Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of
cycloxydim

EC number.: 405-230-9
CAS number.: 101205-02-1

ECHA/RAC/CLH-O-0000003157-76-01/F

Adopted
28 November 2012

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CLH-O-0000003157-76-01/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 (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: **cycloxydim**
EC Number: **405-230-9**
CAS Number: **101205-02-1**

The proposal was submitted by **Austria** and received by the RAC on **17 August 2011**.

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP Regulation	**DSD**
Current entry in Annex VI of CLP Regulation	-	-
Original proposal by Dossier submitter for consideration by the **RAC**	TC: No classification TK: No classification	TC: R 11 Highly flammable TK: No classification
Resulting harmonised classification (future entry in Annex VI of CLP Regulation) as proposed by Dossier submitter	TC: No classification TK: No classification	TC: R 11 Highly flammable TK: No classification

TC= technical compound (min. 940 g/kg)
TK= technical concentrate (min. 400 g/kg max. 450 g/kg)

Note: due to its limited stability, technical cycloxydim is not isolated as TC, but handled, transported, and processed solely as TK which is a (liquid) mixture containing cycloxydim and a solvent.

PROCESS FOR ADOPTION OF THE OPINION

Austria 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 **17 August 2011**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **01 October 2011**.

ADOPTION OF THE OPINION OF THERAC

Rapporteur, appointed by the RAC: **Jose Luis Tadeo**
Co-rapporteur, appointed by the RAC: **Agnes Schulte**

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

The RAC opinion on the proposed harmonised classification and labelling was adopted on **28 November 2012** and the comments received are compiled in Annex 2.

The RAC Opinion was adopted by **consensus.**

OPINION OF THE RAC

The RAC adopted the opinion that **cycloxydim** should be classified and labelled as follows:

Classification & Labelling in accordance with CLP:

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard state-ment Code(s)	Pictogram, Signal Word Code (s)	Hazard state-ment Code(s)	Suppl. Hazard statemen t Code(s)		
606-147-00-2	cycloxydim (ISO); 2-(N-ethoxybutanimidoyl)-3-hydroxy-5-(tetrahydro-2H-thiopyran-3-yl)cyclohex-2-en-1-one	405-230-9	101205-02-1	Repr. 2	H361d	GHS08 Wng	H361d			

Classification & Labelling in accordance with DSD:

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentra tion Limits	Notes
606-147-00-2	cycloxydim (ISO); 2-(N-ethoxybutanimidoyl)-3-hydroxy-5-(tetrahydro-2H-thiopyran-3-yl)cyclohex-2-en-1-one	405-230-9	101205-02-1	F; R11 Repr. Cat. 3; R63	F; Xn R: 11-63 S: (2-)16-36/37-46		

SCIENTIFIC GROUNDS FOR THE OPINION

Cycloxydim is an active substance in the meaning of Directive 91/414/EEC and is therefore subject to harmonised classification and labelling (CLP Regulation Article 36(2)).

PHYSICAL HAZARD ASSESSMENT

Flammability

Summary of the Dossier submitter´s proposal

The Dossier submitter (DS) proposes to classify with F; R11 under DSD, due to the results observed in the EEC/A10 study (burning time of less than 45 seconds). However, classification in accordance with CLP is not proposed based on the result of a study performed according to the UN Recommendations on the Transport of Dangerous Goods (TDG), Manual of Tests and Criteria, 2nd revised edition, Part III, Test N.1, Section 33.2.1.4, in which only brief burning followed by rapid extinction was observed in a preliminary study.

Comments received during public consultation

One comment regarding flammability was received from the UK pointing out that substances that are classified as flammable (F; R11) under DSD are in general classified as flammable also under CLP. However, it was recognised that there are differences between the two test systems, which means that it is not always possible to make a direct translation and that in some cases a different classification could be justified. In spite of the fact that the UN study gave a negative result in the preliminary study, the UK does not think it appropriate to ignore the results obtained in the main EEC/A10 study, also when classifying according to CLP.

Assessment and comparison with the classification criteria

Classification as F; R11, highly flammable according to DSD was proposed for the technical compound (TC, i.e. the dried technical active substance; min. purity 940 g/kg) due to the results observed in the EEC/A10 study (i.e. a burning time of less than 45 seconds).
However, according to the Dossier submitter, the flammability test EEC/A.10 was conducted with the TC isolated from cycloxydim technical concentrate (TK i.e. the mixture containing cycloxydim and a solvent [purity 400 - 450 g/kg]) dissolved in toluene. Since toluene is classified as R11, the test result "highly flammable" may be explained by toluene residues in the test substance, as suggested by the Dossier submitter.
According to CLP, a new study was required referring to the UN "Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria, 2nd revised edition, Part III, Test N.1, Section 33.2.1.4". The result of the flammability test was negative, which leads to no classification for the TC under CLP.
The UN test can be considered valid, in spite of the fact that several repetitions should have been conducted. According to the Dossier submitter, this test was conducted with cycloxydim TC, isolated through a thin film-evaporator using cycloxydim TK dissolved in Solvesso 150 (test report DocID 2010/1155866), which is not classified as R11.
The only difference between the tests EEC/A10 and the UN method is that, when applying the flame, the decision whether the combustion propagates along a 200 mm train of the substance is taken over 2 minutes in the UN method and over 4 minutes in EEC/A10 method. The different time considered in the decision could be responsible of the different results under the two methods.

Another possible reason for the different results could be the presence of toluene solvent residues in the test substance used in the EEC/A10 test.
However, since the exact composition of the test substance used in the EEC/A10 test is not known, the RAC was not in a position to challenge the outcome of that test.
In conclusion, the RAC supports the Dossier submitter's proposal to classify as flammable (F; R11) under DSD and no classification under CLP.

HUMAN HEALTH HAZARD ASSESSMENT

Acute toxicity and Specific Target Organ Toxicity – Single Exposure (STOT-SE)

Summary of the Dossier submitter's proposal

Acute toxicity
Cycloxydim has low oral acute toxicity in rats and mice, and low dermal and inhalation toxicity in rats (rat oral LD_{50}=3940 mg/kg bw, mouse oral LD_{50}>5000 mg/kg bw, dermal LD_{50}>2000 mg/kg bw, LC_{50}>5.28 mg/L air).
Since all estimated LD_{50} and LC_{50} values are above the guidance values in the criteria (both DSD and CLP), no classification is proposed for cycloxydim regarding acute toxicity.

Specific target organ toxicity – single exposure (STOT SE)
No specific, non lethal, target organ toxicity after single exposure was observed in acute toxicity studies. The observed effects in acute toxicity studies covered mostly clinical signs like dyspnoe, apathia, abnormal position, staggering, paresis, twitching and piloerection. No acute neurotoxicity studies were provided. In addition, no human data are available that would support classification for this endpoint.
No classification as STOT-SE under the CLP Regulation is proposed.

Comments received during public consultation

No specific comments were received on these hazard classes.

Assessment and comparison with the classification criteria

Acute toxicity
Cycloxydim has a low acute toxicity following application via oral, inhalation and dermal route. For the oral route, the LD_{50} in Wistar rats (3830 mg/kg for females and 4420 mg/kg for males, combined 3940 mg/kg bw) and in NMRI mice (>5000 mg/kg bw) was above the guidance value of 2000 mg/kg bw (CLP and DSD).
Dermal application to Wistar rats revealed an LD_{50}>2000 mg/kg which is above the guidance value for classification for CLP and DSD.
The 4-hour LD_{50} by head-nose inhalation exposure for cycloxydim as a liquid aerosol was >5.28 mg/l which was above guidance concentration of >5 mg/l and no classification is adequate.
The Dossier submitter proposed no classification for acute toxicity for the oral, inhalation and dermal route. The RAC agreed that no classification on acute toxicity is justified.

Specific target organ toxicity – single exposure (STOT SE)
As no specific target organ toxicity was observed after single exposure and no evidence from other studies was available, the RAC agreed that no classification for STOT-SE was appropriate.

Irritation

Summary of the Dossier submitter's proposal

Skin irritation
No information in humans is available from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
According to the results of a rabbit skin irritation study, cycloxydim is not irritating to the intact shaved rabbit skin. Estimated skin irritation scores (0.1 for erythema) are below the guidance values of the criteria for classification and labelling (according to both DSD and CLP).
No classification is proposed for cycloxydim regarding skin irritation.

Eye irritation
No information in humans is available from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
According to the results of an eye irritation study, cycloxydim is slightly irritating to the rabbit eye. The estimated eye irritation scores (24 – 72 hours) are below the guidance values of the criteria for classification (according to both DSD and CLP).
No classification is proposed for cycloxydim regarding eye irritation.

Respiratory tract irritation
There is no specific information regarding the ability of cycloxydim to cause irritation to the respiratory tract from the acute inhalation toxicity study.
No information in humans is available from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
No classification is proposed for respiratory tract irritation.

Comments received during public consultation

No specific comments were received on skin, eye or respiratory tract irritation

Assessment and comparison with the classification criteria

Skin irritation
Cycloxydim showed only minimal irritating properties. The overall mean score of 0.1 for erythema is well below the guidance values (≥2.3 for CLP, ≥2 for DSD) for classification.
The RAC concluded that no classification as a skin irritant was appropriate.

Eye irritation
Indications of slight eye irritation were observed in rabbits. Individual mean scores for conjunctival redness at 24, 48 and 72 hours after instillation were 0.3 (n=2), 0.6, 1.0 (n=2) or 1.3. The condition that 2 of 3 tested animals should show conjunctival redness ≥2 (CLP) or ≥2.5 (DSD) was never fulfilled at any time point and redness resolved from 48 h until (latest) 8 days after treatment.
The RAC agreed with the proposal of the Dossier submitter that classification for eye irritation is not warranted.

Respiratory tract irritation
There is no human information and no information from animal studies indicating irritating effects on the respiratory tract.
The RAC followed Dossier submitter's proposal and agreed with no classification for this endpoint.

Sensitisation

Summary of the Dossier submitter's proposal

Skin sensitisation
No information in humans is available from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
Effects observed in a skin sensitisation study in guinea pig (Maximisation test), are below the criteria for triggering classification (according to both DSD and CLP). Thus, according to these results, cycloxydim is not sensitising to guinea pig skin, and no classification according to the criteria is proposed with regard to skin sensitisation.

Respiratory sensitisation
No data on respiratory sensitisation is available.

Comments received during public consultation

No specific comments were received on skin or respiratory sensitisation.

Assessment and comparison with the classification criteria

Skin sensitisation
No positive responders were observed in a Guinea Pig Maximization Test with cycloxydim. The RAC agreed on the Dossier submitter's proposal that no classification is proposed.

Respiratory sensitisation
The RAC considered that a conclusion on the classification is not possible due to the lack of data.

Repeated dose toxicity

Summary of the Dossier submitter's proposal
No information is available in humans from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
The repeated dose toxicity of cycloxydim has been investigated after oral application in rats (28 and 90 days of exposure), mice (28 days of exposure) and dogs (28, 90 days and 12 months of exposure). In addition, one study of dermal exposure to rats (28 days) is available.

Rat studies
In a 28 days oral (drinking water) range finding study in the rat, a NOAEL of 1000 ppm (equivalent to 106 mg/kg bw/d) in females was proposed, based on increased relative liver weight at 3000 ppm (252 mg/kg bw/d). The NOAEL of 3000 ppm (equivalent to 272 mg/kg bw/d) was proposed for male rats based on decreased body weight, increased relative liver and kidney weight, increased urea and decreased trigycerides level at 9000 ppm (683 mg/kg bw/d).
In a 90 days oral (drinking water) toxicity study in the rat (range finding study), liver enzyme activities (ALT, ALP) were found to be significantly altered at concentrations of 2700 ppm and 900 ppm (equivalent to 178 or 201 and 72 or 74 mg/kg bw/d in male and female rats respectively). In addition creatinine was shown to be significantly increased at these dose levels in females after one month of exposure. The NOAEL was thus set as 300 ppm (equivalent to 22 mg/kg bw/d in male and 28 mg/kg bw/d in female rats, respectively). Both sexes recovered completely with respect to reduced body weight gain and clinico-chemical changes. No reduction in food consumption was noted in males during the recovery phase.

After repeated dermal application (5 times per week over 4 consecutive weeks) of cycloxydim to Wistar rats, male animals showed significantly reduced body weight gain and reduced food efficiency at a concentration of 1000 mg/kg bw, but no biochemical alterations could be observed. Therefore the NOAEL was set as 300 mg/kg bw for male and 1000 mg/kg bw for female rats.

Mouse studies

In a 28 days oral (drinking water) toxicity study in mice (1st range finding study), the NOAEL was set as 1000 ppm (corresponding to 189 mg/kg bw/d in male and 218 mg/kg bw/d in female mice, respectively), based on a significant increase in relative liver weights over 115% (in male mice) at a concentration of 3000 ppm and 9000 ppm in combination with altered clinico-chemical parameters (enhanced plasma urea levels and deceased plasma cholesterol) in males and females, and the occurrence of hydropic vacuolar parenchymal degeneration of hepatocytes in two males in the highest dose group.

A second 28 days oral (drinking water) toxicity study in mice (2nd range finding study) was provided but with less data-points. Biochemical data was scarce in this study, liver weight and liver enzyme activities are the only parameters that can be used for toxicological assessment. Originally, a NOAEL in B6C3F1/CrIBR mice was established at 100 ppm (22.5 mg/kg bw/d) for males and at 300 ppm (82.5 mg/kg bw/d) for females, based on increased liver weights, and a dose-dependent decrease in LDH activity in male mice. The DS considered the NOAEL to be 100 ppm (22.5 mg/kg bw/d) for males, based on reduced LDH level at 300 ppm and >900 ppm for females based on lack of adverse effects. However, the derivation of the NOAEL upon the reduced LDH is considered to be a very conservative approach, since it is not clear if it is indeed an adverse effect.

Dog studies

In a 28 days oral (feeding) study in dogs (range finding study with 2 dogs/sex/dose), the relative liver weights were significantly increased at ≥120 mg/kg bw/d in both sexes. Liver hypertrophy was noted in the highest concentration tested (360 mg/kg bw/d). In females absolute and relative thyroid weights were clearly increased at ≥120 mg/kg bw/d, but no histopathological changes were evident. The NOAEL was therefore determined to be 40 mg/kg bw/d in both sexes.

The results of a 90 days oral (feeding) toxicity study in dogs (range finding study) showed statistically significant changes in haematological parameters (decreased RBC, increased Heinz bodies, increased MCV and reticulocytes) at 7500 ppm (250 mg/kg bw/d) and statistically significant increase in alkaline phosphatase in male rats, with increased absolute and relative liver weights and hepatocellular hypertrophy. In addition absolute and relative thyroid weights were increased for 121% (males), but reached no statistical significance. The NOAEL in this study was set as 300 ppm (corresponding to 10 mg/kg bw/d) for male and 1500 ppm equivalent to 50 mg/kg bw/d for female dogs.

In a one year chronic toxicity study in dogs, a dose level of 6400 ppm (206 mg/kg bw/d) induced anaemic effects, associated with increased liver weights and increased hemosiderosis in the livers of female dogs. At a dose of 1600 ppm (49 mg/kg bw/d) indications of compensatory reactions to an anaemic process (increased Heinz bodies and platelets) in both sexes were identified, as well as increased liver weight in male animals, associated with altered clinico-chemical parameters (increased alkaline phosphatase activity and reduced albumin concentration). The NOAEL in this study was 400 ppm (12 mg/kg bw/d) for males and females.

RAC comment: The RAC considered Heinz bodies not to be a compensatory reaction to anaemic processes. Moreover Heinz bodies are indicative of damage to red blood cells.

Dossier submitter's summary and discussion of repeated dose toxicity findings relevant for classification as STOT RE according to DSD and CLP

In the sub-acute oral rodent studies (rat and mice), the only effect observed below the cut-off values of 150 mg/kg bw/d and 300 mg/kg bw/d for DSD and CLP, respectively, was increased relative liver weight in female rats (without histological findings) and decreased LDH level in male mice (for which is not clear if it is indeed an adverse effect).

In the sub-acute dermal rat study the only effect observed below the cut-off values of 300 mg/kg bw/d and 600 mg/kg bw/d for DSD and CLP, respectively, was reduced body weight in males.

In the 90 days rat study, the effects observed below the cut-off values of 100 mg/kg bw/d for CLP (but not below the cut-off value for DSD, 50 mg/kg bw/day) were increased ALP in males and females (with no effects on liver weight or histopathological findings) and increased creatinin and urea in females.

For dogs, no cut-off criteria are available at present. In the 28 days dog study, the effects on blood system (reduced haemoglobin in males, reduced RBC in males, increased Heinz bodies in males and females) and liver (increased relative liver weight in males and females, hepatocellular hypertrophy in males and females, increased ALP in males and females) were observed primarily at the highest dose tested (360 mg/kg bw/d).

In the 90 days dog study, the effects on blood system (reduced RBC in males and females, increased MCV, leucocytes and polymorphonuclear neutrophilic granulocytes in males, increased Heinz bodies and platelets in males and females) and liver (increased relative liver weight in males and females, hepatocellular hypertrophy in males and females, increased ALP in males and females) were observed primarily at the highest dose tested (250 mg/kg bw/d).

In the 1 year dog study, the effects on blood system (reduced RBC in males and females, reduced haemoglobin in females, increased MCH, MCV, platelets and Heinz bodies in males and females) and liver (increased relative liver weight in males and females, increased ALP in males and females, but no histopathological findings) were observed primarily at the highest dose tested (206 mg/kg bw/d).

Thus effects observed in the subchronic (oral and dermal) studies in rat, mouse and dog do not meet the criteria for classification and labelling for Specific target organ toxicity - repeated exposure (CLP) or for repeated dose toxicity (DSD).

RAC comment: Increased numbers of Heinz bodies and platelets, increased relative liver weight and elevated ALP concentration observed at 49 mg/kg bw/d (1600 ppm) were considered to be treatment-related effects.

Comments received during public consultation

No specific comments were received on repeat dose toxicity.

Assessment and comparison with the classification criteria

The target organs of interest following repeated (subacute to chronic) administration of cycloxydim are the liver (in rats, mice and dogs), the kidney (in rats) and the haematopoietic system (in dogs).

The main effects observed in the liver were:

a) increases in rat and dog liver weight (probably indicating some hypertrophic or hyperplastic liver cell response. The only microscopic finding attributable to weight increase was reported as 'enlarged (=hypertrophic) hepatocytes' in dogs at high dose of 7500 ppm (250 mg/kg bw/d, after 90 days of treatment.
b) increases in ALP in dogs which is not specific for liver cell damage, but may indicate effects on the bile duct epithelia/system.
c) reduced serum concentrations of triglycerides and/or cholesterol in rat and mouse studies are likely to be related to the observed reduction in food and water consumption.

d) increases in ALT (seen at 900 ppm (74 mg/kg bw/d)) in rats receiving cycloxydim for 90 days may be indicative for liver cell damage, however microscopic degenerative/necrotic liver cell lesions were only reported in one 28 day range-finding study in 2/10 mice (at 9000 ppm (1177 mg/kg bw/d, above limit dose).
e) ALP was elevated in some studies (a possible indication of liver dysfunction), but a reduction was found in other studies at comparably high doses.

Overall, effects on the liver of a serious nature (e.g. liver cell degeneration) were noted at doses above the normal concentration recommended for a limit test (1000 mg/kg bw/d) in the test guidelines for repeated dose toxicity (REACH Test Method Regulation (EC) 440/2008, methods B.7, and B.26) or if observed at doses below the guidance levels for classification as STOT RE, were not considered serious enough. This is the case for liver cell hypertrophy alone, liver weight increase, increased liver enzymes.

The main effects observed on the kidneys were as follows. In rats, increased urea and creatinine concentration indicated renal dysfunction, but the effects were not associated to any other macroscopic or microscopic abnormal finding except increases in kidney weight in rats. Effects were only seen in rats at doses above guidance values for classification (at 900 ppm (201 mg/kg bw/d) after 90 days of treatment and at 9000 ppm (680 mg/kg bw/d) after 28 days of treatment).

Overall, there was no serious effect on the urinary tract that warrants classification.

The main effects observed on the haematopoietic system were:

Increased numbers of Heinz bodies, reduction of red blood cells, and (compensatory) increases in MCV, associated with haemosiderosis after chronic treatment are serious health effects indicating haemolytic anaemia. These toxic effects were only seen in dogs; no indications on anaemic effects were noted in guidance-compliant studies in rats.

a) Heinz bodies are damaged erythrocytes that are composed of denatured protein, mainly haemoglobin and are characteristic for anaemic conditions following chemical insult. Heinz bodies were seen in all three dog studies: the lowest dose was 49 mg/kg bw/d after 1 year treatment, which is above the guidance value (see calculation below).
b) Reductions of red blood cells and haemoglobin were above 20% at 360 mg/kg bw/d in the 28 day study in rats. The effect as such is adverse according to the criteria of Muller et al. (2006). However the effect dose is clearly above the guidance value for oral 28 day studies.
c) Haemosiderosis in the liver of 3/6 female dogs was observed together with reductions of red blood cells and haemoglobin reductions above 10% after 3 and 6 months. Findings are in accordance to the criteria of Muller et al., 2006 advocating classification, but the dosage of 6400 ppm (206 mg/kg bw/d) is far above the guidance value for classification when Haber's law is used (100 mg/kg bw/d divided by 4; serious effect should therefore be evident at about 25 mg/kg bw/d or below).

Overall, cycloxydim causes adverse effects on the haematopoietic system, but the doses causing these effects were high and above the guidance values as referred to in the criteria for classification (3.9.2, Annex I, CLP).

The RAC supported the Dossier submitter's proposal that no classification is warranted for STOT RE.

Mutagenicity

Summary of the Dossier submitter's proposal

No information is available in humans from case reports, epidemiological studies, medical surveillance, reporting schemes or national poisons centres according to the DS.
Cycloxydim was tested in a range of *in vitro* and *in vivo* assays measuring different mutagenic endpoints such as gene mutation in bacterial and mammalian cells, chromosomal mutation and unscheduled DNA synthesis *in vitro* as well as *in vivo* in the micronucleus test in mice and in the Chinese hamster bone marrow chromosomal aberration test.
The substance has been found to be strongly cytotoxic (without S-9 activation); e.g. in mouse lymphoma cells cytotoxic effects were already found at concentrations of 8-10 mg/mL; Chinese hamster ovary cells were even more sensitive showing toxic effects at 1.67 mg/mL. In addition, in some *in vitro* tests, indications of genotoxic potential were found at cytotoxic concentrations: mouse lymphoma forward mutation test was positive at 20 mg/mL, and the Chinese hamster ovary cells showed increased aberrations at a concentration of 3.0 mg/mL.
Nevertheless, in both *in vivo* studies which also investigated chromosomal aberrations, clear negative results were obtained. In the ADME studies it was shown that cycloxydim was detected in the bone marrow from 5 to 120 hours post-administration. Therefore, the systemic availability of cycloxydim in the *in vivo* genotoxicity studies is considered to be plausible.
Effects observed in the *in vitro* and *in vivo* mutagenicity studies do not meet the criteria for classification and labelling for mutagenicity. Thus, it can be concluded that there is no evidence of a genotoxic potential of cycloxydim, and therefore, no classification is proposed.

Comments received during public consultation

No specific comments were received on mutagenicity.

Assessment and comparison with the classification criteria

The available vitro and in vivo tests indicated that cycloxydim has no genotoxic potential. A proposal for classification is therefore not warranted.

Carcinogenicity

Summary of the Dossier submitter's proposal

Carcinogenicity: oral
No information is available in humans from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres according to the DS.
Based on the results of two studies in rats (18- and 24 months) and one in mice (24 months) that were available, there are no indications of treatment-related increases in non-neoplastic and neoplastic responses. Since no oncogenic effects were observed either in rat or in mouse carcinogenicity studies conducted with cycloxydim, no classification is warranted (according to criteria in DSD and CLP).

Carcinogenicity: inhalation
No data available.

Carcinogenicity: dermal
No data available.

Comments received during public consultation

One Member State wished to have more information on tumour incidences. As there were no indications on any dose-related or treatment-related effect the Dossier submitter decided not to change the documentation.

Assessment and comparison with the classification criteria

There was no indication on any treatment-related increased tumour rates in two oral carcinogenicity studies in rats and in one mouse carcinogenicity study. An increased incidence of bile duct proliferation (without any tumour response originating from the bile duct) was observed in male rats in both rat studies.
The RAC agreed with the proposal that classification with regard to carcinogenicity is not required.

Reproductive toxicity

Summary of Dossier submitter's proposal

No information is available in humans from case reports, epidemiological studies, medical surveillance, reporting schemes and national poisons centres according to the DS.
In a two-generation drinking water study in rats (Hellwig et al., 1988), no effects on fertility were observed at any dose tested. At 400 ppm, maternal toxicity included reduced feed and water consumption as well as reduced body weight and/or body weight gain. Therefore, the maternal NOAEL was set at 100 ppm. The developmental NOAEL was set at 400 ppm, based on reduced survival, growth and developmental retardation in pups at 1600 ppm (at a maternally toxic dose).
In a prenatal toxicity rat study (Hellwig & Hildebrand, 1987a), no effects on foetuses were observed below the level at which maternal toxicity occurred, i.e. 400 mg/kg bw/d (measured as a statistically significant reduced body weight and body weight gain of dams). The foetuses of the 400 mg/kg bw/d group showed delayed ossifications which contributed to lower foetal weight/slower development as the consequence of maternal effects (lower body weight/gain). No malformations were observed.
In a prenatal toxicity study with special attention to maternal toxicity (Hellwig & Hildebrand, 1987c), dams showed lower food consumption, statistically significantly reduced corrected body weight gain, statistically significantly decreased RBC, haemoglobin and haematocrit, all at 400 mg/kg bw/d. No detailed foetus examination was conducted, since the emphasis of the study was on maternal toxicity. However, at 400 ppm, no effects on foetal weight were observed.
In a supplemental pre-, peri-, postnatal toxicity study in rat (Hellwig & Hildebrand, 1987b), the persistence of changes to vertebral bodies caused at 400 mg/kg bw/d was investigated. Insufficient cartilaginification of the 13^{th} rib was observed but was reversible at 7 and 21 day p.p., while dumbbell-shaped or bipartite ossification centers of vertebral bodies and missing or incomplete ossification of sternebre were still present at day 7 and 21 p.p. However, it should be noted that at 400 mg/kg bw/d in this study, the dams had very marked reduction of body weight gain from days 6 to 8 (-64%) and marked reduction in body weight gain during treatment days 6 to 15 (-18%).
In an *in vitro* whole embryo culture study in rat, no indication of embryotoxic effects by cycloxydim or by the main metabolite TSO were observed. The effects observed in rat foetuses in other studies were therefore considered to be a consequence of maternal toxicity.
In a prenatal rabbit toxicity study (Merkle & Hildebrand, 1985 and Hellwig, 1986 (amendment)), no effects on rabbit foetuses were observed below the level at which maternal toxicity (at 100 mg/kg bw/d) was observed. Maternal toxicity at 200 mg/kg bw/d was reported as a reduced mean daily food intake (-20% from days 12 to 16), statistically significantly reduced body weight gain from days 11 to 14 and from days 21

to 23. The effects on foetuses at 200 mg/kg bw/d were either without any dose response or within historical control data. No teratogenic effects were observed.

Comments received during public consultation

There were no specific comments received on reproductive toxicity during the public consultation of the CLH proposal. However, during a targeted expert consultation (5-19 November 2012), one Member State Competent Authority and one expert provided information on the interpretation of some data concerning maternal and developmental toxicity effects of cycloxydim and the relevance of the findings for classification. For further details see "*Overall conclusion of the rat developmental toxicity studies (Hellwig & Hildebrand, 1987a-c)"* below.

Assessment and comparison with the classification criteria

Fertility
The RAC agreed with the Dossier submitter's view that in the absence of treatment-related effects on reproductive function, a proposal for classification could not be justified.

Developmental toxicity
2-generation drinking water rat study (Hellwig et al., 1988)
Cycloxydim had smaller effects on F1 pup mortality and viability at Day 0 until Day 4 at 1600 ppm, which was 90% to 94% of control values, corresponding to reductions in food and water consumptions (Table 79, Background document (BD), Annex I) and lower body weight gain in F0 dams (Table 78, BD).
No statistically significant adverse effect on pup survival and development was observed in the F2-pups. The only effect observed was a lower body weight in high dose F2 pups at postnatal day 21 (Table 79, BD). Corresponding findings in F1 dams were significantly reduced body weight gain and significantly lower absolute weight as compared to controls at postnatal day 21 (-13%) and reduced food and water consumption during the lactation phase (-14 % and -23%, resp., BD Table 78,), In general, reduction in food consumption and reduction in body weight gain during gestation and lactation was less prominent in F1 dams compared to F0 dams (see Table 78, BD).
Effects on survival, growth and development (retardations of ear unfolding and eye opening) in F1a and F1b pups of the high dose groups can be associated with effects on F0-dams during the gestation and lactation phases. In F0 dams, the observed reductions in food and water consumption and reduced body weight gain were most prominent during lactation. This can be related to a higher test substance uptake of F0 dams on a mg/kg bodyweight basis during lactation (1600 ppm in drinking water corresponds to ≈250 mg/kg bw/d during lactation versus 120-150 mg/kg bw/d during gestation phase, Table 77, BD) and can be interpreted to cause the reduced F1 pup survival and litter weight at postnatal day 21 (BD Table 79).
A consistent relationship between the observed reductions in food/water consumptions resulting in lower body weight gains and the effects on pup weights and survival was found in both generations. When dams consumed significantly lower amounts of food/water, the effects on pup weight and survival were evident (e.g. at the end of the lactation phase). In general effects were less prominent in F2-pups, this is in line with the observation that F1 dams showed also less severe reductions in food and water consumption.
It is noted that effects on pup weight are also reported in F2 at 100 and 400 ppm but litter size in these two groups is elevated, which may explain in part the reduced individual pup weight compared to the controls. Besides, fetal weight in F2 controls was quite high compared to controls in previous generations so that the significance of the effect in F2 at 100 and 400 ppm is questionable.
No malformations were observed. (Data on delayed or abnormal ossifications are not available.)

Effects seen on pups in the 2-generation study are not relevant to justify classification mainly because they are most likely secondary to maternal toxicity.

Prenatal toxicity study in rabbits - Merkle & Hildebrand, 1985 and Hellwig, 1986 (amendment)

A significantly increased rate of resorptions was observed in rabbits that received 400 mg/kg bw/d on gestation days (GDs) 6-18. At this dose, the rabbits lost body weight during GDs 6-18 (-4% of initial body weight, in controls +3% of initial body weight) and food consumption was reduced by more than 56%. Body weight loss is considered a severe maternal effect and the observed increase in resorptions and the increased incidences of external variations (pseudoankylosis) and skeletal variations (fused sternebrae) were considered to be secondary to non-specific toxicity.

In the absence of treatment-related effects on pup development which could be considered not to be a secondary non-specific consequence of maternal toxicity and in the absence of teratogenic effects, no classification for developmental effects is warranted based in this study.

In contrast to the two foregoing studies, the developmental studies in rats (Hellwig & Hildebrand, 1987a-c) caused the RAC to consider whether cycloxydim could be regarded as a suspected reproductive toxicant:

Prenatal toxicity in Wistar rats (Hellwig & Hildebrand, 1987a)

- Increased foetal incidences of dumbbell-shaped ossification centers in the thoracic region were observed at 400 mg/kg bw/d (30% vs. 2.5% in controls). No increase was seen at 100 and 200 mg/kg bw/d. The Dossier submitter considered the effect as an anomaly consisting of dumbbell-shaped or bipartite vertebral bodies with the involvement of cartilage (combined incidence 34% vs. 5.6%). The Dossier submitter stated that according to current harmonised terminology and classification of rat fetal skeletal effects, these skeletal findings termed 'anomalies' in the study report are today classified as variations.
- Body weight gain in dams receiving 400 mg/kg bw/d during gestation was only mildly affected, on the GD 6-15 it was 92% of the control value and the corrected body weight gain (net weight change during the study) was 91% of controls (see Table 80, BD). A lower foetal weight (around 5%) may be related to the lower body weight gain in dams. The assumptions remains uncertain, as only body weight gain data are available and no absolute values on body weight.
- It is concluded by the Dossier submitter that the foetal weight reductions were correlated with an increase in the number of skeletal retardations. However, mean foetal weight was only slightly lower than the control values (male pups 94.8%, female pups 95.6%, see Table 81, BD). It appears questionable whether a 4-5% lower foetal body weight causes significant increases in skeletal retardations (dumbbell-shaped ossification centers of thoracic region, incomplete ossification of sternebrae; see Table 82, BD).
- Chernoff et al. (2008) underlined that a reduction in food intake and the resultant under-nutrition would be more likely to induce foetal growth retardation, if these effects occur late in gestation when foetal growth is the greatest. The effect of cycloxydim on maternal food consumption is mainly reported at GD 7-8, which is quite early in the embryo-foetal development and it questions its impact on reduced foetal weight.

Supplemental prenatal toxicity in Wistar rats with special attention to maternal toxicity (Hellwig & Hildebrand 1987c)

- This supplementary study confirmed a mild reduction in body weight gain in dams receiving 400 mg/kg bw/d from GD 6-15. Body weight gain from GD 0-20 was 94.7% of the control value (corrected 88.1%, see Table 84b, BD). Absolute body weight at GD 20 reached 99.1% of control values. Foetal weights at 400 mg/kg bw/d were 96% of controls for male pups and 97% for female pups (Table 86, BD).

The study confirmed mild effects on body weight of dams and pups. No information on skeletal effects was given.

Supplementary pre-peri-postnatal toxicity study in Wistar rats (Hellwig & Hildebrand 1987 b)

The effects were summarised by the Dossier submitter as follows: 'The insufficient cartilagination of the 13th rib was reversible (7 and 21 day p.p.), while dumbbell-shaped or bipartite ossification centers of vertebral bodies and missing or incomplete ossification of sternebre were still present at day 7 and 21 p.p. However, it should be noted that at 400 mg/kg bw/d in this study, the dams had very marked reduction of body weight gain from days 6 to 8 (-64%) and marked reduction in body weight gain during treatment days 6 to 15 (-18%)'.

- Dumbbell-shaped of vertebral body/bodies with involvement of cartilage (cartilaginous bone precursor) in the thoracic region was observed at GD 20 at a foetal incidence of 16% in the control group and 67.3% in the 400 mg/kg bw/d treatment group, with litter incidence of 100% compared to 54.6 % in the control group (see Table 90 in BD, prenatal study segment).
- The finding of significantly increased dumbbell-shaped or bipartite ossifications of the vertebral bodies in the thoracic region was confirmed in the postnatal segment study at 400 mg/kg bw/d on postnatal day (PND) 7. The incidences remained significantly elevated on PND 21, i.e.in the same range as on PND 7 (foetal incidence: 27.5 vs. 4.6% in controls, % foetuses/litter: 26.56% vs. 4.41%. see Table 93, BD).
- The finding of significantly increased dumbbell-shaped or bipartite ossifications on the vertebral bodies in the thoracic region is consistent with the findings in the other prenatal toxicity study in rats (Hellwig & Hildebrand, 1987a). In the other study foetal incidences were separately documented for each effect. At 400 mg/kg bw/d the Dossier submitter described in the text (BD) significantly increased foetal incidences of 'dumbbell-shaped or bipartite vertebral bodies with involvement of the cartilage', while in the table 82 (BD) it says 'dumbbell-shaped ossification centers, thoracic region' at foetal incidence of 30% vs. 2.5% in controls. As this effect was judged as an anomaly, the terms are considered to describe the same effect. The persistence of the effect as seen in the postnatal segment study from Hellwig & Hildebrand (1987b) corresponds to the proposed classification as dumbbell-shaped vertebral bodies with involvement of cartilage.
- The summary of maternal body weights effects (see Table 88, BD) highlights that maternal body weight gain was significantly lower (36% of control value) during the first days of treatment (GD 6-8). For the whole treatment period, dams treated with 400 mg/kg bw/d on GD 6-15 gained body weight at 88.2% compared to body weight gain of controls. No data are given on the absolute body weights. Foetal weight was at 92.6% of the control value (see Table 89, BD).
- It remains questionable whether a 12% reduction of maternal body weight gain during GD 6-15 as compared to the controls and a 7% lower total weight of the foetus are sufficiently severe effects to explain the significant increases in skeletal retardations (see Table 90, BD). The marked reduction during GD 6-8 and the mild to moderate reduction of body weight gain over the total period of GD 6-15 indicates that animals are mainly affected during the first days of treatment and have adapted during the following days.
- The second part of this study (postnatal segment) demonstrated that pup survival on PND 21 was significantly lower than in controls (Table 91, BD). Mean number of live pups/dam was also significantly lower (11 live pups/dam) compared to 12.3 in control dams. As the treatment of dams stopped at GD 15 treatment during lactation period was not the cause of pup deaths.
- The body weight gain was reduced in dams at GD 15 (79.2% of the control values, Table 88, Group 4, BD). However no data on absolute body weight and on body weight at PND 21 was reported in this dossier.

- Examinations of pups on PND 7 and PND 21 after birth showed that the observed skeletal anomalies had a continuous tendency towards lower incidences at PND 7 and PND 21 However, two of the three reported skeletal effects (dumbbell-shaped or bipartite ossifications on vertebral bodies in the thoracic region and incomplete ossification of sternebrae) remained at significantly higher level (at PND 21% fetus/litter 26.56% vs. 4.41% in controls, Table 93, BD).

Overall conclusion of the rat developmental toxicity studies (Hellwig & Hildebrand, 1987a-c):

The observed adverse effects on pup survival, growth and development in rats could not completely be attributed to maternal toxicity. According to the classification criteria (3.7.2.4.3, Annex I CLP), cycloxydim was not so toxic that maternal death or severe inanition was the result, nor were they prostate and incapable of nursing the pups. Therefore it is not reasonable to assume that developmental toxicity is produced solely as a secondary consequence of maternal toxicity and so to discount the developmental changes.

The following key events as reported in the rat studies support this view.

Two developmental rat studies (Hellwig and Hildebrand, 1987a,b) revealed significantly increased rates of skeletal effects consisting of dumbbell-shaped ossification centers of thoracic vertebrae with involvement of cartilage, incomplete ossification of the sternebrae and (only in one study) insufficient cartilaginification of 13th rib at 400 mg/kg bw/d cycloxydim.

Postnatal follow-up demonstrated a tendency towards lower incidences at PND 7 and PND 21. However the incidences of skeletal effects were still significantly higher for incomplete ossification in the thoracic region and the sternebrae, only the delayed cartilaginification of the 13th rib reached similar incidences as control animals.

The observed skeletal abnormalities were identified as malformations in accordance with the harmonised classification system on foetal skeletal terminology (Solecki et al., 2001, Makris et al., 2009). The effects may also occur spontaneously. The observation that their incidences in decreases from the day of Caesarean section (i.e. 5 days after finalisation of treatment), PND 7 to PND 21, but remained elevated compared to controls, is in agreement with the interpretation of a persistent structural change (malformations).

The Dossier submitter assessed the most critical effect 'dumbbell-shaped or bipartite ossification centers of vertebral bodies, thoracic region, with involvement of cartilage' as an anomaly and noted that according to the current terminology and classification harmonized criteria this effect is classified as a variation.

Although one expert commented during the targeted expert consultation (5-19 November, 2012), that dumbbell-shaped ossification centers in the thoracic region should be regarded as a variation or retardation, the other commenting expert (MSCA) provided a proposal for the interpretation of the dumbbell-shaped vertebral bodies as malformations, if the cartilaginous bone precursor is affected as well as the subsequent process of ossification. The involvement of the cartilage has been documented by the Dossier submitter.

As an outcome of a harmonization workshop on terminology and classification of foetal abnormalities Solecki et al. (2001) distinguished between "dumb-bell" and "dumb-bell ossification", with the former being considered as a malformation and the latter a variation. It is stated that 'The term dumbbell implies that the bone precursor is affected as well as the ossification site and the change is likely to be permanent. Therefore the condition would classify it as a malformation. Dumbbell ossification would suggest that only the ossification site is abnormally shaped and, as with bipartite ossification, this alteration would be classified as a variation.'

In the update of the harmonisation activity on developmental abnormalities, Makris et al. (2009) proposed that a dumbbell-shaped thoracic centrum was a structural abnormality involving the bone precursor (cartilage), while dumbbell ossification or bipartite ossification was a change of the ossification state.

Thus the RAC concluded that the effect 'dumbbell-shaped' or 'bipartite ossification centers of vertebral bodies' in the thoracic region, with involvement of cartilage is

a malformation. Taking into account its persistence until PND 21 it was considered as evidence for developmental toxicity.

Comparison with the criteria for classification

(Criteria in 3.7.2.4.3 Annex I, CLP)
"Classification shall not automatically be discounted for substances that produce developmental toxicity only in association with maternal toxicity, even if a specific maternally-mediated mechanism has been demonstrated. In such cases, classification in Category 2 may be considered more appropriate than Category 1.
However, when a substance is so toxic that maternal death of severe inanition results, or the dams are prostate and incapable of nursing the pugs it is reasonable to assume that developmental toxicity is produced solely as a secondary consequences of maternal toxicity and discount the developmental effects."
Cycloxydim did not cause severe disturbance of general health conditions of treated dams at doses which caused reduced pup weights, reduced survival and developmental variations and retardations.
As maternal toxicity at 400 mg/kg bw/d in the developmental studies consisted of lower bw gain (-9% in Hellwig and Hildebrand 1987a, 5.3% % in Hellwig and Hildebrand, 1987c, -9% and -21% in prenatal and postnatal segment in Hellwig and Hildebrand, 1987b) with most of this reduction observed during the first few days of the exposure period and no other sign of general health disturbance, it is unlikely to contribute the foetal skeletal findings to lower maternal bw gain.
The reduction of bw gain was mainly observed during the day 6-8. As ossification occurs during the late gestation period, it is unlikely that the skeletal effects were caused as nonspecific consequence of mild-moderate lower bw gain.
Lower maternal growth may have affected foetal growth. However, the magnitude of the reduction foetal weight reduction was only small (5-7% in three studies, Hellwig & Hildebrand 1987a, b in which pup data were available).
Only for the prenatal toxicity study on maternal toxicity (Hellwig & Hildebrand 1987c) data on absolute maternal bw were given. Dams receiving 400 mg/kg bw/d during GD 6-15 showed 5.3% reduction in bw gain and bw at GD 20 was 99.1% compared to controls.
In conclusion, the RAC considered that the level of maternal toxicity was not sufficiently severe to explain the reduced pup weights, lower pup survival and skeletal anomalies as only secondary to maternal toxicity. The observed tendency of reduced incidences of the skeletal anomalies after birth and after termination of exposure, appears to confirm the retardational nature of the effects. However persistence of significantly increased incidences of skeletal effects until postnatal day 21 cannot be interpreted in a way that these effects are only minor developmental changes that do not justify classification as for developmental toxicity. The criteria (3.7.2.4.3., Annex I, CLP) say that *"Classification is not necessarily the outcome in case of minor developmental changes, when there is only small effects on foetal/pup body weights, or retardation of ossification when seen in association with maternal toxicity".*
Consistent evidence of significantly increased incidences of 'dumbbell-shaped or bipartite ossification centers of vertebral bodies, thoracic region, with involvement of cartilage' from several rat studies is considered as a malformation. The persistence of this skeletal anomaly until postnatal day 21 counter argues against the interpretation of a minor developmental change. Information on potential functional impairment related to this skeletal anomaly that may occur during life stages later than postnatal day 21 is not available.
The fact that this lesion occurred spontaneously (although at significantly lower rates) in control animals and its overall incidences decreased by postnatal day 21 was considered as indicative for a less serious effect that does not justify classification in Cat. 1B.
In conclusion, the RAC was of the opinion that there is evidence of developmental effects that could not solely be attributed to maternal effects and therefore the observed developmental effects fulfil the requirements for classification with Repr. 2, H361d (CLP).

As the criteria for DSD are very similar to the CLP criteria, classification with Repro Cat 3, R63, is warranted according to the DSD.

ENVIRONMENTAL HAZARD ASSESSMENT

Summary of the Dossier submitter´s proposal.

Degradation and environmental distribution

The criteria for rapid degradation are not fulfilled since:

- Cycloxydim was hydrolytically rather stable at neutral and alkaline conditions (DT_{50} at pH 7 =172 and 264 days, DT_{50} at pH 9 =206 and 958 days) in two hydrolysis studies.
- In the photolysis study cycloxydim was rapidly photolytically degraded but the main product BH 517-T1SO, detected with >60% of AR in both solutions (pH 7 and pH 9), is considered stable.
- Aquatic toxicity studies for metabolites BH 517-TSO, BH 517-T1SO, BH 517-T2S and BH 517-TGSO are available but they are missing for BH 517-T1S and BH 517-T2SO.
- No data are available with regard to the ready biodegradability.
- In water/sediment studies the substance was degraded with a DT50 whole system of:
    - System "Kellmetschweiher" (pH 8.8) =30.6 d (SFO),
    - System "Berghäuser Altrhein"(pH 8.5) =14.3 d (SFO)

  The arithmetic geomean =20.8 d.
- The mineralization to CO_2 was low with maximal amounts of 4.8% at day 100 in "Kellmetschweiher" system and 13.9% at day 100 in "Berghäuser Altrhein" system.

The adsorption and desorption of cycloxydim and its metabolites were studied in different soils and the results show that parent compound and its metabolites are characterised by a low adsorption.

No measured bioconcentration factor is available. The log K_{ow} at 25ºC and pH 7 is 1.36 indicating low potential for bioaccumulation.

Acute (short-term) aquatic toxicity.

Six acute aquatic toxicity tests for fish, Daphnia, algae and aquatic higher plant were submitted. According to these tests the most sensitive species is *Daphnia Magna* with an EC_{50} >70.8 mg/L.

Chronic (long-term) aquatic toxicity.

Five chronic aquatic toxicity tests for fish, Daphnia, algae and aquatic higher plant were submitted. According to these tests the most sensitive species is fish *(Oncorhynchus mykiss)* with a NOEC =21.5 mg/L.

On the basis of these data, the Dossier submitter proposes not to classify the substance for aquatic hazard according to both DSD and CLP.

Comments received during public consultation

No specific comments were received on this endpoint.

Assessment and comparison with the classification criteria

The RAC supports the Dossier submitter's proposal of no classification under DSD and CLP (2nd ATP) regarding environmental hazards, according to the following assessment.

Degradation

According to the information supplied in the dossier cycloxydim does not fulfil the criteria for rapidly degradable substances.

> Cycloxydim was hydrolytically rather stable at neutral and alkaline conditions (in two hydrolysis studies, DT_{50} at pH 7 =172 and 264 days, DT_{50} at pH 9 =206 and 958 days).

It is rapidly photolytically degraded; however, the main product BH 517-T1SO, detected at concentrations >60% of AR in both solutions (pH 7 and pH 9) is considered stable.

There is no available data with regard to the ready biodegradability.

In water/sediment studies the substance was degraded with a DT_{50} whole system (arithmetic geomean between two system) =20.8 d. Therefore the degradation cannot be considered as rapid, since *the substance is not ultimately degraded within 28 days with half-life <16 days corresponding to a degradation rate >0.043 day^{-1}.*

There are also two metabolites which appear at concentrations >10% AR: BH 517-TSO (76.2% at 60 d) and BH 517-T1S (11% at 100 d). However, there are not data about DT_{50}, and therefore they should be considered stable. In addition, the mineralization to CO_2 was low with maximal amounts of 13.9% at day 100, which confirms the conclusion of no rapidly degradable.

Soil degradation studies were also supplied in the dossier, and although according to the laboratory studies, cycloxydim is rapidly degradable with a DT_{50} (12ºC) <1.9 d, its main metabolite BH 517-TSO (90.4% at 1 d) shows a DT_{50} (12ºC) >16 days. Although field studies show a faster degradation than laboratory studies, cycloxydim should not be considered rapidly degradable because of the evidences of the other tests.

In conclusion, cycloxydim should be considered not readily / not rapidly degradable.

Bioaccumulation

No measured BCF is available. The log K_{ow} (=1.36 at 25ºC and pH =7) shows a low potential for bioaccumulation.

Toxicity

Cycloxydim shows a low toxicity, both acute and chronic, for the three trophic levels (fish, Daphnia and algae). According to these tests the most sensitive species in the acute studies is *Daphnia Magna* with an EC_{50} >70.8 mg/L.

In chronic studies on invertebrates, algae and aquatic plants, the endpoints (NOEC/EC10s) are >10 mg/L. There is not a suitable chronic test for fish because the available prolonged toxicity study following the OECD 204 guideline cannot be considered a chronic test[1]. However, LC_{50} for fish is >100 mg/L and therefore, applying the surrogate approach, fish data warrant no classification for long term hazards.

Conclusions on environmental classification according to Directive 67/548/EEC

Cycloxydim does not meet the criteria for ready degradation**.** This conclusion is based on the water/sediment-study with a $DT_{50\ \text{whole system}}$ geomean =20.8 d (pH 8.8 – 8.5).

No experimental data on the bioconcentration factor is available. However since the measured log Kow value is 1.36 (at pH 7 and 25°C) cycloxydim has a low potential of bioaccumulation in aquatic system.

Cycloxydim shows low acute and chronic toxicity to aquatic organisms (fish, Daphnia, algae and aquatic higher plants) because all relevant acute endpoints (EC/LC_{50}) are

[1] Technical Guidance Document on Risk Assessment. Part II. Pag. 186.

>70.8 mg/L and the available chronic endpoints for invertebrates, algae and aquatic plants (NOEC/EC_{10}) are >10 mg/L.

Thus, no classification is proposed regarding environmental hazards.

Conclusions of environmental classification according to Regulation EC 1272/2008

Acute Aquatic Hazard
The relevant acute endpoints (EC/LC_{50}) of cycloxydim are higher than 1 mg/L (>70.8 mg/L), therefore no classification for acute aquatic hazard is proposed.

Chronic Aquatic Hazard
Although cycloxydim is considered a not rapidly degradable substance, the available chronic endpoints (NOEC/ EC_{10}) are higher than 10 mg/L.
A suitable chronic test for fish has not been submitted but the LC50 (fish) is >100 mg/L and therefore, applying the surrogate approach, fish data warrant no classification for long term hazard.
According to these data no classification for long term aquatic hazards is proposed.
Note: Aquatic toxicity studies for metabolites BH 517-TSO, BH 517-T1SO, BH 517-T2S and BH 517-TGSO are available but are missing for BH 517-T1S and BH 517-T2SO. Thus a reliable classification regarding the hazard to aquatic environment for all degradation products is not possible.

ANNEXES:

Annex 1	Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier submitter
Annex 2	Comments received on the CLH report, response to comments provided by the Dossier submitter and the RAC (excl. confidential information)
Annex 3	Comments received during a targeted expert consultation related to the potential reproductive toxicity of cycloxydim (5-19 November 2012)