Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

Bifenazate (ISO)

EC number: 442-820-5
CAS number: 149877-41-8

CLH-O-0000003146-79-02/F

Adopted

5 December 2013

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

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CLH-O-0000003146-79-02/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:

Chemicals name: Bifenazate

EC number: 442-820-5

CAS number: 149877-41-8

The proposal was submitted by **The Netherlands** and received by the RAC on **26 March 2013.**

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).

PROCESS FOR ADOPTION OF THE OPINION

The Netherlands 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 **26 March 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **10 May 2013**.

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by the RAC: **Norbert Rupprich**

Co-rapporteur, appointed by the RAC: **Helena Polakovicova**

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

The RAC opinion on the proposed harmonised classification and labelling was reached on **5 December 2013** 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 **Bifenazate** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	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	No current Annex VI entry										
Dossier submitters proposal	607-715-00-2	bifenazate (ISO); isopropyl 2-(4-methoxybiphenyl-3-yl)hydrazinecarboxylate	442-820-5	149877-41-8	STOT RE 2 Skin Sens. 1B Aquatic Acute 1 Aquatic Chronic 1	H373 H317 H400 H410	GHS08 GHS07 GHS09 Wng	H373 H317 H410		M =1 M =1	
RAC opinion					STOT RE 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H373 H317 H400 H410	GHS08 GHS07 GHS09 Wng	H373 H317 H410		M =1 M =1	
Resulting Annex VI entry if agreed by COM					STOT RE 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H373 H317 H400 H410	GHS08 GHS07 GHS09 Wng	H373 H317 H410		M =1 M =1	

Classification and labelling in accordance with the DSD

	Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
Current Annex VI entry	No current Annex VI entry							
Dossier submitters proposal	607-715-00-2	bifenazate (ISO); isopropyl 2-(4-methoxybiphenyl-3-yl)hydrazinecarboxylate	442-820-5	149877-41-8	R43 N; R50-53	Xi; N R: 43-50/53 S: 24-37-60-61	N; R50-53: C ≥ 25 % N; R51-53: 2,5 % ≤ C < 25 % N; R52-53: 0,25 % ≤ C < 2,5 %	
RAC opinion					R43 N; R50-53	Xi; N R: 43-50/53 S: (2-)24-37-60-61	N; R50-53: C ≥ 25 % N; R51-53: 2,5 % ≤ C < 25 % N; R52-53: 0,25 % ≤ C < 2,5 %	
Resulting Annex VI entry if agreed by COM					R43 N; R50-53	Xi; N R: 43-50/53 S: (2-)24-37-60-61	N; R50-53: C ≥ 25 % N; R51-53: 2,5 % ≤ C < 25 % N; R52-53: 0,25 % ≤ C < 2,5 %	

HUMAN HEALTH HAZARD ASSESSMENT

RAC evaluation of acute toxicity

Summary of the Dossier submitter's proposal

Based on the available acute toxicity studies the dossier submitter (DS) did not propose to classify Bifenazate for acute oral, dermal or inhalation toxicity.

Comments received during public consultation

No comments were received during public consultation

Assessment and comparison with the classification criteria

Oral
Bifenazate was tested in an acute oral test with rats at a dose of 5000 mg/kg. No treatment-related effects were observed. In an acute oral test with mice at 5000 mg/kg one female died on day 8 after dosing. This animal presented the following unspecific clinical effects the day before death: lacrimation, lethargy, irregular gait, laboured breathing, and decreased faecal volume. According to CLP and DSD criteria a substance is not classified for acute oral toxicity if the oral LD_{50} is > 2000 mg/kg.

Dermal
Bifenazate was tested in an acute dermal test with rats at a dose of 5000 mg/kg. No mortality and no treatment-related effects were observed. According to CLP and DSD criteria a substance is not classified for acute dermal toxicity if the dermal LD_{50} is > 2000 mg/kg.

By inhalation
The only available inhalation study with Bifenazate is an acute inhalation study with rats at a dose of 4400 mg/m³ (4.4 mg/l), at which high dust concentration, no mortality was observed. A few treatment related observations were noted immediately following the exposure, including respiratory (moist rales with gurgling sounds due to fluid in the lung) and secretory (chromodacryorrhea, red/brown nasal discharge) symptoms. Similar signs were exhibited by animals for up to a week following exposure. During the remainder of the 14-day post-exposure observation period, test animals were generally without symptoms. According to CLP and DSD criteria a substance should not be classified for acute inhalation toxicity if the inhalation LC_{50} is above 5 mg/l (dusts and mists).

In summary, Bifenazate does not meet the classification criteria for acute toxicity under CLP or DSD (oral, dermal, or by inhalation). There were no comments received during public consultation. The RAC supports the proposal of the dossier submitter (DS) not to classify Bifenazate for acute oral, dermal and inhalation toxicity.

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

Summary of the Dossier submitter's proposal

Based on the assessment of the non-lethal adverse effects caused by Bifenazate at limit doses in the acute oral and inhalation studies, the DS did not propose classification for specific target organ toxicity - single exposure.

Comments received during public consultation

No comments were received during public consultation.

Assessment and comparison with the classification criteria

Non-lethal adverse effects in acute toxicity studies (limit test design) were only observed in the oral mice study and the rat inhalation study, not in the oral and dermal rat study.

In the acute oral study with mice at 5000 mg/kg one female died. In this animal the following unspecific clinical effects were observed: lacrimation, lethargy, irregular gait, laboured breathing, and decreased faecal volume. Based on these adverse effects in one animal at the rather high oral dose of 5000 mg/kg (beyond the cut-off level for category 2 of 2000 mg/kg) it is the RAC's opinion that the criteria for STOT SE (category 1 and 2) are not fulfilled. Oral toxicity testing did not result in narcotic effects, thus STOT SE (category 3) is not triggered either.

In the acute inhalation study in rats at a dose of 4400 mg/m³ (4.4 mg/l), a few treatment related observations were noted immediately following the exposure, including respiratory (moist rales) and secretory (chromodacryorrhea, red/brown nasal discharge) symptoms. Similar signs were exhibited by animals for up to a week following exposure but not later.
It is the RAC's opinion that the criteria for STOT SE (category 1 and 2) are not fulfilled; the adverse effects are considered transient and only occurred at a rather high dose of 4400 mg/m³. The clinical symptoms observed do not indicate narcotic effects. Although it cannot be excluded that the adverse effects observed may be at least partly irritative in origin, it is the RAC's opinion that these adverse effects do not warrant STOT SE Category 3 for respiratory tract irritation.

No comments were received during public consultation. RAC agreed with the DS that no classification for Bifenazate for STOT SE is warranted.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier submitter's proposal

Based on the negative result of a rabbit skin irritation study (OECD Test Guideline 404) the DS did not propose to classify Bifenazate for skin irritation.

Comments received during public consultation

No specific comments were received during public consultation.

Assessment and comparison with the classification criteria

Two out of six rabbits showed slight erythema half an hour after the 4-hour application. During the relevant observation period (24, 48 and 72 hours post application) no signs of skin irritation (erythema or oedema) were observed. There were no persistent effects. Thus it is concluded that the substance does not meet the classification criteria for skin irritation. The RAC agrees with the DS that no classification for Bifenazate for skin corrosion or skin irritation is warranted Bifenazate.

RAC evaluation of eye corrosion/irritation

Summary of the Dossier submitter's proposal

Based on an eye irritation study in rabbits, Bifenazate was found to be slightly irritating to the rabbit eye. Comparing the degree of eye irritation with the CLH and DSD classification criteria the DS concluded that Bifenazate does not need to be classified for eye irritation.

Comments received during public consultation

No specific comments were received during public consultation.

Assessment and comparison with the classification criteria

With reference to the CLH report, Bifenazate is reported to be mildly irritating to the rabbit eye. Table 4.4.2-2 of the CLH report summarises the effects i.e. some conjunctiva redness, chemosis and discharge was seen one hour after application (score of 1) with redness persisting until 24 h. However, it is evident that for all tested animals the relevant time-weighted experimental scores were below the relevant cut-off levels.

No comments were received during public consultation. Overall, the RAC agrees with the DS that no classification for Bifenazate for eye corrosion/irritation is warranted.

RAC evaluation of skin sensitisation

Summary of the Dossier submitter's proposal

Based on a negative Buehler test and a positive Guinea pig maximisation test (GPMT) the DS proposed to classify Bifenazate for skin sensitisation. The DS proposed to sub-classify Bifenazate as Skin Sens. 1B because intradermal induction in the GPMT was performed with a dose containing more than 1% Bifenazate.

Comments received during public consultation

Comments received during public consultation (4 member states) supported classification of Bifenazate as a skin sensitiser (either with no sub categorisation or with category 1B; the latter however without detailed justification). In response to these comments the DS clarified their preference for subcategory 1B and that subcategory 1A could be excluded.

Assessment and comparison with the classification criteria

In a Buehler test, Guinea pigs were induced topically with 100% w/v of Bifenazate (purity 90.4%). The induction caused no dermal responses. Following challenge with 100% w/v, no dermal elicitation responses were observed in the control or the test group. The sensitivity of this strain of animals was positively tested with dinitrochlorobenzene (DNCB). The following tabular summary of the Buehler test result is based both on the CLH report and the DAR:

Buehler test (OECD 406)	**Induction** [%]			**Challenge** [%]	**Observation**			
	topical day 0 6 h	topical day 6-8 6 h	topical day 13-15 6 h	topical day 27-29 6 h	Erythema			
					30 h after challenge		54 h after challenge	
					total	[%]	total	[%]
control (10 animals)	-	-	-	100%	0/10	0%	n.a.	
treatment group (20 animals)	100% (no irritation)	100% (no irritation)	100% (no irritation)	100%	0/20	0%	n.a.	

n.a.: not available/unknown

Bifenazate was additionally tested in a GPMT. In this test there was a sensitisation rate of 85% with an intradermal induction dose of 6%. The following tabular summary of the GPMT result is based both on the CLH report and the DAR:

GPMT (OECD 406)	**Induction** [%]		**Challenge** [%]	**Observation**			
	intradermal day 0	topical day 6-8 48 h	topical day 20-22 24 h	Erythema*			
				48 h after challenge		72 h after challenge	
				total	[%]	total	[%]
control (10 animals)	-	-	60%	0/10	0%	n.a.	
treatment group (20 animals)	6%	60% (no erythema)	60%	17/20	85%	n.a.	

* Mild scabbing was noted at the test side in 2 control group and 3 test group animals.

The negative Buehler test does not overrule the positive GPMT. For Bifenazate, the classification criteria for skin sensitisation under CLP and DSD (more than 30% of the tested animals need to show a positive response) were fulfilled. Thus the RAC concluded (in agreement with the DS and the comments received during PC) to classify Bifenazate for skin sensitisation (under both CLP and DSD).

In the GPMT, there was a high sensitisation rate (85%) following an intradermal induction dose of 6%. There was no testing of an intradermal induction dose of 1% or lower; thus there is no information whether Bifenazate would result in 1A or 1B, e.g. when based on an extended GPMT with a lower intradermal induction dose. With specific reference to the results in the GPMT the RAC preferred not to specify a sub-categorisation. The DS in their response to comments argued that

the negative result in the Buehler test showed that Bifenazate is not a category 1A (and therefore proposed 1B). The RAC recognised that the current draft guidance does not address this specific situation where there is a completely negative Buehler test; thus without clear guidance showing that a negative Buehler test precludes the subcategory 1A the RAC preferred not to specify a sub-category for Bifenazate.

Overall, the RAC concluded that Bifenazate fulfils the criteria for classification as a skin sensitiser (Skin Sens. 1 according to the CLP and Xi; R43 according to the DSD).

RAC evaluation of repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal

The CLH report contains a detailed description and assessment of the Bifenazate data on repeated dose toxicity. For rats, mice and dogs various toxicity studies (mainly feeding studies) with different exposure durations are available. Haemolytic anaemia is the key effect in the repeated dose studies. In the subacute toxicity studies with rats and mice haemolytic anaemia is associated with increased mortality at high doses.

An overview of the relevant data for repeated dose toxicity, can be found in table 4.7-11 of the CLH report and in the tables presented in the following RAC assessment section.
The key data motivating the DS to propose a STOT RE 2 classification according to the CLP regulation were:

- Increased mortality at 319 mg/kg/d in the 28-day oral rat study
- Increased mortality at 155 mg/kg/d in the 28-day oral mouse study
- A 20% reduction of haemoglobin (Hb) at 24 mg/kg/d in the 1-year oral dog study

The chosen cut-off levels for the 28-day studies (rats, mice) were 300 mg/kg/d (STOT RE 2) and 150 mg/kg/d (Xn; R48/22, DSD), those for the 1-year dog study were 25 mg/kg/d (STOT RE 2) and 12.5 mg/kg/d (Xn; R48/22). For the 28-day oral rat and the 1-year oral dog study the effective dose was similar to the cut-off level for STOT RE 2; for the 28-day oral mouse study the effective dose was about 50% of the corresponding cut-off level for STOT RE 2.

The DS made reference to DSD criteria stating that when studies with varying duration are available, those of the longest duration should normally be used for the purpose of classification. Chronic studies should be evaluated on a case-by-case basis. In contrast to DSD criteria, the CLP criteria do not state any preference for the duration of studies. Thus, given the specific preference in the DSD criteria for longer-term studies, the DS proposed not to classify Bifenazate with R48/22 (DSD).

Comments received during public consultation

Four member states supported the classification proposal of the DS. Two of them indicated that there might be further relevant adverse effects in addition to haemolytic anaemia. One of the member states suggested to also consider DSD.

During public consultation, industry submitted a position paper (Chemtura, 2013), 1) proposing a minimum reduction of Hb of 20% as key criterion for decision finding and 2) indicating that normally the study of longest duration should be used (with reference to the CLP regulation). They specifically referred to the results of the 104-week rat and 78-week mouse study which showed reductions of Hb of less than 10% overall at dosages close to the cut-off levels for STOT RE 2. Following this analysis, industry proposed that classification for STOT RE 2 was not justified. In their response, the DS took the view that based on the CLP regulation and guidance, the results of all relevant studies of different durations of exposure needed to be taken into account.

Assessment and comparison with the classification criteria

The key adverse effects relevant for classification for repeated dose toxicity are haemolytic anaemia and enhanced mortality. The acute oral toxicity of Bifenazate is low (see section Acute Toxicity).

The following tables present study specific cut-off levels, effective doses and the highest doses tested (if there was no effective dose). Because the re-calculated doses in mg/kg/d differ slightly between males and females, the lowest numbers are used in the table. Furthermore, the table focuses on the relevant dose-related parameters for haemolytic anaemia (LOAEL) but NOAELs are not indicated. There are other adverse effects reported at relevant doses (e.g. liver lesions in the 90-day diet study in rats); however, the corresponding reporting of data lacks sufficient quantitative information to provide enable a conclusion on classification.

Cut-off levels and dose-response data for oral repeated dose toxicity studies with emphasis on key data for haemolytic anaemia					
RAT studies, oral administration					
	R48 /25	**STOT RE 1**	**R48 /22**	**STOT RE 2**	**Dose-response data**
Rat 28 d	15 no ED nearby the cut-off level Borderline situation for 33 mg/kg/d with Hb reduction of ~ 10% and pigmentation of spleen	30 no ED nearby the cut-off level Borderline situation for 33 mg/kg/d with Hb reduction of ~ 10% and pigment in spleen	150 Borderline for R48/22 because of pigments in spleen + Hb reduction of ~15% at 66 mg/kg/d)	300 STOT RE 2 because of mortality, pigments and Hb reduction of 17.5% at 319 mg/kg/d	Doses tested: 33, 66 and 319 mg/kg/d 33 and 66 mg/kg/d: RBC, Hb ↓ % unknown, increased pigment in spleen WHO 2006: Hb ↓ of 10.6% at low dose and of 15% at medium dose (females) **319 mg/kg/d (effective dose):** RBC, Hb ↓ % unknown; Congestion and pigment in spleen and liver WHO (2006): Hb ↓ of 17.5% (females) **Mortality,** pale appearance
Rat 90 d	5 no ED nearby the cut-off level	10 no ED nearby the cut-off level	50 no ED nearby the cut-off level	100 ? HDL of 28 mg/kg/d too low	Doses tested: 3, 14 and 28 mg/kg/d 3 mg/kg/d: No decrease of RBC / Hb 14 and 28 mg/kg/d (no effective dose): Hb ↓ (less than 10%), pigmentation in spleen
Rat 2 y	0.625 no ED nearby the cut-off level	1.25 no ED nearby the cut-off level	6.25 No ED at 4 mg/kg/d	12.5 Borderline for 10 mg/kg/d because of Hb reduction of about 10% and haemo-siderosis in spleen	Doses tested: 1, 4 and 10 mg/kg/d 1 mg/kg/d: No haemolytic effects reported. 4 mg/kg/d: RBC ↓ (6.6%) (Chemtura 2013), No significant Hb↓ Haemosiderosis in spleen (CLH report, not in IND statement) 10 mg/kg/d (no effective dose): RBC ↓ (9.8% at week 26) (Chemtura, 2013) Hb ↓ (8.4% at week 26) (Chemtura, 2013) Haemosiderosis in spleen

Mouse studies, oral administration					
	R48 /25	**STOT RE 1**	**R48 /22**	**STOT RE 2**	**Dose-response data**
Mouse 28 d	15 no ED nearby the cut-off level	30 no ED nearby the cut-off level	150 R48/22 because of mortality at 155 mg/kg/d	300 STOT RE 2 because of mortality at 155 mg/kg/d	Doses tested: 34 and 155 mg/kg/d 34 mg/kg/d: No decrease of RBC / Hb reported, increase of pigment in spleen. WHO 2006: RBC ↓ ~ 5% (ns) **155 mg/kg/d (effective dose)** RBC ↓ % unknown, increased pigment in spleen and liver, **mortality (preceded by e.g. ataxia and tremors)** WHO 2006: RBC ↓ ~ 8% (significant $p < 0.05$)
Mouse 90 d	5 no ED nearby the cut-off level	10 no ED nearby the cut-off level	50 no ED nearby the cut-off level	100 ? HDL of 24 mg/kg/d too low	Doses tested: 8, 16 and 24 mg/kg/d 8 mg/kg/d: No decrease of RBC / Hb reported, no increase of pigments. 16 and 24 mg/kg/d (no effective dose) Increased incidence of pigments in spleen, no reduction of RBC / Hb.
Mouse 78-w	0.8 no ED nearby the cut-off level	1.7 no ED nearby the cut-off level	8 no ED nearby the cut-off level	17 no ED nearby the cut-off level	Doses tested: 2, 15 and 35 mg/kg/d 2-15 mg/kg/d: No haemolytic effects reported. 35 mg/kg/d (no effective dose): RBC ↓ (3.5%, Chemtura 2013)

Dog studies, oral administration					
	R48 /25	**STOT RE 1**	**R48 /22**	**STOT RE 2**	**Dose-response data**
Dog 28 d	15 Per-centage of Hb reduction unknown	30 Per-centage of Hb reduction unknown	150 Per-centage of Hb reduction unknown	300 Per-centage of Hb reduction unknown	Doses tested: 7, 28, 49 and 58 mg/kg/d 7 mg/kg/d: RBC, Hb ↓ % unknown 28 mg/kg/d: RBC, Hb ↓ % unknown, pigments in liver 49 and 58 mg/kg/d (no effective dose) RBC, Hb ↓ % unknown, pigments in liver 150 and 300 mg/kg/d: slight cholesterol increase compared to controls
Dog 90 d	5 Per-centage of Hb reduction unknown	10 Per-centage of Hb reduction unknown	50 Per-centage of Hb reduction unknown	100 Per-centage of Hb reduction unknown	Doses tested: 1, 10 and 25 mg/kg/d 1 mg/kg/d: No reduction of RBC / Hb reported, no increase of pigments 10 and 25 mg/kg/d (no effective dose): RBC, Hb ↓ % unknown Urine: brown coloration and ↑ bilirubin Liver: brown pigments 100 mg/kg/d: slight cholesterol increase compared to controls
Dog 1 y	1,25 no ED nearby the cut-off level	2,5 no ED nearby the cut-off level	12,5 no ED nearby the cut-off level	25 STOT RE 2 because of a reduction of Hb of ~20% at the dose of 24 mg/kg/d	Doses tested: 1-9-24 mg/kg/d 1 mg/kg/d: No haemolytic effects reported 9 mg/kg/d: Hb ↓ < 10%, Urine: brown coloration and bilirubin ↑, pigments in liver and kidney **24 mg/kg/d (effective dose):** **Hb ↓ ~ 20%,** Urine: brown coloration and ↑ bilirubin, pigments in liver and kidney

ED = effective dose; HDL= highest dose level tested

The following table presents an overview of the key information for deciding the classification for specific target organ toxicity.

	Classification according to the DSD or CLP criteria			
Study duration/species	**R48/25**	**STOT RE 1**	**R48/22**	**STOT RE 2**
28-d rat	no	no	Borderline	**Criteria fulfilled**
28-d mouse	no	no	**Criteria fulfilled**	**Criteria fulfilled**
28-d dog	insufficient/unclear data	insufficient/unclear data	insufficient/unclear data	insufficient/unclear data
90-d rat	no	no	no	insufficient/unclear data
90-d mouse	no	no	no	insufficient/unclear data
90-d dog	insufficient/unclear data	insufficient/unclear data	insufficient/unclear data	insufficient/unclear data
long-term rat	no	no	no	Borderline
long-term mouse	no	no	no	no
long-term dog	no	no	no	**Criteria fulfilled**

The 28-day rat and mouse data show substance-related mortality near the relevant cut-off level of 300 mg/kg/d and thus justify classification with STOT RE 2. Based on the data available it cannot be judged whether the corresponding haematotoxicity is the main or a minor cause for the mortality observed. For that reason, the RAC proposed not to assign a specific target organ to the STOT RE 2 classification. The long-term studies in rat, mouse and dog are not consistent with respect to a STOT RE 2 classification. The criteria are not fulfilled for the mouse, for the rat there is a borderline situation (because of an Hb reduction of about 10% and haemosiderosis in spleen around the cut-off level), and for the dog the criteria for classification are just fulfilled (20% Hb reduction in the relevant dose range). Clear information about the severity of haemosiderosis in the relevant organs in the studies reported is not available. The overall interpretation of the available data is that the more severe adverse effects occur in the shorter-term repeated-dose toxicity studies (mortality in mouse and rat). However, based on the classification criteria for haematoxicity there is at least borderline concern for the results of the longer-term studies (dog, rat) as well.

The CLP regulation does not address the relative importance of studies with different durations of exposure. The CLP guidance however gives more weight to studies with longer durations (28 days or more). However, there is no CLP guidance indicating that relevant results of shorter-term repeated-dose toxicity studies should be overruled by the results of longer-term repeated-dose toxicity studies. Thus, when integrating the results from both shorter- and longer-term repeated-dose toxicity studies, the classification criteria for STOT RE 2 are fulfilled.

The evidence for a DSD classification (R48/22) is much weaker. While the results of the 28-day studies in the rat and mouse indicate some concern for R48/22, all of the longer-term studies (rat, mouse, dog) do not support a R48/22 classification (see table above). It should be recognised however, that the evaluation of some studies (especially the shorter-term dog studies) is compromised by the absence of appropriate information on the magnitude and severity of effects.

Based on the overall assessment of the studies with a wide range of duration of exposure and the DSD criteria which put more weight on the study with the longest duration of exposure, the RAC agrees with the DS that there is not sufficient concern for a DSD classification and therefore proposes not to classify Bifenazate according to the DSD legislation.

In contrast, when integrating the overall results from shorter- and longer-term repeated-dose toxicity studies, the RAC came to the conclusion that for Bifenazate the classification criteria for STOT RE 2 are fulfilled.

RAC evaluation of germ cell mutagenicity

Summary of the Dossier submitter's proposal

Based on the results of *in vitro* and *in vivo* mutagenicity studies, the DS did not consider Bifenazate to be a genotoxic substance and therefore proposed not to classify Bifenazate for germ cell mutagenicity.

Comments received during public consultation

One MS generally supported non-classification for mutagenicity.

Assessment and comparison with the classification criteria

The following table contains a summary of the available mutagenicity data. There are negative findings for gene mutations in *in vitro* tests (Ames test and Mouse lymphoma test). *In vitro* testing for chromosome aberrations in Chinese Hamster Ovary (CHO) cells was negative, as was *in vivo* testing for chromosome aberrations (micronucleus test). Thus, overall, these findings indicate that Bifenazate should not be considered a genotoxic agent.

The RAC agreed with the DS that classification of Bifenazate for germ cell mutagenicity is not warranted.

	DNA damage	**Gene mutation**	**Chromosome aberration**
In vitro	-	Ames test: negative Gene mutation in mouse lymphoma cells L5178Y(TK): negative	Chromosome aberrations in CHO cells: negative
In vivo	-	-	Micronucleus test: negative

RAC evaluation of carcinogenicity

Summary of the Dossier submitter's proposal

For Bifenazate, two carcinogenicity feeding studies were available: a 104-week combined toxicity and carcinogenicity study in rats and a 78-week carcinogenicity study in mice. The DS concluded that for Bifenazate there was no evidence of treatment-related neoplastic lesions in either study. The DS expressed that no classification for Bifenazate for carcinogenicity is warranted.

Comments received during public consultation

One MS generally supported non-classification for carcinogenicity.

Assessment and comparison with the classification criteria

In the CLH report, there was no detailed reporting of the negative results of the two carcinogenicity studies (rat, mouse). As to carcinogenicity, the only information is that there are no treatment-related neoplastic lesions. The DAR (2003, vol. 3 B6) did not contain any further detailed data on carcinogenicity. Based on this scarce information, the RAC had no possibility to develop an independent assessment of the carcinogenic potential of Bifenazate.

However, the RAC had access to the main parts of the original study reports (Ivett, 1999a and 1999b) and checked the specific data related to tumour-type. There were no statistically significant increases in tumour incidences in the various tissues analysed, nor were there any indications of a dose response relationship below the level of statistical significance with the possible exception of the neoplastic findings in the liver of male mice.

The neoplastic lesions both in the mouse and rat liver are reported in the following two tables. In male mice, there was an increased incidence of hepatocellular adenomas at the high dose. In female mice and rats (both sexes) liver tumour incidences are considered incidental and unrelated to treatment. According to the study director this "increase [in male mice] was not significant, was without a dose response, there was the absence of an increase in hepatocellular hyperplasia and

altered foci, and such neoplasms are considered common spontaneous findings in mice". However, in the study report, there was no explicit comparison of the increased incidence of the hepatocellular adenoma in male mice with historical control data. The WHO report on Bifenazate (WHO, 2006) compared the increased incidence of liver adenomas in male mice (~20% at the high dose versus ~10% in the control and other test groups) with the historical control incidences ranging from 4.3% to 14.9%. However, in the WHO report there is no information regarding the adequacy and reliability of these historical control incidences. Control incidences between 20 and 26% are reported for hepatocellular adenomas in CD-1 mice in 10 mouse carcinogenicity studies performed between 1991 and 2004 in the same laboratory (Baldrick and Reeve, 2007). It has to be noted that the liver adenoma incidences in the Bifenazate study in three of the exposure groups (control, lowest and medium dose) are about 10%, which is not consistent with the range of control incidences (20 to 26%) in the Baldrick and Reeve publication (2007).

Neoplastic findings in CD-1 Mice (Ivett, 1999a)		**Male mice**				**Female mice**			
Based on Table 14C of the original study report		1	2	3	4	1	2	3	4
Liver	**Number examined**	49	49	50	48	50	50	50	49
	Adenoma, hepatocellular	5	6	5	**10**	1	0	0	0
	Carcinoma, hepatocellular	0	1	0	0	0	0	0	1
	Haemangiosarcoma	1	1	1	0	1	0	0	0
	Haematopoietic neoplasia	2	1	1	2	4	3	4	3

Neoplastic findings in Sprague-Dawley Rats (Ivett, 1999a)		**Male rats**				**Female rats**			
Based on Table 15D of the original study report		1	2	3	4	1	2	3	4
Liver	**Number examined**	60	60	60	60	60	60	60	60
	Adenoma, hepatocellular	0	0	0	0	0	0	2	0
	Carcinoma, hepatocellular	0	3	2	1	0	0	0	0
	Cholangioma	0	0	1	0	0	0	0	0
	Hematopoietic neoplasia	2	5	1	3	0	1	0	0

To summarise and assess the liver tumour data: the increased incidence of adenomas (20%) in male mice at the high dose (compared to 10% in the concurrent control) is without statistical significance; there is no increase of liver carcinomas in male mice. There is neither an increased incidence of liver adenomas or carcinomas in female mice, nor in both sexes of rats. Thus, the only indication of carcinogenic activity was restricted to benign neoplastic findings in one sex of one species, and these findings were not statistically significant.

The RAC concluded that Bifenazate did not show a carcinogenic potential in the 104-week combined toxicity and carcinogenicity study in rats and the 78-week carcinogenicity study in mice. Hence, the RAC agreed with the DS that no classification for Bifenazate for carcinogenicity is warranted.

RAC evaluation of reproductive toxicity

Summary of the Dossier submitter's proposal

Based on the results of two developmental toxicity studies (rat, rabbit, both by gavage) and a two-generation reproduction study (rat, feeding study) the DS concluded that there was no evidence of reproductive toxicity of Bifenazate (for either effects on fertility or developmental toxicity). The DS proposed not to classify Bifenazate for reproductive toxicity.

Comments received during public consultation

One MS generally supported non-classification for reproductive toxicity.

Assessment and comparison with the classification criteria

During the opinion development, additional details on reproductive toxicity studies (Schardein, 1996, 1997a, 1997b) were requested by the Rapporteurs in order to develop an independent opinion. The assessment of original reproductive toxicity studies by the Rapporteurs led to some concerns that were submitted for comments to the RAC.

Two-generation reproduction study

A two-generation reproduction study was performed in accordance with OECD 416 (Schardein, 1999). The animals were exposed to Bifenazate (purity 92.5%) at dietary levels of 0, 20, 80 and 200 ppm. There was a second subsequent two-generation study with dietary levels of 20 ppm and lower in order to assess the parental body weight effects noted in the first study at 20 ppm. In the first study, there was a decreased body weight and body weight gain at all doses. Parental animals did not show any clinical signs. In parental animals there were no treatment-related macroscopic or microscopic findings in the organs/tissues investigated. An abnormal oestrus cycle was noted "in one or a few" F0 females of the high dose group (not in the F1 generation).

There were no effects on mating, fertility and gestation parameters in any of the parental generations. Sperm was evaluated in the F0 generation, and there were no abnormalities observed. The development of the F1 and F2 pups was considered normal. For the various pup-related parameters it was indicated that there were "no treatment-related findings", except for a minimal delay in sexual maturation for the males at the mid and high dose group and for the females in the high dose group. In the CLH report it is stated that: "In male pups, preputial separation was checked from day 40 onwards. In the control group 100% separation was reached within 51 days. In the low, mid and high dose group it was reached within 48, 53 and 51 days respectively. This delay is not considered an adverse effect."

In the CLH report, the experimental data on the process of vaginal opening in the F1 pups was summarized as follows (there are no further corresponding data): "In female pups the process of vaginal opening was completed in the control group on day 36 and in the low dose group somewhat earlier, on day 34. However, in the mid dose group the process was completed on day 40 and in the high dose group on day 47. This is considered to be induced by exposure to Bifenazate and to be an adverse effect. However, it is unclear whether it is due to the *in utero* exposure or due to the post-natal exposure and related to the decreased body weight gain." This toxicological assessment in the CLH report is different to the one in the original report (Schardein, 1999): "Vaginal patency parameters were not affected in any of the F1 pups. With the exception of one pup in the 200 ppm group (in the litter of dam no. 59866), all female pups had vaginal opening by postnatal day 40. The 200 ppm group pup in litter no. 59866 had vagina opening on PND 47. This single occurrence was not considered to be due to test article administration." The following table refers to table 40 of the original study report (Schardein, 1999).

Cumulative percentage of pups with completed vaginal perforation	PND[1] of completion of vaginal opening			
	Control	Low dose	Medium dose	High dose
93% (28/30)	34-35	33-34	35-36	37
97% (29/30)	35	33-34	36	39

[1] PND = post natal day

RAC considered that reference to the group summary data on vaginal perforation (cumulative percentage of pups with completed vaginal perforation for PND 30 to 47) might support the conclusion in the original study i.e. that the effect was not due to test article administration.

Developmental toxicity study in rabbits

There is a developmental toxicity study in rabbits according to OECD 414 (Schardein, 1997b). Dams were exposed by gavage to Bifenazate (purity 92.5%) at doses lower than in rats: 0, 10, 50 and 200 mg/kg/d during days 7-19 of gestation. Maternal toxicity was not observed in this study; however, based on range finding studies, it is assumed that the high dose is quite close to the LOAEL for maternal toxicity. In each dose group there was one abortion. No adverse effects were reported for the foetuses (no adverse effects on intrauterine growth and survival, no treatment-related fetal malformations or developmental variations).

As it was not possible to interpret the dose-response data as presented in the CLH dossier or the DAR, the RAC referred to the original study report. In general for developmental toxicity studies, the "malformation profile" with historical control data is considered essential background information for an independent assessment of the data.

Malformations in the Bifenazate rabbit study (based on table 11 of the original study report, Schardein, 1997b):

	Malformation	Historical control data	Groups			
			1	2	3	4
Number of foetuses examined		Reference: 1432 litters 9832 foetuses	113 (0 mg/kg)	135 (10 mg/kg)	95 (50 mg/kg)	97 (200 mg/kg)
External examination	Short tail	8 foetuses in 8 litters	0	0	1	0
Visceral examination	Lungs: Lobular agenesis	1 foetus in 1 litter	1	0	0	0
	Retroesophageal aortic arch	no HCD	1	0	0	0
Skeletal examination	Vertebral anomaly with or without associated rib anomaly	117 foetuses in 102 litters	3	2	1	1
	Rib anomaly	19 foetuses in 18 litters	0	0	0	1
	Rib(s) with spherical enlargement	10 foetuses in 9 litters	0	0	1	0

None of the malformations in the test groups of the rabbit study were statistically significantly different from the concurrent controls and historical control data. There was either only one malformation in total in any of the dose groups or the number of malformations (vertebral anomalies) decreased from the control to the high dose. Thus in the rabbit there is no indication of a treatment-related induction of malformations.

Developmental toxicity study in rats

A developmental toxicity study was performed in rats according to OECD 414 (Schardein, 1997a). Dams were exposed by gavage to Bifenazate (purity 92.5%) at doses of 10, 100 and 500 mg/kg/d during days 6-15 of gestation. Maternal toxicity was observed in the mid and high dose group (mainly clinical signs and decreases in food consumption and body weight). No adverse effects in

the foetuses were reported (no adverse effects on intrauterine growth and survival, no treatment-related foetal malformations or developmental variations).

As it was not possible to interpret the dose-response data as presented in the CLH dossier or the DAR, the RAC referred to the original study report.

Malformations in the Bifenazate rat study (based on table 12 of the study report, Schardein, 1997a):

	Malformation	**Historical control data**	**Groups**			
			1	**2**	**3**	**4**
Numbers of foetuses examined			374 (0 mg/kg)	352 (10 mg/kg)	353 (100 mg/kg)	344 (500 mg/kg)
External examination	Umbilical herniation of intestine	5 foetuses in 5 litters 3250 litters 45930 foetuses	0	0	**1**	**1**
Visceral examination	Retroesophageal aortic arch	1 foetus (in 1 litter) 3250 litters 34685 foetuses Litter incidence range on a study basis: 0-4.5%	0	0	0	**2** Litter incidence: 1/24 = 4.2%
Skeletal examination	No malformations		0	0	0	0

None of the malformations in the rat study were statistically significantly different from the concurrent control group. In addition to these specific malformations, another foetus in the 500 mg/kg/d group (different litter) had a soft tissue developmental variation (major blood vessel variation, consisting of a retroesophageal right subclavian artery and right subclavian and right carotid arteries that arose independently from the aortic arch).

The study director's assessment of the external malformations is summarised as follows: "Although the percentage of affected foetuses per litter in the high dose group was higher than in the historical control range, the difference was slight and these single occurrences of umbilical herniation in the mid and high dose groups were not attributed to the test article." As to the visceral malformations the study director stated: "The percentage of foetuses per litter in the 500 mg/kg/d group with retroesophageal aortic arches (0.9%) was above the range of values in the WIL historical control data (0.0-0.3%). However, the difference was slight, and these two occurrences in a single litter were not attributed to the test article."

In addition to comments by RAC members, industry submitted a position paper (Chemtura, October 24, 2013) including a discussion of the relevance of the isolated malformation findings.

Based on all comments received, the RAC developed their opinion on the "retroesophageal aortic arch" issue: In the 500 mg/kg/d group the litter incidence for the aortic arch malformation was 4.2%. Historical control data revealed a litter incidence range of 0 to 4.5%. The industry position is that the percentage litter incidence in the study is consistent with the historical control data. However, he RAC was reluctant to directly compare the study litter incidence with the upper limit of the historical range. It is worth recognising that this litter incidence (on a study basis) only occurred in ~ 1 out of 130 control groups (3250/25). In 129 from 130 historical control groups, this type of malformation was not observed. Based on this incidence data, the RAC was not convinced that the aortic arch malformations in the Bifenazate study were not attributed to the test article.

In their position paper, industry furthermore considered the individual animal data from the rat developmental toxicity study and reported that the dam and its litter (with the 2 aortic arch

malformations) were atypical in comparison with others from the same treatment group (500 mg/kg/d). A crucial difference was that the specified dam failed to grow normally prior to the onset of treatment with a loss of body weight (minus 3 g) over the first 6 days of the study. The pre-dosing body weight gain (group mean value including the specified dam) was 30 g. The specified dam was in a poor clinical condition; 25% of the litter were resorbed early in pregnancy. None of the other dams and litters in this dose group had a similar profile or showed evidence of any treatment-related effects. For this reason the RAC recognised that the data from the specified dam should be considered with caution and possibly be excluded when assessing the results of the study. Overall, taking into account both the very low incidence of the malformation (retroesophageal aortic arch) and the non-treatment related bad clinical condition of the specified dam, the RAC concluded that this rat study did not indicate a developmental toxicity potential of Bifenazate.

Overall conclusion on reproductive toxicity

Fertility impairment

No specific comments were received during public consultation. One MS generally agreed with no classification for reproductive toxicity. Based on the unaffected fertility parameters in the two-generation reproduction study in rats the RAC agreed with the DS that no classification for Bifenazate for adverse effects on sexual function or fertility was warranted.

Developmental toxicity

The assessment of the developmental toxicity potential of Bifenazate was based on the results of three experimental studies: the 2-generation reproduction study in rats and the developmental toxicity studies in rabbits and rats.

In the context of the 2-generation reproduction study, developmental landmarks were tested in the F1 pups. Rather small effects on the completion of vaginal opening in the high dose group were not considered sufficient evidence for classification. Bifenazate did not induce developmental toxicity in rabbits. There was a detailed discussion of the malformation data in the rat study with specific reference to the original data. Initial concern on isolated rat malformations (retroesophageal aortic arches) could be invalidated.

Thus the RAC concluded that Bifenazate did not induce developmental toxicity in either rabbits or rats. Based on the total developmental toxicity data available, the RAC concluded not to classify Bifenazate for developmental toxicity.

ENVIRONMENTAL HAZARD ASSESSMENT

RAC evaluation of environmental hazards

Summary of the Dossier submitter's proposal

The DS proposed to classify Bifenazate according to the CLP criteria as Aquatic Acute 1 (H400) with an M-factor of 1 and Aquatic Chronic 1 (H410) with an M-factor of 1. According to the criteria of DSD the proposal is N; R50-53 with specific concentration limits (SCL) of C ≥ 25 % N; R50-53, 2,5 % ≤ C < 25 % N; R51-53 and 0,25 % ≤ C < 2,5 %; R52-53. The proposal is based on the results achieved in acute and chronic aquatic toxicity studies for Bifenazate with LC_{50} of 0.36, 0.42 and 0.76 mg/l in algae, invertebrates and fish, respectively and on the lowest NOEC of 0.017 mg/l obtained for fish. In addition, Bifenazate is not rapidly degradable and not readily biodegradable.

During the preparation of the opinion for Bifenazate the DS additionally clarified that there was a typing error in the CLH report and that the lowest LC_{50}value for fish was 0.58mg/l and not 0.76 mg/l.

Comments received during public consultation

Four MSs contributed during the public consultation. The conclusion that Bifenazate is not rapidly degradable was supported by two MSs, and not questioned by others.

One MS noted that test guidelines for the degradation studies should be specified. In response to comments, the DS provided the information included in the DAR. Three MS supported the proposed classification and labelling, one MS suggested Bifenazate should be classified based on the aquatic toxicity of the degradation product D3598, since this is more toxic than Bifenazate. Given that the available information showed that both Bifenazate and the degradation products are present in the test solution and thus the toxicity is not solely due to the degradation product but also to Bifenazate, the DS preferred to base the classification on the results obtained for the parent compound.
One MS suggested to use the lowest available $L(E)C_{50}$ or NOEC values for classification and labelling of acute and chronic effects of the substance and proposed to add the results of two acute toxicity studies with salt water organisms available in the DAR but not in the CLH report. The DS preferred not to use these studies for classification and labelling, considering uncertainties in the actual concentration of Bifenazate and total equivalents in these studies with reference to the remarks of the Rapporteur Member State (RMS) for the DAR who considered the studies not acceptable for the purpose of the risk assessment. One MS asked for an explanation of how the correction for purity and recovery were performed in the aquatic toxicity tests. In response to comments, the DS provided the required additional information.

Further information is provided in the RCOM document (Annex 2) to the opinion.

Assessment and comparison with the classification criteria

Degradability:
Bifenazate is susceptible to hydrolysis under standard conditions at pH 4, 7 and 9. Several degradation products were formed at levels >10%. Photodegradation of Bifenazate was reported in three tests with sodium acetate buffer and in one test with natural water. The DT_{50} results ranged from 0.83 hours (natural water, pH 7, at 25°C) to 21.1 hours (sodium acetate buffer, pH 5, at 25°C).

Five known degradation products were identified in studies with buffered solutions and one unidentified degradation product which reached 18.0% of Applied Radioactivity (AR). According to the DAR, all degradation products were found also in the study with natural water and they all appeared also in the dark control. In the dark, Bifenazate degrades mainly to D9472 (40.5% of AR after 30 days) which is reported as stable to degradation.
The ready biodegradability of Bifenazate technical (purity 97.9%) was studied in a test according to OECD 301B. The CO_2 production after 28 days was 11.7% for Bifenazate expressed as a percentage of $ThCO_2$. Based on these results, Bifenazate was considered as not readily biodegradable.

Simulation tests in two aerobic water/sediment systems (sandy loam and clay loam) performed on ^{14}C-Bifenazate demonstrated rapid dissipation of the test substance from the system with a DT_{50} of <0.25 days (+6 hours) and a DT_{50} of <0.25 days for water. No DT_{50} value was determined in sediment. After 100 days, non-extractable residues in sediment increased to 46.9% of AR in a sandy loam system and to 65.2% of AR in a clay loam system. Degradation leads to formation of two major metabolites (D3598 and D9472).
Mineralisation after 100 days was 33.7% of AR in a sandy loam system and 18.9% of AR in a clay loam system.

In an anaerobic water sediment study with a loam system, ^{14}C-Bifenazate dissipated from the system with a DT_{50} of 77 days at 25°C, equivalent to 116 days at 20°C. Bound residues in the sediment amounted to 28.4% of AR after 119 days and to 51.5% of AR after 12 months. Major metabolites were A1530 (with maximum of 24.8% of AR in the system after 10 months) and desmethyl-D3598 (with a maximum of 14.7% of AR in the system after 8 months). DT_{50}s for these metabolites could not be estimated. Mineralisation after 119 days was 0.07% of AR and 0.17% of AR after 12 months.

The RAC agreed with the proposal of the DS that Bifenazate was not readily biodegradable (DSD) based on the results of the ready biodegradability test according to OECD 301B and not rapidly degradable (CLP) based on the results of simulation water/sediment studies. Although primary degradation of Bifenazate in water sediment studies is rapid (DT_{50} < 0.25 day in aerobic system), the observed mineralisation is low (maximum of 33.7% of AR after 100 days in aerobic river

system). Based on the acute aquatic toxicity data, the toxicity of primary degradation products (D3598, D9472) is comparable to the toxicity of Bifenazate and indicates that they are classifiable for the environment. However, relevant information on aquatic toxicity of all degradation products was not available. Thus, it could not be demonstrated that further degradation products of Bifenazate do not fulfil the criteria for classification as hazardous to the aquatic environment.

Bioaccumulation:
A bioconcentration study was not available. The log K_{ow} of 3.4 for Bifenazate indicated a potential for bioaccumulation. Bifenazate did not meet the criteria for bioaccumulation according to CLP (log K_{ow}> 4) but fulfilled the criteria for bioaccumulation according to DSD (log K_{ow}> 3).

Aquatic toxicity:
Several acute and chronic aquatic toxicity studies for Bifenazate and its metabolites D3598, D9472 and D1989 are reported in CLH report. The lowest reliable aquatic toxicity results were as follows (the key studies for classification are highlighted in bold):

Trophic level	Species	Short-term result	Long-term result
Fish	*Lepomis macrochirus*	**96h LC_{50}=0.58 mg/l**	
	Oncorhynchus mykiss	96h LC_{50}=0.76 mg/l	**87d NOEC=0.017 mg/l growth**
Aquatic invertebrates	*Daphnia magna*	48h EC_{50}=0.5 mg/l	21d NOEC=0.15 mg/l reproduction
	Crassostrea virginica	**96h EC_{50}=0.417 mg/l**	
Aquatic algae and plants	*Pseudokirchneriella subcapitata*	96h ErC_{50}> 2.02 mg/l	96h NOEC=0.25 mg/l
	Navicula pelliculosa	96h ErC_{50}=1.4 mg/l	96h NOEC=0.52 mg/l
	Anabaena flos-aquae	96h ErC_{50}> 4.48 mg/l	96h NOEC=1.13 mg/l
	Skeletonema costatum	**96h ErC_{50}=0.36 mg/l**	96h NOEC=0.20 mg/l

Summary of the most relevant short-term aquatic toxicity studies for the key degradation products (D3598, D9472):

Trophic level	Test compound	Species	Result
Fish	D3598	*Oncorhynchus mykiss*	96h LC_{50}=0.044 mg/l
	D9472	*Oncorhynchus mykiss*	96h LC_{50}=0.21 mg/l
Aquatic invertebrates	D3598	*Daphnia magna*	48h EC_{50}=0.051 mg/l
	D9472	*Daphnia magna*	48h EC_{50}=0.78 mg/l
Aquatic algae and plants	D3598	*Pseudokirchneriella subcapitata*	96h ErC_{50} > 1.8 mg/l
	D9472	*Scenedesmus subspicatus*	96h ErC_{50}=1.8 mg/l

On the basis of the information in the DAR, most of the tests were performed according to GLP and OECD or EPA guidelines. Although the purity profile of the test substance (90.2% - 92.4%) was below the typical purity of 98.0% and the minimal purity of 95.0%, the composition of the test substance was considered acceptable. The tests on fish and *Daphnia magna* were performed in a flow-through system with the $L(E)C_{50}$ based on mean measured concentrations of Bifenazate. In these studies, the lowest and the highest test concentrations were analysed for the metabolite D3598. The tests on algae were performed in a static system and the E_rC_{50}/NOEC was expressed based on the measured concentration of Bifenazate at test initiation. The concentrations of Bifenazate and its metabolites in algal tests dropped during the testing period indicating that the metabolite D3598 also degrades rapidly in static solutions.

Aquatic acute toxicity studies were available for all trophic levels. The lowest acute aquatic toxicity value for Bifenazate was obtained with the marine diatom *Skeletonema costatum* with E_rC_{50} (96h)

of 0.36 mg/l based on measured Bifenazate concentrations at test initiation. The reported LC_{50} (96h) values were 0.58 mg/l for bluegill sunfish (*Lepomis macrochirus) and* 0.76 mg/l for rainbow trout (*Oncorhynchus mykiss)* based on mean measured Bifenazate concentrations (> 80% of nominal, formation of D3598 confirmed).

The acute toxicity in the marine mollusc *Crassostrea virginica* resulted in an EC_{50} (96h) of 0.416 mg/l based on the mean measured Bifenazate plus D3598 concentrations (> 80% of nominal).

With regard to chronic toxicity of the substance the lowest value has been obtained for the fish *Onchorhynchus mykiss* with a NOEC (87d) of 0.017 mg/l for growth based on mean measured Bifenazate concentrations (0.0192 mg/l based on total equivalents).

With regard to the proposal of one MS to classify Bifenazate based on the aquatic toxicity data of the degradation product D3598 that appeared to be more toxic than the parent compound in short-term fish and *Daphnia magna* studies, the RAC concluded that there was no clear evidence that the aquatic toxicity could be attributed solely to this degradant. The available data from different degradation studies showed that the formation of degradation products and the composition of test solution were not always constant as they were test conditions dependent.

The RAC supported the DS approach to classify Bifenazate based on the aquatic toxicity data for Bifenazate expressed as Bifenazate equivalents because this approach also takes into account toxicity of primary degradation products.

Classification according to CLP:

Acute aquatic hazard:
Acute toxicity data are available for all three trophic levels. The lowest reliable short-term aquatic toxicity value is E_rC_{50} (96h) of 0.36 mg/l for the marine diatom *Skeletonema costatum.* This result is very similar to the acute toxicity value for fish *Lepomis macrochirus* with LC_{50} (96h) of 0.58 mg/ and the mollusc *Crassoostrea virginica* with EC_{50} (96h) of 0.42 mg/l. Bifenazate therefore fulfills the criteria for classification as Aquatic Acute 1 (H400) with an M-factor of 1 ($0.1 < L(E)C_{50} < 1$ mg/l).

Chronic aquatic hazard:
Bifenazate is non-rapidly degradable. Adequate chronic toxicity data are available for all trophic levels. The lowest NOEC value (87d) of 0.017 mg/l is reported for fish *Oncorhynchus mykiss*. This value is below the threshold value of ≤ 0.01 mg/l for non-rapidly degradable substances. Bifenazate therefore fulfils the criteria for classification as Aquatic Chronic 1 (H410) with an M-factor of 1 ($0.01 < NOEC \leq 0.1$ mg/l).

Classification according to DSD:

The available $L(E)C_{50}$ for fish, daphnia and algae is < 1 mg/l. As the substance is not readily biodegradable with log K_{ow} > 3, Bifenazate should be classified as N; R50-53 with specific concentration limits (SCL) of
N; R50-53: C ≥ 25 %
N; R51-53: 2,5 % ≤ C <25 %
R52-53: 0,25 % ≤ C < 2,5 %.

In summary, the RAC agreed with the original proposal of the DS.

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Schardein, J.L. (1997b) A developmental toxicity study of D2341 in rabbits. Unpublished report (study No. WIL-155037).

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; 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 rapporteurs' comments (excl. confidential information).