritative to the respiratory tract after inhalation exposure and classification as STOT SE 3 could be considered; however, since a chemical mixture was tested the data are not sufficient to conclude on classification of quizalofop-P-tefuryl for this endpoint. Slight body weight loss (up to 5% in males and 8% in females) during the first week after exposure with recovery thereafter was observed. No abnormalities were recorded at necropsy. No classification for acute inhalation is proposed by the DS, as the LC_{50} was >3.9 mg/L for both males and females rats.

Comments received during public consultation

Two Member State Competent Authorities (MSCAs) supported the DS's proposal to classify quizalofop-P-tefuryl as Acute Tox 4; H302, and proposed no classification for dermal or inhalation toxicity.

Assessment and comparison with the classification criteria

Oral

The 95% confidence limit of oral LD_{50} for male and female rats is between 764-1342 mg/kg bw and is hence in the range 300 - 2000 mg/kg bw relevant for classification in category 4 for acute oral toxicity according to the CLP criteria. On this basis, RAC recommends that quizalofop-P-tefuryl be classified as **Acute Tox 4; H302**.

Dermal

Taking into account that the dermal LD_{50} value in male and female rabbits is above the threshold value for classification (2000 mg/kg bw), quizalofop-P-tefuryl **should not be classified for acute dermal toxicity** according to the CLP criteria.

Inhalation

Taking into account that the LC_{50} was >3.9 mg/L for both males and females rats, and that the signs of respiratory system irritation were reversible within one week after exposure to a formulation containing quizalofop-P-tefuryl, and that no remarkable abnormalities were recorded at necropsy RAC considers that quizalofop-P-tefuryl **does not meet the CLP classification criteria for acute inhalation toxicity**.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The DS did not propose classification of quizalofop-P-tefuryl for STOT SE.

Comments received during public consultation

One MSCA commented in favour of that the presented data do not warrant classification of quizalofop-P-tefuryl as STOT SE.

Assessment and comparison with the classification criteria

According to the CLP Regulation specific target organ toxicity (single exposure) is defined as specific, non lethal target organ toxicity arising from a single exposure to a substance or mixture. In an oral acute toxicity study in rats symptoms such as hypoactivity and lacrimation were observed in animals only after administration of lethal doses, and lower doses were not tested. No treatment-related changes were observed at necropsy.

In the acute dermal toxicity study in rabbits non-specific toxic symptoms were observed after occlusive administration on skin of quizalofop-P-tefuryl at the limit dose of 2000 mg/kg bw/d.

In the inhalation toxicity study in rats a mixture containing 60% of quizalofop-P-tefuryl was used. At the highest technically attainable concentration (corresponding to 3.9 mg/L of air of quizalofop-P-tefuryl) and at lower concentrations, respiratory (rales and laboured breathing) and secretory (nasal discharge and lacrimation) symptoms, which disappear after the end of exposure, were noted. The toxicodynamics of symptoms at various concentrations was not provided and necropsy findings were evaluated as unremarkable. Technical quizalofop-P-tefuryl is an orange waxy solid with very low vapour pressure, and hence high air concentrations are difficult to achieve.

Taking into account the physical properties of the substance and that the existing data do not provide sufficient evidence of significant and/or severe toxic effects in organs of experimental animals following single exposure at generally low exposure doses/concentrations, RAC considers that quizalofop-P-tefuryl **does not warrant classification for STOT SE**.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The skin irritation potential of quizalofop-P-tefuryl was assessed in a standard skin irritation, GLP-compliant study (OECD TG 404) in three females and three males New Zealand White rabbit. Neither erythema nor oedema was seen in any of the animals; the average individual scores over 24, 48 and 72 hours were zero.
The DS proposed no classification for skin corrosion/irritation.

Comments received during public consultation

One MSCA indicated support for the DS's proposal not to classify quizalofop-P-tefuryl for skin corrosion/irritation. No parties provided comments proposing classification.

Assessment and comparison with the classification criteria

In the available study, no skin irritation reactions were observed in any of the six tested rabbits at any time (24, 47 and 72hours) after removal of the test material (all scores were 0). To classify in Category 2, at least 4 out of 6 animals should demonstrate skin reactions, with a mean score of ≥2.3 for erythema and/or oedema; it is therefore clear that the classification criteria are not met and RAC considers that quizalofop-P-tefuryl **does not warrant classification for skin corrosion/irritation**.

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The eye irritation potential of quizalofop-P-tefuryl was tested in a standard GLP eye irritation study (OECD TG 405) in three females and three males of New Zealand White rabbit strain. There were no corneal or iridial effects. Conjunctival redness of grade 1, in a scale having grades 0-3, was present in all animals at the 1 hour reading and in one animal only at the 24 hour reading. The 24/48/72 h mean values for conjunctival redness was well below 2. No fluorescein staining was present and no other signs of eye irritation were seen.
The DS did not propose classification for serious eye damage or eye irritation.

Comments received during public consultation

Two MSCAs supported the DS's proposal not to classify quizalofop-P-tefuryl for serious eye damage/eye irritation.

Assessment and comparison with the classification criteria

As the individual eye irritation scores for cornea, iris and conjunctival chemosis were 0, and for conjunctival redness the mean score was 0.06 over 24-72 hours, RAC agrees that quizalofop-P-

tefuryl **does not warrant classification for eye damage**.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

The potential of quizalofop-P-tefuryl to cause respiratory sensitisation was not investigated in the CLH dossier.

Assessment and comparison with the classification criteria

Since no data were presented for this endpoint RAC concluded that no classification can be proposed.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The potential of quizalofop-P-tefuryl to cause skin sensitisation was investigated in a GLP-compliant Magnusson and Kligman Guinea Pig Maximisation test (M&K GPMT; Denton, 1998) according to OECD TG 406 and a GLP-compliant Buehler test (Lilja, 1989) according to OECD TG 406 (with some deviations).

In the Buehler test (Lilja, 1989) the skin sensitization potential of technical quizalofop-P-tefuryl was assessed in Guinea pigs. Following nine induction procedures with the undiluted test substance, followed by a challenge application with undiluted test substance, no evidence of an allergic potential was observed.

In the GPMT study (Denton, 1998) twenty test animals and ten control animals were used. During the intradermal induction 20% solutions of technical quizalofop-P-tefuryl in Freund's Complete Adjuvant emulsion or in Alembicol D (Coconut Oil fractionated) were used.

A summary of the skin reactions are shown in the following table:

Challenge	**Number of positive reactions**			
	Test animals		Control animals	
	24 hrs	48 hrs	24 hrs	48 hrs
50% w/w in Alembicol D	15/20	12/20	1/10	0/10
25% w/w 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				
20% w/w in Alembicol D	14/20	13/20	9/10[a]	6/10[a]
Alembicol D Vehicle alone	12/20	1/20	5/10[a]	1/10[a]

[a]The study did not used naive controls at rechallenge

The data from the first challenge indicates that quizalofop-P-tefuryl dissolved in Alembicol D has a sensitisation potential. Overall the number of animals responding to quizalofop-P- tefuryl 50% w/w in Alembicol D is much higher (12 out of 20 animals) compared to Alembicol D Vehicle control (5 out of 20 animals). Given that the response was relatively weak (at the most >30% (7/20) animals gave a positive reaction at the first challenge), and that the intra-dermal induction dose was high (20%), the DS proposed classification as Skin Sens. 1B; H317.

Comments received during public consultation

One MSCA supported the DS's proposal to classify quizalofop-P-tefuryl as Skin Sens. 1B, H317 and two MSCAs suggested classifying quizalofop-P-tefuryl in Category 1 without sub-categorisation.

Assessment and comparison with the classification criteria

In the original report of the M&K GPMT (Denton, 1998) the authors noted that during the challenge test the skin responses in the exposed Guinea pigs were generally more persistent and more frequent than in control animals; however, the interpretation of these data was compromised by a high incidence of slight or well defined responses in the exposed animals at the site of application of Alembicol D (vehicle) alone. Therefore the animals were re-challenged with one concentration of quizalofop-P-tefuryl (20% w/w in Alembicol D) and with the vehicle to naive sites on the flanks. Positive skin reactions were noted with high incidences in both exposed animals and negative control animals which questions the validity of the study and the evaluation.

Taking into account the negative results of the Buehler test and the low rate of animals considered as sensitised in the GPMT, in which a relatively high number of test animals produced positive skin responses to vehicle alone, RAC considers that **classification of quizalofop-P-tefuryl as a skin sensitiser according to the CLP criteria is not justified.**

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

The CLH dossier contains several standard repeated dose toxicity studies of quizalofop-P-tefuryl using the oral route in mice (28-day and 95-96-day studies), rats (28-day and 90-day studies) and dogs (28-day, 90-day and 1-year studies), and the dermal route in rats (28-day study).

Based on results of these studies the DS did not propose classification of quizalofop-P-tefuryl for STOT RE. Other than the effects on testes observed in rats and dogs, for which the hazard class reproductive toxicity is more relevant, it was concluded that there was no toxicity in the available studies to support classification.

Significant hepatic effects (increased weight and histopathology) were observed at 134 mg/kg bw/d in the rat 90-day study and at 18-22 mg/kg bw/d in the mouse 90-day study. There were no effects at ≤ 100 mg/kg bw/d to justify classification. Effects seen in the mouse were considered to be adaptive changes, consistent with PPARα activation induced by quizalofop-P-tefuryl. Classification is not applicable where species-specific mechanisms of toxicity, demonstrated with reasonable certainty to be not relevant for humans, are shown to be responsible for the effects; for example this is the case for liver effects resulting from peroxisome proliferation. There were also findings of significance in the adrenals, heart, kidneys, spleen and thymus of rats, mice and/or dogs. However, the DS considered that there was a lack of consistency across studies of different duration with the same species and between species. They concluded that generally, the findings were isolated and did not form a coherent profile of repeated dose toxicity, and hence they proposed to remove the current classification as STOT RE 2.

Comments received during public consultation

There was one MSCA comment which disagreed with the DS proposal to remove quizalofop-P-tefuryl's harmonised classification as STOT RE 2, as they considered the effects observed in the repeated-dose studies in mice and dogs and the developmental toxicity studies in rats and rabbits to justify classification.

Assessment and comparison with the classification criteria

According to the CLP regulation, classification with STOT RE is triggered by the occurrence of *significant* (and/or *severe* for Category 1) *toxic effects* seen at doses below specified guidance values. For STOT RE Category 2, the relevant guidance values for oral exposure are 100 mg/kg bw/d (rat 90-day study) and 300 mg/kg bw/d (rat 28-day study).
In the 28-day oral (feed) repeated dose toxicity study in rats, at 40.3–84.2 mg/kg bw/d (i.e. below the guidance value of 300 mg/kg bw/d) only an increase in actual and relative liver weight was observed.

In the 90-day oral (feed) repeated dose toxicity study in rats at 33.4–41.6 mg/kg bw/day (i.e. below the guidance value of 100 mg/kg bw/d) in addition to the increase in actual and relative liver weight, also increase in albumin, ALP and decrease of globulin in the blood was noted. These effects are not considered to meet the classification criteria as significant toxic effects.

In the 28-day oral (feed) repeated dose toxicity study in mice at 213–472 mg/kg bw/d (close to the guidance value of 300 mg/kg bw/d) increased mortality, liver necrosis, myocardial degeneration, lymphoid cell depletion and atrophy of the spleen was observed. Hepatocellular hypertrophy and necrosis in all animals were noted. Increased mortality, liver necrosis and myocardial degeneration are considered as significant toxic effects according to section 3.9.2.7.3, Annex I of the CLP Regulation; however, the scale of dissemination of liver necrosis or number of foci of necrosis was not given. In the same 28-day oral (feed) study in mice at 164–280mg/kg bw/d, liver necrosis was seen in all animals, while at 48-75 mg/kg bw/d, liver necrosis was seen in 5 males and 2 females.

In the 95-96-day oral repeated dose toxicity study in mice at 36-79 mg/kg bw/d (below the guidance value of 100 mg/kg bw/d) body weight was decreased in males, significant adverse changes in clinical biochemistry were noted (52% increases in activity of alkaline phosphatase, 43% increase of glucose and 11% increase of albumin in males, 31% increases in blood urea nitrogen and 29% increase in glucose in females) together with liver enlargement, hepatocellular hypertrophy and with liver necrosis in 4 males and two females out of 10 exposed animals for each sex.

In the 90-day oral (feed) repeated dose toxicity study in dogs at 51-77 mg/kg bw/d (below the guidance value of 100 mg/kg bw/d) there was a significant decrease in levels of haemoglobin and haematocrit in males (30%/27% respectively), increased bilirubin (200%), urea nitrogen (61%) and creatinin (29%). Relative liver weight was increased in males, but no histopatological changes were reported in organs other than testes. Clinical signs observed included black faeces, diarrhoea or soft stool with wet red material indicating serious intestinal effects.

In the 1-year oral (feed) repeated dose toxicity study in dogs (6 animals/sex/dose) at 51-77 mg/kg bw/d treatment-related diarrhoea was noted in males. Two females were 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. No treatment-related findings were seen in dogs exposed at that dose at terminal kill.

In dogs exposed for one year with feed at 24-36 mg/kg bw/d no effect of toxicological significance was found.

Taking into account the significant toxic effects in the 28- and 90-day repeated dose toxicity studies in mice and dogs at doses below the guidance values, RAC is of the opinion that quizalofop-P-tefuryl warrants classification as **STOT RE 2; H373 (May cause damage to organs through prolonged or repeated exposure)**.

It is proposed not to specify the affected organs noting that significant effects were seen in various organs such as heart, blood, intestinal tract, lymphoid tissue and liver, and that also the mortality seen in several studies were taken into account. No route of exposure is thus proposed.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier Submitter's proposal

For the existing classification (Muta 2), it was not possible to identify the reports used in the past evaluation or the scientific justification. However, based on the five available *in vitro* and three *in vivo* genotoxicity studies – all negative - the dossier submitter concluded that quizalofop-P-tefuryl does not warrant classification and that the current classification as Germ cell mutagenicity Category 2 should be removed from Annex VI of the CLP Regulation.

Comments received during public consultation

Four MSCAs agreed with the proposal of not classifying quizalofop-P-tefuryl as mutagenic.

Assessment and comparison with the classification criteria

Quizalofop-P-tefuryl was clearly negative in four acceptable mutagenicity *in vitro* studies. In one *in vitro* study (mammalian chromosome aberration test) with methodological flaws (low number of examined metaphases), quizalofop-P-tefuryl was negative with metabolic activation, while the result without metabolic activation is not interpretable given weaknesses in study design.

In three acceptable *in vivo* studies (two mouse bone marrow micronucleus assays and one UDS assay in rats), quizalofop-P-tefuryl had clear negative results.

Taking into account the negative results of genotoxicity and mutagenicity studies *in vitro* and *in vivo* RAC concluded in agreement with the DS that **no classification is warranted** for this endpoint.

RAC evaluation of carcinogenicity

Summary of the Dossier Submitter's proposal

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. There was a 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 (under Directive 91/414/EEC; Chemtura Corporation) has acknowledged these tumours to be treatment-related.

An increased incidence of Leydig cell tumours was observed at mid and high dose levels i.e. at the same dose levels as hepatocellular tumours. An 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).

In rats, the increased incidence of hepatocellular adenomas and carcinomas were observed at doses ≥ 39.5 mg/kg bw/d (males) and ≥ 48.7 mg/kg bw/d (females) of quizalofop-P-tefuryl, however, as discussed in Annex I of CLH report, these findings were considered not to be relevant to humans as they appear to occur as a consequence of peroxisome proliferation.

An increased incidence of Leydig cell tumours was observed at mid and high dose levels, but full information on this study was not available to the DS. As the effects are secondary to the altered hepatic metabolism of testosterone, through the pleiotropic effects of PPARa agonism, they are considered not to be relevant to humans.

The relevance of the increased incidence of rare renal squamous cell carcinomas in rats was considered and the incidences were found to be outside the historical control range, thus it was decided that the tumours may be treatment-related and potentially relevant for human hazard assessment. Taking that data into acount, the DS proposed classification of quizalofop-P-tefuryl as Carc. 2, H351.

Comments received during public consultation

Five MSCAs agreed with classification as Carc. 2; H351. One MSCA further noted that the data are not enough to dismiss relevance to humans of the hepatotoxicity and hepatocarcinogenicity on the basis of the argument that the substance is a peroxisome proliferator.

Assessment and comparison with the classification criteria

Quizalofop-P-tefuryl showed no evidence of carcinogenicity in the mousein an acceptable carcinogenicity study. However in rats, the substance caused an increase in the incidence of hepatocelular adenomas and carcinomas in female and male rats; however this increase may be related to activation of PPARα receptor and peroxisome proliferation in liver, a mechanism of tumour formation, which is not considered relevant for humans. This mechanism seems to be plausible in rats, and it might be also involved in an increase of Leydig cell tumours observed in rats at mid and high dose levels of quizalofop-P-tefuryl. RAC however considers that there are doubts as to whether peroxisome proliferation is the only mechanism for cancer formation, and hence the liver tumours cannot be completely dismissed. In rats there was also a low incidence of rare renal squamous cell carcinoma at 1250/1500 ppm (1/50 male and 2/50 females). A mechanistic explanation for this increase of renal squamous cell carcinomas is not available and they are considered relevant for human hazard assessment of quizalofop-P-tefuryl.

Quizalofop-P-tefuryl is not genotoxic and mutagenic, therefore this mechanism of action for cancer causation is not relevant.

In summary, RAC considers that quizalofop-P-tefuryl has been demonstrated to be carcinogenic in one of the two animal species tested and due to the uncertainty related to the mode of action (MoA), is of the opinion that quizalofop-P-tefuryl warrants classification as **Carc. 2; H351 (Suspected of causing cancer)**.

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

The adverse effects seen in animals treated with quizalofop-P-tefuryl clearly demonstrate a potential hazard to sexual function/fertility and development. Such data is sufficient to justify classification with Repr 1B. However, there is uncertainty surrounding the quality of the studies, the completeness of the parameters measured, and the possibility that the MoA is not relevant to humans. The DS considered that the proposed MoA involving activation of PPARα receptors was plausible and was in line with a recent EFSA review. These considerations led the DS to the conclusion that Repr. 2, H361fd is more appropriate than the current harmonised classification of Repr. 1B, H360Df.

Comments received during public consultation

Two MSCAs agreed with the proposed classification as Repr 2; H361fd noting that the observed testicular effects, the effects on fertility and development, may be, to a certain extent, explained by the activation of hepatic PPRAα; however, there is insufficient evidence to conclude that this is the only MoA for quizalofop-P-tefuryl. The effects occur mostly only at doses toxic to parental animals and it is unknown whether these effects occur secondary to parental toxicity of quizalofop-P-tefuryl or secondary to the hepatotoxicity. Therefore, classification in Repr. 2; H361fd was supported by these MSCAs.

One MSCA agreed with the classification proposal Repr 2; H361fd, noting that a more strict classification as Repr 1B; H360FD is also possible. Two MSCAs supported the rationale for classification of quizalofop-P-tefuryl as Repr. 2, H361f, but did not support revision of the current classification of quizalofop-P-tefuryl in Repr. 1B to Repr. 2 for adverse effects on the development of the offspring.

In summary, all five commenting MSCAs agreed that classification as Repr 2; H361f, can be justified. Three MSCAs agreed with Repr 2; H361d, including one noting that Repr 1B; H360D is also an option, while two other MSCAs preferred classification as Repr 1B; H360D.

Assessment and comparison with the classification criteria

Sexual function and fertility

The reproductive toxicity of quizalofop-P-tefuryl has been assessed in a two-generation reproductive toxicity study (1993a) in rats and repeated dose toxicity studies in rats, mice and dogs.

In the repeated dose studies with quizalofop-P-tefuryl, testicular damage was observed in rats, dogs and mice. Originally, the dog was found to be the most sensitive species, with aspermatogenesis of the testes and epididymial aspermia observed in a 90-day study at 51-64 mg/kg bw/d, the highest dose tested. A targeted pathology review of the dog testes, epididymis and prostate glands, by the laboratory performing 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 quizalofop-P-tefuryl. Further, due to the age of the animals in this study, and lack of sexual maturity, these age-related abnormalities in the testes 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 substance (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 short-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 in rats (decreased testes weight, testicular degeneration, aspermatogenesis and aspermia) were seen only at doses 134-145 mg/kg bw/d in the 90-day study together with the following effects: markedly reduced food consumption and body weights; changes in haematology and clinical chemistry parameters (small decrease in haemoglobin, increase in platelets, liver enzymes, urea nitrogen, albumin, and globulin); 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). Hepatocellular hypertrophy, probably being a reflection of activation of the PPARα receptor and peroxisome proliferation in liver, was seen in all animals (10/10 males and 10/10 females), which corresponds to the macroscopic observation of accentuated lobular pattern and to increased liver weights. Secondary effects were seen in the epididymis and pituitary gland. Changes seen as secondary to testicular degeneration were accumulation of intralumenal cellular debris in the epididymis and increased numbers of "castration cells" in the anterior pituitary.

The testicular toxicity in mice was only seen in a 28-day study at the highest dose tested (285-452 mg/kg bw/d). Since all mice at the top dose level died between day 5 and 7, lost weight and were presumably starving from the first day of exposure, the testicular toxicity at the lethal dose could be a secondary non-specific consequence of other toxic effects.

The proposed MoA for rat testicular toxicity is decreased circulating testosterone as a consequence of increased conversion to oestrogen, via PPARα-related induction of aromatase. This 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-P-tefuryl 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. However, no direct evidence for this MoA of quizalofop-P-tefuryl has been provided.

The indirect evidence for this MoA is based on the toxic properties of quizalofop acid, which is a major metabolite of quizalofop-P-tefuryl. Quizalofop acid is a substance that has been shown to be a potent activator of rodent PPARα (EFSA Journal 2010;8 (10): 1718; see Annex II of the CLH report). In Annex II to the CLH report, the applicant presented a scientific rationale that the testicular and hepatic toxicity of quizalofop-P-tefuryl is rather linked to the toxic action of its metabolite quizalofop acid, and not to its other metabolite tetrahydrofurfuryl alcohol (THFA). Therefore the mechanism of action of quizalofop-P-tefuryl is different from that of THFA.

In 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/d for males (F0-F1) and 0, 2.1-2.3, 24.5-25.7 or 68.1-76.4 mg/kg bw/d 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.

Parental toxicity

No treatment-related mortalities or clinical signs were observed in 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, for 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 to the controls. In addition, slight reductions in pre-mating period food consumption were observed at 900 ppm for the F1 generation. Considerable increase in absolute and relative liver weight was noted in adult F1 males exposed at 16.9-20.5 or 52.8-68.8 mg/kg bw/d (300-900 ppm) and in adult F1 females exposed at 68.1-76.4 mg/kg bw/d (900 ppm). At microscopic examination, liver hypertrophy was noted in adult F1 females exposed at 24.5-25.7 or 68.1-76.4 mg/kg bw/d (300 and 900 ppm) and chronic progressive nephropathy with renal pelvis dilatation was noted in adult F1 females exposed at 68.1-76.4 mg/kg bw/d (900ppm). These changes in internal organs reflect the maternal systemic toxicity of quizalofop–P-tefuryl at these doses.

Effects on fertility

For the F0 generation, there was no evidence of any effect of 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.

Mating performance

F1 Generation	**0 ppm**	**25 ppm**	**300 ppm**	**900 ppm**
% / Number of 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 of 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. Review of the reported individual animal data showed discrepancies in the number of live and dead pups at birth and 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.

Comparison with the criteria

At the dose range of 52.8-68.8 mg/kg bw/d for males (F0-F1) and at 68.1-76.4 mg/kg bw/d for females there was a clear reduction in fertility in the F1 generation in matings aimed at producing the F2b generation. It should be noted that at least to some extent this reduction in fertility was due to better performace of concurrent control animals in F2b mating, which were more fertile (80.8%) than concurrent control in the first mating (F2a mating) of F1 generation (50%). The large difference in fertility of the two concurrent control groups (50% and 80.8%) reduces the reliability of this study. Since no reduction in fertility was seen in F2a matings in this study, this evidence, coming only from the F2b mating, is considered to provide some evidence of a fertility effect, but not sufficient to place the substance in category 1B.

The effect on fertility in the two-generation study as well as the testicular effects seen in repeated dose toxicity studies in rats were only observed at dose levels clearly inducing parental systemic toxicity seen as reduced body weight, reduced food consumption, chronic progressive nephropathy with renal pelvis dilatation and an increase in absolute and relative liver weight and

liver hyperthropy, hypothesised to be related to induction rat hepatic PPARα.

RAC is of the opinion that the current classification of quizalofop-P-tefuryl or fertility in **Category 2 (Repr. 2; H361f)** should be kept, as there is some evidence from several studies in experimental animals of an adverse effect on sexual function and fertility. Due to some uncertainties in study reliability and due to uncertainties regarding the proposed MoA, the evidence is however not considerd sufficiently convincing to place the substance in Category 1.

Developmental toxicity

The effect of quizalofop-P-tefuryl on developmental toxicity has been assessed in a two-generation reproduction toxicity study (York, 1993a) in rats, including a preliminary dose range finding study (York, 1991a), a prenatal developmental toxicity study in rats (York, 1990a), including a preliminary dose range finding study (Schardein, 1989) and a prenatal developmental toxicity study in rabbits (York, 1991b), including a preliminary dose range finding study (York, 1990b).

Two-generation study

In the two-generation reproductive toxicity study (York, 1993a), 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.

The body weight of the live pups at birth was comparable for all groups including the control, but the pup body weight at 900 ppm was lower than that of controls from day 7 (at 21 days of age, approximately 31%, 29%, 29% and 32% lower than controls 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 controls 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.

In the two-generation reproductive toxicity study (York, 1993a), malformations and necropsy findings are reported for dead offspring (most probably dead on day 0 till day 4 post partum) and offspring sacrificed at 21 day of age, although the methodology for examining dead pups for internal or skeletal anomalies is not provided or recommended in OECD TG 416. However, there is a recommendation that pups found dead on day 0, if not macerated, should preferably be examined for possible defects and cause of death, and preserved.

Hydrocephaly was observed in some dead pups (in F1b and F2b only, but not in F1a and F2a) at 900 ppm. The pups with hydrocephaly occurred in litters where most, if not all, pups were dead at birth or by day 4 after birth. The method of examination used to confirm the presence of hydrocephaly is not reported. Whether appropriate examination of the pups was undertaken and the diagnosis was correct cannot be confirmed. The data are therefore judged to be uncertain. Hydrocephaly was not detected in the rat prenatal developmental toxicity with severe maternal toxicity.

At necropsy on day 21, the kidney hydronephrosis incidence was increased in F1a pups at 900

ppm with 9 pups (12.5%) being affected. For the F2a generation 4 pups (6.8%) at 900 ppm were similarly affected and 4 (4.2%) control pups were also affected. As the incidence of occurrence was inconsistent across the generations, this was not considered as conclusive evidence for an effect of treatment.

In summary, in the 2-generation study there are indications that quizalofop-P-tefuryl (at 900 ppm dietary exposure) affected the total litter size and pup viability at birth, as well as pup body weight gain during lactation. The same dose also induced maternal systemic toxicity. The reduction in total litter size and pup viability at birth indicates some developmental toxicity *in utero* and it cannot be explained by a potential alteration at or from lactation. It is also noted that these developmental effects were only observed at a dose level causing marked maternal toxicity. 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.

Prenatal developmental toxicity studies

1. In the preliminary prenatal developmental toxicity study in rats (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/d on gestation days (GD) 6 to 15 and terminated on day 20 for evaluation of maternal and developmental effects.

Maternal lethality was observed at 200 mg/kg bw/d and higher with all rats failing to survive the dosing period. At 100 mg/kg bw/d, 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 bw/d was selected as the highest dose level for the subsequent prenatal developmental toxicity study. No maternal toxicity was observed at 25 mg/kg bw/d. Developmental toxicity was not evident at 25 or 100 mg/kg bw/d based on a very limited evaluation of the foetuses (counting of live and dead implantations only).

2. In 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/d on GD 6 to 15 and terminated on day 20 for evaluation of maternal and developmental effects.
At 100 mg/kg bw/d, 10 pregnant 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 bw/d and 8% in controls), the number of viable foetuses was decreased (10 at 100 mg/kg bw/d and 13 in controls) and mean foetal body was lower than controls by 29%.

The incidence of some of the malformations seen in the 100 mg/kg bw/d group (anasarca, cleft palate, diaphragmatic hernia, intraventricular septal effects, omphalocele) exceeded that of the concurrent and historical control groups; however, it is noted that the foetuses were from litters severely compromised by excessive maternal toxicity (dose causing 40% mortality of pregnant dams) and therefore no clear association between quizalofop-P-tefuryl and teratogenicity can be made from this dose.

The intermediate dose of 30 mg/kg bw/d 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/d. No developmental toxicity was seen at either 30 or 10 mg/kg bw/d.

3. In the preliminary study 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/d on GD 7 to 19 and terminated on day 29 for evaluation of maternal and developmental effects.

At the highest dose level of 100 mg/kg bw/d, two rabbits died (on days 13 & 19), two aborted (days 23 & 27) and one 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/d, one rabbit died (day 19), one aborted (day 21) and three survived to day 29 with marked body weight loss. The three surviving rabbits had live foetuses *in utero* but also increased post-implantation loss (up to 90% in individuals).

At 25 mg/kg bw/d, one rabbit aborted (day 29) and the cause of death was attributed to gastritis. The remaining four rabbits survived to day 29 with moderate body weight loss but only two were pregnant; increased post-implantation loss was not observed.

Although one rabbit at 10 mg/kg bw/d aborted (day 26), this was not ascribed to treatment. There was no clear effect of this dose on maternal body weight. One of the four remaining rabbits was not pregnant and three had live foetuses *in utero* on day 29.

All rabbits given 2.5 mg/kg bw/d survived until study termination and showed no signs of maternal toxicity; one was not pregnant.

The reported conclusion of this study is that maternal toxicity was evident at doses of 25 mg/kg bw/d and higher as body weight loss, abortion and/or death.

Developmental toxicity was evident at the 50 and 100 mg/kg bw/d dose levels. There was no evidence of teratogenicity at any dose level. Based on these findings, dose levels of 0, 2.5, 10 and 20 mg/kg bw/d were selected for the subsequent prenatal developmental toxicity study in rabbits.

4. 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/d on GD 7 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 bw/d and no developmental toxicity.

Comparison with the criteria

The existing data provide some evidence that quizalop-P-tefuryl affects the development of animals; however, the adverse developmental effects are mainly seen at dose levels causing maternal toxicity, and may hence be secondary non-specific consequences of this toxicity. In addition, there is a proposed, but not concluded, MoA which is considered not relevant to humans. Considering these uncertainties, RAC is of the opinion that the current classification of quizalop-P-tefuryl as Repr. 1B, H360D should be revised to **Repr. 2; H361d**, in line with the DS's proposal.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

The DS proposed that a revision of the classification and labelling should be considered. Quizalofop-P-tefuryl is currently classified as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410 with no M-factors assigned. The DS, based on available data, proposed to retain the environmental hazard classification as Aquatic Acute 1; H400 and Aquatic Chronic 1; H410 and to add an M-factor of 1 to both hazards based on acute aquatic toxicity to the bluegill sunfish (96-h LC_{50} = 0.23 mg/L) and chronic aquatic toxicity to *Lemna gibba* (14-d NOEC = 0.38 mg/L) for not rapidly degradable substances, respectively.

Furthermore, based on available studies included in the CLH report, the DS stated that the metabolites of quizalofop-P-tefuryl, quizalofop acid and THFA, are less toxic than the parent substance.

Degradation

Based on available hydrolysis studies (OECD TG 111; EPA Guideline Subdivision N 161-1 (Hydrolysis) and EU Method C.7.) the DS concluded that quizalofop-P-tefuryl is rapidly degraded (

quizalofop-P-tefuryl degraded very rapidly (DT_{50} and DT_{90} <1 day) to the metabolites quizalofop acid and THFA. Quizalofop acid then degraded with a DT_{50} of 25 – 35 days and DT_{90} of 88 – 117 days and THFA with a DT_{50} of 0.3 – 0.4 days and DT_{90} of 0.9 – 1.4 days in the total system. At the end of water/sediment studies CO_2 accounted for 10 – 81 % and unextractable residues for 11 – 42 % of AR.

Although quizalofop-P-tefuryl undergoes rapid primary degradation (fairly rapid hydrolysis) and ultimate mineralisation in water/sediment studies, it is not readily biodegradable (only 8% degradation after 28 days). Therefore the DS concluded that based on the available information on degradation and following the CLP guidance (version 4.1, June 2015), quizalofop-P-tefuryl does not meet the criteria for 'rapid degradability'.

Aquatic Bioaccumulation

The log Pow of quizalofop-P-tefuryl is 4.32 which is above the CLP trigger value of 4 intended to identify substances with a potential to bioaccumulate.

However, in a flow-trough study (EPA OPP 165-4) with bluegill sunfish (*Lepomis macrochirus*) the maximum BCF in whole fish was 340 after 28 days exposure. Depuration was very rapid (>97% after 14 days), with an elimination DT_{50} < 1 day. Based on the available measured bioaccumulation data, the DS concluded that a low risk of bioaccumulation in aquatic food chains was demonstrated. The metabolites quizalofop acid as well as other metabolites were considered not bioaccumulative (EFSA, 2008). Therefore, the DS proposed not to consider quizalofop-P-tefuryl as bioaccumulative substance for classification purposes.

Aquatic Toxicity

The ecotoxicological test results for quizalofop-P-tefuryl from available acute and chronic studies are summarised in the following table and sections.

Test organism / guideline, test method	Short-term result (endpoint)	Long-term result (endpoint)
Bluegill sunfish (*Lepomis macrochirus*) / EPA OPP 72-1, GLP	**96-h LC_{50} = 0.23 mg/L**	-
Rainbow trout (*Oncorhynchus mykiss*) / USA, EPA PAG	96-h LC_{50} = 0.51 mg/L	-
Daphnia magna / EPA OPP 72-2	48-h EC_{50} = >1.5 mg/L	-
Navicula pelliculosa (diatom) / OECD TG 201	72-h E_bC_{50} = 0.60 mg/L 72-h E_rC_{50} = 1.3 mg/L	72-h NOE_rC = 0.13 mg/L
Pseudokirchneriella subspicata / USA, EPA PAG	72-h E_bC_{50} = >1.9 mg/L 72-h E_rC_{50} = >1.9 mg/L	-
Aquatic plants (*Lemna gibba*) / USA, EPA PAG	-	Overall 14-d NOEC = 0.38 mg/L

For fish, as for aquatic invertebrates, no chronic toxicity study with quizalofop-P-tefuryl was available based on the quick disappearance of quizalofop-P-tefuryl in water/sediment systems. The major degradation product, quizalofop acid, is stable to hydrolysis and, therefore, a 28-days chronic toxicity study on rainbow trout (*O. mykiss*) and the 21-days chronic toxicity study on *D. magna* were conducted with this substance (quizalofop acid).

Chronic exposure of *O. mykiss* to quizalofop acid resulted in a 28-day LC_{50} of >20 mg/L and NOEC of 20 mg/L.

The 21-day NOEC of the quizalofop acid to *D. magna* was 3.2 mg/L based on survival and mean reproduction rates.

Further testing with the metabolite quizalofop acid revealed significantly lower toxicity to *Scenedesmus subspicatus* (72-h ErC_{50} >32 mg/L).

The metabolite THFA was also considered of low toxicity (72-h ErC_{50} of >100 mg/L) to *P. subcapitata*.

The effect of quizalofop acid on aquatic plants was assessed in *L. gibba* in a 7-day study. The results showed no inhibitory effects on growth at nominally 3.2 mg/L.

Based on the available information on aquatic toxicity, the DS identified fish as the most sensitive trophic group in acute aquatic toxicity studies and based the acute aquatic hazard classification on the 96-h LC_{50} of 0.23 mg/L (mean measured concentrations (mmc)) for the bluegill fish (*L. macrochirus*).

The most sensitive species in chronic aquatic toxicity studies is aquatic plants (*L. gibba*) with an overall 14-d NOEC of 0.38 mg/L (mmc) (based on lighter frond colouration and reduced root growth). However, since no chronic aquatic toxicity data are available for fish and aquatic invertebrates, the DS based the long-term aquatic hazard classification on the lowest $L(E)C_{50}$ for fish.

Comments received during public consultation

Three MSCAs submitted comments, of which one of them agreed with the DS's proposal to classify quizalofop-P-tefuryl as Aquatic Acute 1 (M=1) and Aquatic Chronic 1 (M=1) without any further comment.

One MSCA agreed with the classification as well as with the proposed M-factors but noted that the CLH report includes only one long-term toxicity study on fish, conducted with the degradant

quizalofop acid, with a reported NOEC of 20 mg/L. Given there are 2 acute fish toxicity tests conducted with the parent substance, both of which report LC_{50} values in the range of 0.1-1 mg/L, the NOEC of 20 mg/L seems to be unreliable and therefore, the classification of quizalofop-P-tefuryl should be based on the surrogate approach for fish.

Another MSCA pointed out that the endpoint of the algae study conducted with *P. subcapitata* should not be used for classification purposes because the study does not fulfill the validity criteria of the guideline and the study results should only be regarded as supplementary information. However, it should be noted that these study results do not have any influence on the proposed classification.

Assessment and comparison with the classification criteria

Degradation

RAC agrees with the DS's proposal that quizalofop-P-tefuryl does not meet the criteria for rapid degradability based on available hydrolysis, photolytic degradation studies, results obtained in a ready biodegradation test and water/sediment studies. The information provided in the CLH report does not allow a conclusion as to whether all metabolites are non-classified, hence RAC concludes that quizalofop-P-tefuryl is considered to be not rapidly degradable for classification purposes.

Aquatic Bioaccumulation

Reliable information from a fish bioconcentration study shows quizalofop-P-tefuryl to have a whole fish BCF of 340 L/kg (no lipid-normalised and growth corrected BCF data where provided in the CLH report), which is less than the CLP trigger value of ≥ 500. The main metabolite quizalofop acid and other metabolites were not considered to bioaccumulate. RAC agrees with the DS's conclusion that the substance is not bioaccumulative for classification purposes.

Aquatic Toxicity

RAC notes that there are no data available for chronic aquatic toxicity for fish and aquatic invertebrates on quizalofop-P-tefuryl. RAC also concurs with the DS's assessment that the metabolites of quizalofop-P-tefuryl, quizalofop acid and THFA, are less toxic than the parent substance. Furthermore, RAC notes that the long-term hazard classification should be based on the most stringent outcome (according to CLP, Annex I, Figure 4.1.1) by comparing the classification derived from the assessment of the trophic level with chronic data (CLP, Annex I, Table 4.1.0(i)(b)) with that made using the acute toxicity data for the other trophic levels combined with degradation and/or bioaccumulation data (CLP, Annex I, Table 4.1.0(b)(iii)).

Acute toxicity

RAC agrees with the DS that the lowest acute endpoint for quizalofop-P-tefuryl was observed for the bluegill fish (*L. macrochirus*) with an acute 96-h LC_{50} of 0.23 mg/L (mmc).

Chronic toxicity

RAC agrees with the DS that the lowest chronic endpoint for quizalofop-P-tefuryl was observed for aquatic plants (*L. gibba*) with a chronic 14-d NOEC of 0.38 mg/L (mmc) based on lighter frond colouration and reduced root growth (as additional symptoms of toxicity reported at mean measured concentrations of 0.87 mg/L and above). Another chronic endpoint is available for the diatom *N. pelliculosa* with a chronic NOEC of 0.13 mg/L based on biomass and growth rate.

Conclusion on classification

Quizalofop-P-tefuryl is considered to be not rapidly degradable and does not fulfil the criteria for bioaccumulation. Based on the available and reliable information and in agreement with the DS's proposal, RAC is of the opinion that quizalofop-P-tefuryl should be classified as:

Aquatic Acute 1 based on a 96-h LC_{50}=0.23 mg/L for *L. macrochirus,* **with an acute M-factor of 1**, as 0.1 < L(E)C_{50} ≤ 1 mg/L.
No adequate chronic data are available for fish and aquatic invertebrates, therefore the long-term aquatic hazard classification is based on the surrogate approach (CLP, Annex I, Table 4.1.0(b)(iii)) for fish, resulting in a classification as **Aquatic Chronic 1 with a chronic M-factor of 1**.

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and by RAC (excluding confidential information).