Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

bifenthrin

ECHA/RAC/ CLH-O-0000001740-81-01/A2

Adopted

24 May 2011

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

[ECHA has compiled the comments received via internet that refer to several hazard classes and entered them under each of the relevant categories/headings as comprehensive as possible. Please note that some of the comments might occur under several headings when splitting the given information is not reasonable.]

Substance name: bifenthrin
CAS number: 82657-04-3

General comments

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**The German CA supports to establish a harmonised classification & labelling for bifenthrin, which is an active ingredient in biocidal products (Dir. 98/8/EC) and formerly in plant protection products (non-inclusion into Annex I to Dir. 91/414/EEC).** **Substance identity** **1) On the one hand, the given CLH-Dossier on the ECHA website and on the CIRCA website differ in several points.** **2) On the other hand, the technical dossier which was provided via circa is not congruent with its related CLH-Dossier (which is included in the technical dossier).** **1)** **The given purity in the CLH-Dossier on the ECHA website is ≥ 930 g/kg. In the**	FR: this end-point has been discussed with ECHA and the conclusion is that a harmonisation with the biocidal dossiers is supported. FR: agree with a harmonised classification & labelling for bifenthrin. The CLH report will be modified in agreement with the discussions in the frame of Dir. 98/8/EC. FR: Agree. The purity will be modified, into 911 g/kg to be consistent with the	Noted Noted <u>Substance identity</u>

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		CLH-Dossier which was released on the CIRCA website the given purity is ≥ 911 g/kg. The German CA would prefer the 911 g/kg, because this is the purity for the two main isomers/the main enantiomeric pair of Bifenthrin whereas the purity of ≥ 930 g/kg is related to all 8 isomers. (Knowledge of the peer reviewed mode of 98/8/EG) **Moreover, the given IUPAC name in the two dossiers is different.** **In the "ECHA CLH-Dossier", a mixture of 4 isomers is stated as IUPAC name:** **Reaction mass of 2-methyl-3-phenylbenzyl (1R,3R)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1R,3R)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(E)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate.** **In the "CIRCA CLH-Dossier", a mixture of 2 isomers is stated as IUPAC name:** **Mixture of 2-methyl-3-phenylbenzyl (1R,3R)-(Z)-3-(2-chloro-3,3,3-**	fact that the active substance is defined as being only the two main isomers.	Now the term "bifenthrin" specifically relates to the cis-Z isomers. Inconsistencies have been checked and corrected.

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		trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate. **In the confidential Annex of the "CIRCA CLH-Dossier", the content for all 4 isomeric pairs is stated. In accordance with RIP 3.10, only the cis-Z-isomeric pair is the main component of Bifenthrin. The other 6 isomers (3 isomeric pairs) must be stated as impurities and not as constituents. Therefore, the following IUPAC name should be used in all CLH-Dossiers: Reaction mass of 2-methyl-3-phenylbenzyl (1R,3R)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate and 2-methyl-3-phenylbenzyl (1S,3S)-(Z)-3-(2-chloro-3,3,3-trifluroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylate.** **In both CLH-Dossiers, it is stated in section 1.2 Composition of the substance that bifenthrin includes 4 isomers. This should be corrected as the substance bifenthrin has 3 chiral carbon atoms and as a consequence consists of 8 isomers, i.e. 4 enantiomeric pairs.** **2)**	FR:do not agree. As concluded for the biocidal dossiers and for harmonisation, the IUPAC Name of the active substance will be: 2-methylbiphenyl-3-ylmethyl (1RS)-cis-3-[(Z)-2-chloro-3,3,3-trifluroprop-1-enyl]-2,2-dimethylcyclopropanecarboxylate. FR: agree, the document will be amended.	<u>IUPAC name</u> It seems that both versions of the IUPAC name are okay. Rapporteur agrees to the French proposal. Noted.

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		In the technical dossier, all 8 isomers are given as constituents under point 1.2 Composition in IUCLID. According to RIP 3.10, only the two main isomers ((1R,3R)-(Z)) and ((1S,3S)-(Z)), the cis Z-isomer pair, should be listed as constituents. The other 6 isomers must be included as impurities due to their content of less than 10%. **A second point is the given concentration of the isomers in the technical dossiers. The concentrations for the isomeric pairs in the confidential annex are given in relation to 100% Bifenthrin (the impurities are not taken into account). The same concentrations are given for each isomer in the technical dossier. As a consequence, the concentration of the isomers in Bifenthrin is nearly 200%. Therefore, the concentration should be amended. In reference to the racemic mixture, the concentration of the isomers must be ca. 50% of the given concentration in the technical dossier. Additionally, it must be considered that the purity of the Bifenthrin is 91.1% (respectively 93% relating to 8 isomers) and not 100%.**	FR agree. the document will be amended	Noted.
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 1: Footnote: Please specify how bifenthrin is defined in this annex VI dossier. We suggest to replace footnote to main text on page 5.**	FR: thank you for your comment, this will be done.	Noted.

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		Page 5: Please also include the labeling according to Regulation EC 1272/2008 (CLP criteria) and the Specific Concentration Limits regarding Aquatic toxicity according to Directive 67/548/EEC.	FR: the CLH report has been amended	Noted, confirmed and amended by M-factor suggested for Aquatic Chronic 1 (H410) after implementation of the 2nd ATP of the CLP Regulation
		In some parts (e.g. page 14, distribution) the µ in µg is replaced by a square. Please adapt.	FR: the CLH report has been amended	Noted
		The provided summaries contain sometimes limited details on the observed effects. Would it be possible to add the more extensive summaries made for the Biocide regulation to the IUCLID	FR: It was agreed at CARACAL that Robust Study Summaries are not required for Biocidal substance submitted before the end of 2009. Necessary information are already present in the CLH report.	Limited details Rapporteur recognises the NL concern on sometimes limited details (e.g. reprotox and carcinogenicity, or long-term toxicity studies with fish and invertebrates). Rapporteur proposes some kind of pragmatic approach. For RDT and carcinogenicityadditional information has been added to the background document.
02/04/2010	**France / Antony Fastier / AFSSA**	**We agree with the proposal classification of Bifenthrin:** **Based on Directive 67/548/EEC criteria:** **Xn ; Carc. Cat 3; R40** **T; R23/25** **Xi; R43** **Based on CLP criteria:** **Carc.2 – H351** **Acute Tox. 3 – H331** **Acute Tox. 3 – H301** **Skin Sens. 1 – H317**	FR: Thank you for your support	Noted. However, instead of Acute Tox. 3 with H301 there is Acute Tox. 2 with H300.

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02/04/2010	**Belgium / Frederic Denauw / MSCA**	**Please find the belgian comments :** **Health effects** **We agree the proposed classification.** **T; R25 (Acute Tox.3 – H301): LD50 oral rat (M): 168.5 mg/kg** **T; R23 (Acute Tox.3 – H331): LC50 inhalation rat (F) (4h, droplet aerosol): 0.8 mg/L** **R43 (Skin Sens.1 – H317): skin sensitizer in guinea pig maximisation test** **Xn; R48/22 (STOT Rep.1 – H372):** **- 28-day oral rat: clonic convulsions and tremors, followed by death of all animals by day 15 at 400 ppm (34.5/32.6 mg/kg bw/d), clonic convulsions and tremors + mortality (6/10M and 1/10 F) at 300 ppm (21.9/21.6 mg/kg bw/d)** **- 90-day oral rat: tremors at ≥100 ppm (≥7.5/8.5 mg/kg bw/d)** **Carc. Cat.3; R40 (Carc. Cat.2 – H350):** **- not genotoxic** **- not carcinogenic in rats** **- in mice, tumors were observed in:** **- the urinary bladder (dose related increase of hemangiopericytoma in M, statistically significant at high dose, the relevance of these lesions for humans is questionable),** **- the lung (stat. signif. increase of**	FR: Thank you for your support	Noted. But see discussion on RDT and carcinogenicity.

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		bronchio-alveolar adenoma and adenocarcinoma in F, neither dose related nor showing dose trends), - the liver (dose-related increase of adenoma and adenocarcinoma in M, not statistically significant, based on the historical controls they were considered unlikely to be treatment related) and - lymphoblastic lymphosarcoma and leukemia (in F, stat. signif. at high dose). Without robust mechanistic data it cannot be excluded that these effects are relevant to humans.		
08/04/2010	**Poland / MSCA**	**Taking into account information provided in Proposal for Harmonized Classification and Labelling we agree with the harmonized classification proposed by France CA. We have some remarks to the information which can be found on the page number 5. On this page there are information on proposed classification based on Directive 67/548/EEC criteria and based on CLP criteria. There are also information on proposed labelling but only based on 67/548/EEC Directive. This page should also include information about proposed CLP labelling: signal word, hazard statements, pictograms.**	FR: The CLH report has been amended.	Noted.
		This page should also include information about proposed specific concentration limits for environmental	FR: The CLH report has been amended.	Noted.

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		classification – according to the Directive 67/548/EWG. **We propose also to change statement "A M factor =10 000 is proposed" for "Under CLP a M factor 10 000 is proposed"**	FR: The CLH report has been amended.	The RAC opinion provides classification proposals for CLP (now after implementation of 2nd ATP) and DSD, including SCL and M-factors.
08/04/2010	**Portugal / Maria do Carmo Palma / MSCA**	**The proposed Classification and Labelling fulfills the criteria established both in CLP Regulation and 67/548/EEC Directive (health and environment).Therefore, we support the proposal.**	FR: Thank you for your support	Noted.
08/04/2010	**UK / Daniel Merckel / MSCA**	**-page 5: please consider adding the specific concentration limits (from the preparations directive) for the purpose of classification of mixtures containing this substance.** **-page 5, purity: this is quoted as the mass of "active" substance per kilogram. Could it be given as a percentage instead, as it is in section 1.2?** **(ECHA: transferred from Other hazards and endpoints)**	FR: The CLH report has been amended. FR: do not agree: for harmonisation with biocidal dossiers, we think that purity should stay in g/kg and typical concentration in %w/w	Noted. Noted (there seems to be a rule for the biocidal products)

Carcinogenicity

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26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 31** **In the long-term study in rats, no**	FR: Thank you for your support	Carcinogenicity

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		carcinogenic effects were described in the study report. In the long-term study in mice, increased incidences of urinary bladder pericytoma (initially qualified as leiomyosarcoma, later on in some expert statements, this finding was also referred to as submucosal mesenchymal lesion or as decidual type or spindle cell type mesenchymal proliferation). Submucosal mesenchymal lesions are discussed in literature to be of no relevance to humans. A slight increase of liver adenoma and adenocarcinoma was detected in males, which showed little dose-relationship. Incidence of lymphoblastic lymphosarcoma and leukaemia showed considerable variability across the dose groups, even though the highest incidence was detected in high dose group, a dose-relationship is not too obvious. Bronchiolar-alveolar adenocarcinoma and adenoma were significantly increased in all dose groups, but showed no dose-relationship. **From our point of view the findings in liver, lungs and lymphoid tissue raise little need for classification as a carcinogen. Due the uncertainties in the nature of the lesions in urinary bladder and their relevance for humans, we are reluctant to give advice on the need for classification of**		See background document for further discussion of carcinogenicity.

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		bifenthrin.		
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 33 : We agree with the proposed classification**	FR: Thank you for your support	Noted.
02/04/2010	**France / Antony Fastier / AFSSA**	**We agree with the proposal classification of Bifenthrin:** **Based on Directive 67/548/EEC criteria:** **Xn ; Carc. Cat 3; R40** **T; R23/25** **Xi; R43** **Based on CLP criteria:** **Carc.2 – H351** **Acute Tox. 3 – H331** **Acute Tox. 3 – H301** **Skin Sens. 1 – H317** **(1) 5.7.6 Summary and discussion of carcinogenicity** **In the oncogenicity study in mice, tumors were multi-site (urinary bladder, lung, liver and leukemia) therefore without robust mechanistic data the carcinogenic potential of bifenthrin could not be excluded. Therefore we agree with the proposal classification Xn, carc cat 3 R40/ carcinogenicity cat 2. H351.** **(ECHA: copied from the General comments)**	FR: Thank you for your support	Noted. However, instead of Acute Tox. 3 with H301 there is Acute Tox. 2 with H300.
08/04/2010	**UK / Adrea Caitesn / MSCA**	**Page 32** **It would be useful to include the historical control incidence for the**	FR: The historical control incidence for the mouse tumors are not available in the study report.	Noted. Additional historical control data for the liver and urinary bladder tumours in male mice have been added

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		mouse tumours. This will enable the reader to make a more informed decision on whether the increased tumour incidence in mice supports classification for carcinogenicity or not.		to the background document.
08/04/2010 **Confidential claim on the comments removed since 12 August 2010**	**Belgium / FMC Chemical sprl / Company-Manufacturer** **(ECHA: Same comment was sent several times)**	**p 33 for the conclusion on Bifenthrin (CAS 862657-04-03) regarding Category 2 - H350 classification. Tables are attached in zip file** **<u>Executive Summary</u>** **Bifenthrin has been registered in the European Community since the mid-1980's. The data base supporting registration included a mouse oncogenicity study containing initial findings of an increased incidence of what was believed at the time to be leiomyosarcomas in the bladder of male mice at the high dose. Since that time, much more information has become available about the lesions observed in this bifenthrin study, all of which mitigates concern to the extent that there is serious doubt that bifenthrin induces an oncogenic response; and even if it did, in the worst case, the findings are not relevant to man. However, more recently France required an R40 statement (2007), and ECHA proposed a similar statement based on a judgment that bifenthrin shows**	FR: According to the 67/548/EC directive criteria, classification as Carc. Cat..3; R40 is proposed when "*carcinogenic effects [are observed] only at very high dose levels exceeding the maximum tolerated dose. The MTD is characterized by toxic effects which, although not reducing lifespan, go along with physical changes such as about 10% retardation in gain weight.*" The slight increase of urinary bladder tumors observed in male mice was statistically significant at the higher dose level. Furthermore, tumors were multi-site (urinary bladder, lung and leukemia), therefore without robust mechanistic data the carcinogenic potential of bifenthrin could not be excluded. France maintains its proposal of classification as Carc. Cat. 3; R40 (Carc. 2 – H351).	Carcinogenicity: All the comments by FMC have been carefully checked. The current background document now contains a detailed discussion of all the carcinogenicity issues raised by industry. Based on this additional discussion in the background document RAC finally concluded to follow the original proposal of the dossier submitter to classify bifenthrin for carcinogenicity (CLP Carc. 2).

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		oncogenic potential (2009). **This document provides an overall weight-of-evidence summary of the relationship between bifenthrin and its oncogenic potential. It further introduces observations with regard to the maximum tolerated dose that heretofore have been overlooked and that further diminish if not entirely eliminate concern about the findings in the mouse. A Pathology Working Group (PWG) of distinguished pathologists considered that there was no statistically significant incidence of tumors in mice, and a study panel of the International Life Sciences Institute (ISLI) noted that the unusual leiomyosarcoma tumor (the initial identification) has never been observed in man. Follow-up publications by Karbe and others found that the urinary bladder lesions classified at the time of the study as leiomyosarcomas are more properly described as submucosal mesenchymal lesions (SMLs), which the scientific community no longer considers as tumors and which have no relevance to humans for cancer risk assessment. Equally important, the oncogenic findings which ECHA CLH Report cited in males and females occurred above the maximum tolerated dose**	FR: The incidence of the urinary bladder tumors achieved statistical significance in the high dose males (29% compared to control). The panel of pathologists considered that top dose response was equivocal and failed to provide persuasive evidence of compound-related effect but a tumorigenic potential of bifenthrin in mice cannot be excluded as robust mechanistic data are not provided.	

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		(MTD). Additionally, these findings were in senescent animals that had been exposed to the MTD for an inordinate 24 months instead of the usual 18 months duration (33% longer), which is the standard basis for regulatory judgments. **Taking all the information into account, it is difficult to conclude scientifically on the basis of a single study using either a weight-of-evidence or strength-of-evidence approach that bifenthrin has met the criteria for a carcinogen under EU Directive 67/548/EEC or the Classification, Labelling and Packaging (CLP) Regulation EC 1272/2008. There is no evidence of treatment-related tumors, and this is most surprising considering the extreme study conditions. Therefore, products containing the active substance bifenthrin should not carry a label with an R40 statement based on oncogenicity.** **Historical Review of Member State Views on Bifenthrin Carcinogenicity** **Bifenthrin has been registered in several European countries since the mid-1980s. During the EU country registration processes, the carcinogenicity potential of bifenthrin**	FR: It should be noted that there has never been any discussion about classification of bifenthrine by the Technical Committee C&L. Besides, the public consultation shows that the proposed classification is widely supported by the other member states.	

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		has been addressed. At that time there were conflicting views among different country toxicologists on the carcinogenetic potential of bifenthrin to humans. Between 1986 and 1994, regulatory authorities in Belgium, Netherlands, Sweden, and the UK accepted the view that the lesions found in the mouse study were tumors, but noted in the main that they were not relevant to man and in some cases questioned whether the evidence met the criteria for a carcinogen. Italy granted registration in 1992 without requiring an R40 statement, and the Netherlands in 1986 considered there were "insufficient indications to consider the substance carcinogenic". **Using the information in the mouse study, and re-interpretation of the data (PWG report) available at that time, several EU countries have concluded that bifenthrin does not have any carcinogenic risk to man. Examples of the country conclusions are as follows:** **United Kingdom (Taylor 1994)** **"In 1987, the Scientific Subcommittee (SCC) of the ACP noted a statistically significant increase in the incidence of urinary bladder leimoyosarcomas in male mice receiving 600 ppm in the**		

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		diet. The SCC agreed with FMC's assertion that the leiomyosarcomas arose via an epigenetic mechanism and were of no risk to humans. Our toxicologist has since assessed the re-evaluation of the study by the panel of expert pathologists (led by Dr. Butler) and has concluded that the tumors (reclassified as urinary bladder submucosal tumors/sarcomas or focal proliferative lesions) are not a hazard to humans. Our toxicologist also agreed with Dr. Butler's conclusion that the liver and lung tumors noted in mice did not result from exposure to Bifenthrin." **Netherlands (Rudolphie and Den Tonkelaar 1986)** **"Sufficient toxicological data have been submitted for a registration for edible crops. In the chronic study in mice an increase in leiomyosarcomas in the bladder was observed. Because these were only found in male animals, and increased tumor incidence was not observed in the chronic study in rats, and because mutagenicity tests were negative, there are insufficient indications to consider the substance as carcinogenic."** **Belgium (Mouins 1991)**		

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		"Favorable opinion from the CSHP after study of the new evaluation (i.e. PWG report): the tumors which develop in the bladder wall of the mouse are tumors of the smooth muscle. Since this type of lesion has not been reported in man, bifenthrin should not present any risk of carcinogenicity for man under normal conditions of use". **On the other hand some countries considered that an R-40 should be considered, or another chronic study in mice conducted.** **Italy: (Lopriano and Boncristiani 1992): At first Italy proposed a carcinogenicity classification with an R-40 classification. However, after re-evaluation, no R-40 phrase was required, nor was another chronic mouse study required.** **Germany: Originally, Germany also considered a carcinogenic classification. The first registration of bifenthrin in Germany occurred in 2007 and the suggestion for a R-40 labeling was included (BfR 2007), but was not implemented in their labeling requirements.**		

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		France: Currently, based on France's review of the 91/414 dossier, R-40 labeling has been implemented for new plant protection products containing bifenthrin. **Since these conclusions were made, the only new information that has become available is as follows: 1) The original tumors were reclassified by ILSI as submucosal mesenchymal lesions, not tumors (Halliwell 1998); 2) SMLs have been determined to have low malignancy potential and no relevance to humans by two independent panels of toxicologists (including ECB decision on benalaxyl); and 3) The highest dose administered (600 ppm) exceeds maximum tolerated levels (MTD). This new information only lessens concern about bifenthrin's carcinogenic risk. It is therefore unclear why the classification of bifenthrin would change, based on previously known or new information.** **There is no indication that synthetic pyrethroids are carcinogenic as a class of chemicals. The US Agency for Toxic Substances and Disease Registry states that "there is no evidence that pyrethrins or pyrethroids cause cancer in people or in animals. The International Agency for Research on**		

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		Cancer (IARC) has determined that the carcinogenicity to humans for three pyrethroids (deltamethrin, fenvalerate, permethrin) is not classifiable". **Current ECHA Proposal for Classification and Labeling with regard to Carcinogenicity** **The CLH Report on bifenthrin (Proposal for Harmonised Classification and Labelling; December 2009) proposed a classification Carcinogenicity Category 3; R40 based on induction of tumors in one species without supporting evidence. According to the report, males contained tumors of the urinary bladder, and females of the lung as well as lymphoblastic lymphoma and leukemia. In the CLH Report on Bifenthrin, the ECHA Summary and Discussion of carcinogenicity (Section 5.7.6) states the following:** **"In the oncogenicity study in Swiss Webster mice (Geiger, 1986) increased incidence of leiomyosarcoma in the urinary bladder were observed in males at 50, 200, 500 and 600 ppm (statistically significant at 600 ppm only). These tumors were slowly growing and did not metastasize. After re-evaluation of this study by a panel**		

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		of pathologists, it was concluded that the mouse bladder tumor was not a leiomyosarcoma but rather a tumor arising in the sub-mucosa. This latter tumor has an unknown pathogenesis,may arise from the vascular mesenchyme and may be qualified as a pericytoma (predominantly benign). Other tumors such as lymphoblastic lymphosarcoma and leukaemia were observed in females and are statistically significant at the very high dose (600 ppm). Besides, statistically significant bronchiolar-alveolar adenocarcinoma and adenoma were observed in females at low, medium and very high doses. Based on the available information, it cannot be considered that these effects are not relevant to humans as long as mechanistic explanations or further information are not provided showing that these tumors are specific to the mice and cannot be extrapolated to humans." **Overall, bifenthrin was considered by the draft ECHA document to present:** **-No carcinogenic effect in rats** **-A carcinogenic effect in mice** **-An absence of genotoxic effect or other supporting evidence for carcinogenicity**		

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		ECHA has recently proposed a new classification system to replace EU Directive 67/548/EEC, and under this system bifenthrin was proposed to be classified as Category 2 – H350 (according to CLP criteria) because evidence of carcinogenicity in mice is obtained from a single study; therefore there is "limited evidence of carcinogenicity effects". **The purpose of the following sections is to critically evaluate the evidence for bifenthrin carcinogenicity against the criteria for classification.**		
		EVALUATION OF EVIDENCE FOR BIFENTHRIN CARCINOGENICITY AGAINST CRITERIA FOR CLASSIFICATION **1. The conditions of the mouse oncogenicity study exceeded the normal requirements for testing oncogenic potential.** **In the mouse chronic study, an increase in submucosal mesenchymal lesions (SMLs) occurred only in males and only at the HDT (600 ppm), a dose**	FR: RMS agrees with the applicant's comment. This item has been taken into account in the assessment.	

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		in excess of the MTD, making the SMLs at such a dose irrelevant for human cancer risk assessment purposes. The highest dose to be used in a carcinogenicity study is the maximally tolerated dose (MTD). US and EU authorities generally define the MTD as the maximum dose of a chemical that can be given without altering "the animals's normal life span" (European Medicines Agency 2008). The MTD is generally associated with "minimal toxicity" and "no more than 10% decrease in body weight gain relative to controls" predicted from a subchronic (90-day) study. The selection of doses for the mouse chronic study was based on two 28-day subchronic studies. In the first, mice were dosed at 50, 100, 200 and 300 ppm, and there were no effects. In the second, at 500, 600, 750 and 1000 ppm, tremors were observed in all groups and mortality in females was 0/10, 2/10, 5/10 and 10/10 in these dose groups, respectively. The dose of 600 ppm was clearly above the MTD (20% mortality for females). For males, deaths were only observed at 1000 ppm (7/10). The LOEL from the 28-day study was therefore 500 ppm for tremors and the NOEL was 300 ppm in the mouse carcinogenicity study.		

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		In the two-year study, groups of mice received 50, 200, 500 and 600 ppm continuously. The body weight gain (BWG) in males receiving the highest dose was decreased by >10% for much of early part of the study. The changes in BW and BWG are summarized in Tables 2 and 3. **• The reduction in absolute body weight was only 3.8% to 6.0% (males), but the reduction in mean body weight gain (BWG) was much more pronounced. The average reduction in BWG compared to controls over weeks 4 through 20 (n=12) were:** **200 ppm 500 ppm 600 ppm** **Males 6.4% 13.5% 19.1%** **Females 6.2% 6.9% 4.2%** **• At 13 weeks (90 days), the reductions in relative BWG were 7.2%, 14% and 18% (males) and 7.1%, 3.1% and 1.0% (females) at 200, 500 and 600 ppm, respectively.** **• At the HDT, all 50 mice of both sexes displayed clinical signs (tremors) from day 2 to day 163. At 500 ppm, all mice again showed clinical signs (tremors) from day 2 to day 67. At lower doses (50 and 200 ppm), few if any mice displayed signs that were bifenthrin-related. From approximately 20 weeks until the end of the study, the mice**		

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		gradually adapted to the bifenthrin such that they no longer showed clinical signs or body weight gain decrements. **While body-weight gain reductions exceeding guidance were observed at 600 ppm, the exposure at this level did not interfere with normal life-span.** **The study duration was 24 months instead of the typical 18 months. The extended duration of the study provided time for the late-in-life lesions to develop in animals severely stressed for much of their lives. The incidence of the lesions observed in mice at the end of their life-span dosed at levels above the MTD should not be characterized as evidence of carcinogenicity.** **2. Bifenthrin does not induce tumors in male urinary bladder** **The PWG conclusion discussed below represents the best science on the incidence of urinary bladder lesions. These experts assert that the lesions are not statistically significant at the high dose, and are therefore not treatment related. Considering that the high dose exceeded the MTD and that the study duration was 6 months longer than the standard study (24**	FR: The incidence of the urinary bladder tumors achieved statistical significance in the high dose males (29% of treated males compared to control). The panel of pathologists considered that top dose response was equivocal and failed to provide persuasive evidence of compound-related effect but a tumorigenic potential of bifenthrin in mice cannot be excluded as robust mechanistic data are not provided.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		months vs. 18 months), so that animals were not just exposed to 33% more chemical but were also senescent, one might argue that bifenthrin has no potential to cause urinary bladder tumors even under extreme conditions. **a. Relevance of mouse bladder lesions. The urinary bladder lesions classified at the time of the study as leiomyosarcomas are more properly described as submucosal mesenchymal lesions (SMLs), with no relevance to humans for cancer risk assessment. Further, the incidence of bladder lesions was only observed at the highest dose tested and was not statistically significant. Thus, the lack of human relevance of these lesions is based on basic toxicological considerations as well as on pathology (Butler et al. 1997; Wells 2006; Cohen 2002; Halliwell 1998; Karbe 1999).** **The submucosal mesenchymal lesion (SML) is not a neoplasm (Butler et al. 1997; Wells 2006; Cohen 2002; Halliwell1998; Karbe 1999). The lesion, observed only in mice, shares morphologic and immunochemical features with the decidual reaction of aging mice forming non-neoplastic lesions. These lesions consist of spindle and epitheloid cells, may contain round**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		eosinophilic granules, and possess nuclear progesterone receptors and cytoplasmic desmin. The decidual reaction derives from endometrial stromal cells, while the mesenchymal lesion develops from mesenchymal cells near the trigone area, carrying or developing progesterone receptors. The non-neoplastic lesions occurring in the bladders of male mice at the highest dose tested were SMLs and not tumors as originally described in the study. These lesions have not been found in rats or hamsters of either sex. This type of lesion has never been reported in the human urinary bladder (Butler 1997). **The majority of bladder tumors in humans are epithelial in origin, unlike the SMLs in mice. Further, the SMLs were not associated with the formation of urinary tract calculi. This is one of the mechanisms discussed by Meek et al. (2003) in connection with establishing a framework for human relevance of carcinogenic modes of action (MOAs). Examples of rodent urinary bladder carcinogens included melamine (Case Study 7; Table 4), which caused carcinomas specifically in male rats at 300 but not at 150 mg/kg/day. Limited human relevance was indicated by the fact that exposure**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		would need to be extremely large for it to precipitate out and form calculi; and humans, being bipedal, have a greater ability to pass urinary calculi in urine. **An IPCS framework for analyzing the relevance to humans of animal tumors was recently reviewed (Boobis et al. (2006). After reviewing several cancer MOAs that are sufficiently well understood for such relevance to be estimated, the issue of relative exposure was mentioned: "If a high experimental dose of a given compound is needed to result in an obligatory step in a MOA, then the relevance to human risk becomes a matter of exposure. Thus, the exposure assessment step of the subsequent risk characterization is critical to the proper evaluation of human cancer potential." As such, in the bifenthrin mouse chronic study, males at 600 ppm showed an elevation of bladder lesions (N.S.), whereas at 500 ppm there was no increase. Mean measured bifenthrin consumption by males dosed at 600 ppm was 123 mg/kg/d for the first 13 weeks, 102 mg/kg/d for 53 weeks and 92 mg/kg/d at termination. If bifenthrin were present in food at 0.05 ppm (i.e. 0.05 mg/kg of diet), mice at 600 ppm would need to consume 2000 kg food/kg body**		

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		wt/day to reach an exposure level of 100 mg/kg/day. For a 50 kg human, this would be equivalent to consuming 100,000 kg of food/person/day for a lifetime. This calculation shows that it would be impossible in practice for a person to eat sufficient food to be concerned about the oncogenicity of dietary bifenthrin exposure. **b. Histopathology of bladder lesions. Butler et al. (1997) concluded that the origins of the lesions, including both smooth muscle and vascular, suggested that they were derived from the vascular mesenchyme. This is different from the smooth muscle histological origins of leiomyosarcomas. According to the report by Wells (2006), these tumors are best described as "submucosal mesenchymal lesions" or SMLs. Furthermore, Cohen (2002) stated that for SMLs, "it is unclear whether these arise from a regenerative process or whether they represent true neoplasms"; Halliwell (1998) reached similar conclusions. Karbe (1999) stated that the scientific community does not consider SMLs as tumors. The bifenthrin SMLs had different histological (staining) properties from leiomyosarcomas. Further, the lesions were localized (i.e., there was no metastasis, unlike**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		leiomyosarcomas, which are highly malignant). These lesions were also concluded to be species-specific to the mouse; and were not found in other mammals, including humans. Therefore, SMLs should not be used for cancer risk assessment. **c. Statistical significance of bladder lesions. The statistical significance of common tumors should be evaluated at the statistical decision level of $p < 0.01$ using the Haseman rule for pair-wise comparisons (Haseman 1990). In the bifenthrin dossier submitted by FMC for evaluation of bifenthrin under 98/8 (Troubac and McCarthy, November 2003), the lesion incidence data was first reported. A re-examination of slides by the Pathology Working Group (Butler 1997) determined that the nominal increase observed was not statistically significant ($p=0.068$; Table 1). It is only when other bladder lesions are combined with the SMLs that there is a marginal statistical significance ($p=0.05$). Bladder lesion incidence was only increased in male mice at the highest dose tested (HDT) (600 ppm). There was no increase in bladder lesions in females, or in rats of either sex.** **Lesions in mice dosed at 500 ppm for**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		24 months were not significant at any level. Bladder lesion incidence at the highest dose tested (p=0.068) was not statistically significant at a p < 0.01 level, which should be the standard applied for common tumors. **d. Precedence: Decision for Benalaxyl regarding bladder lesions. The incidence of SMLs in mice, and the implications for classification has been addressed in the review of other plant protection products proposed for Annex 1 listing under Directive 91/414/EEC. The March 2001 Addendum 3 to the Monograph for benalaxyl addresses a very similar situation as was found with bifenthrin.** **In their initial review, the RMS for benalaxyl proposed a classification of carcinogenic category 3 with R40 labelling. ISAGRO disagreed with the conclusion; at their request a Pathology Peer Review (PPR) was conducted on sections of urinary bladder tumors from 3 male Swiss mice used in the oncogenicity study. The original diagnosis was "transitional cell carcinoma". The PPR determined this diagnosis to be incorrect and that the lesions in question were "submucosal mesenchymal tumors" of the mouse**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		urinary bladder. A Pathology Working Group was then convened and an independent panel of pathologists examined the urinary bladder sections, without prior knowledge of the diagnosis of the study pathologist or the PPR. They also concluded that the lesions were not carcinomas, but were in fact submucosal mesenchymal lesions. **Among the conclusions of the panel:** **• 'The lesion has been reported in the literature for many years under a variety of neoplastic and non-neoplastic diagnostic terms including leiomyosarcoma** **• The lesion is unique to mice; its counterpart has not been reported in any other laboratory species or in humans.** **• If it is assumed that the lesion is neoplastic, its non-epithelial nature is important since the vast majority of spontaneous and chemically induced mouse and human urinary tumors are of epithelial origin.'** **The International Life Sciences Institute, Risk Science Institute (ILSI, RSI) convened a working group to review the scientific knowledge of SMLs. This group noted that the SMLs have primarily been diagnosed in two**		

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		strains of mice (CD-1 and Swiss Webster), and that the incidence of this type of lesion was probably higher than published estimates (as high as 17%) based on the fact that they are small and localized in their occurrence to areas of bladder not typically well examined. There is agreement among scientists that the lesion is non-epithelial in origin, is unique to mouse urinary bladder, and has no counterpart in any other species, including humans. **With due consideration of the nature of the urinary lesions, the RMS (Portugal) for benalaxyl withdrew classification of benalaxyl as carcinogenic category 3. In a meeting of the Commission Working Group on the Classification and Labelling of Dangerous Substances, the European Chemicals Bureau agreed not to classify benalaxyl for carcinogenicity (2001). Given that the same type of lesions are in question for bifenthrin, with the same strain of mouse, with a similar initial diagnosis and subsequent re-characterization by leading pathologists as SMLs, it seems similarly warranted that the proposed classification of Category 3 be withdrawn for bifenthrin based on the current state of scientific**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		understanding. **e. Conclusions: Bladder lesions. An increased incidence of submucosal mesenchymal lesions (SMLs, previously denoted erroneously as leiomyosarcomas) of the urinary bladder in male mice was only observed at a dose (600 ppm, the HDT) above the LOEL/NOEL (500/200 ppm) for significantly reduced body weight, reduced body weight gain and increased incidence of clinical signs in males. Such lesions have not been found in humans. It is suggested that the SML increase, which was not statistically significant (p=0.068) and was restricted to males, was a direct result of severe systemic toxicity at a dose that was above the MTD for males (600 ppm). In comparison, data are presented showing that 600 ppm was at the MTD for females because they showed clinical signs without consistent effects on body weight or body weight gain. This consideration, in the absence of genotoxicity at non-cytotoxic doses, removes the relevance of SMLs for cancer risk assessment purposes. There is no evidence of treatment-related bladder tumors, and this is surprising considering the extreme study conditions. A similar situation with benalaxyl resulted in a**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		withdrawal of Carcinogenicity category 3; R40 labelling. **3. Bifenthrin does not cause lung tumors** **Female mice originally were observed to have higher incidences of combined lung adenomas and carcinomas than control animals. A re-evaluation of these tumors by Butler (1997) observed no significant trends for oncogenicity and no significant pair-wise comparison for adenomas, adenocarcinomas or the combination of these two tumor types at the highest dose level. The only positive pair-wise comparisons were observed at the low dose only for adenomas, and the low- and mid-doses for combined adenomas and carcinomas ($p<0.05$). Using Haseman's rule for common tumors, none of these values is statistically significant. No significant pair-wise comparisons were observed for carcinomas at any dose level. In addition, there was no significant dose-related trend for these neoplasms, and no observed progression from adenomas to carcinomas which would warrant combining the two types of tumors for analysis of incidence. Finally, the control incidence of these tumors was 28%; the tumor is a**	FR: According to the 67/548/EC directive criteria, classification as Carc. Cat..3; R40 is proposed when "*carcinogenic effects [are observed] only at very high dose levels exceeding the maximum tolerated dose. The MTD is characterized by toxic effects which, although not reducing lifespan, go along with physical changes such as about 10% retardation in gain weight."* The slight increase of bronchiolar-alveolar adenocarcinomas and adenomas observed in female mice was statistically significant at the higher dose level (48% of treated females compared to control) and it is therefore considered that bifenthrine induces lung tumours.	

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		common background finding in Swiss Webster mice, with a background incidence of 4 to 57% (Wells 2006). **Considering that the high dose exceeded the MTD and that the study duration was 6 months longer than the standard study (24 months vs. 18 months) meaning animals were not just exposed to 33% more chemical but were also senescent, one might argue that bifenthrin has no potential to cause lung tumors in mice.** **4. Bifenthrin does not cause lymphoblastic leukemia** **The ECHA CLH Report notes that there is an increased incidence of lymphoblastic lymphosarcoma and leukemia at 600 ppm in females. However, the question of lymphoblastic leukemia in female mice in the chronic study has already been addressed in the Draft Assessment Report (Bifenthrin_DAR_04_Vol 3_B6_public[1].pdf; pp. 143-148) prepared by the RMS (France) for the review of bifenthrin under Directive 91/414/EEC. It was concluded that "the incidence rate of occasional non-neoplastic and neoplastic entities was slightly increased in high dose mice when compared to controls." (pp. 144)**	FR: According to the 67/548/EC directive criteria, classification as Carc. Cat..3; R40 is proposed when "*carcinogenic effects [are observed] only at very high dose levels exceeding the maximum tolerated dose. The MTD is characterized by toxic effects which, although not reducing lifespan, go along with physical changes such as about 10% retardation in gain weight.*" The slight increase of lymphoblastic leukemia observed in female mice was statistically significant at the higher dose level (44% of treated females compared to control) and it is therefore considered that bifenthrine induces leukaemia.	

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		However, although the incidence of lymphoblastic leukemia in females was elevated at the 600 ppm ($p<0.05$), the incidence of all lymphoid tumors was not increased significantly above control at any dose in females. It was concluded that the observed incidence pattern (for lymphoblastic leukemia) was not compound-related (pp. 145): **"Lymphoblastic leukemia had a statistically significant ($p=0.024$) incidence in high dose females as judged by pairwise comparison with the control using Fisher's exact test. Time-to-tumor tests revealed no significant trends for either the mortality or onset functions while the prevalence function was significant. Combining all lymphoid tumors in female mice results in an incidence pattern of 38%, 38%, 40%, 32%, 47% for groups I through V respectively. None of the treatment group are significantly different than the control as judged by pairwise comparisons with the control using Fisher's exact test on the combined incidence data. The lack of a dose response plus the large number of control animals affected indicated that the compound had little or no effect on the development of these tumors. The pathologist's conclusion was that the**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		observed incidence pattern was not compound related." **We should re-iterate that this increased incidence of lymphoblastic lymphosarcoma and leukemia was only at the HDT (600 ppm) in females, a dose that exceeds the MTD. Furthermore, the 18 month study has been recognized as the standard because experts realize the confounding factors introduced into the interpretation of study results when exposing senescent animals to chemicals. Thus, bifenthrin does not cause lymphoblastic leukemia, even in highly stressed animals.** **5. Bifenthrin does not cause liver tumors** **The ECHA CLH Report notes a slight dose-related increase in liver adenocarcinoma and adenomain males from 200 ppm that is not statistically significant. In the original report, the study pathologist concluded that due to the absence of the precursor (putative preneoplastic lesions), the low incidence of the tumor in high dose males and the absence in females, that hepatocellular neoplasms were unlikely to be treatment-induced; therefore,**	FR: A "*slight dose-related increased incidence of liver adenocarcinoma and adenoma in males from 200 ppm but not statistically significant*" has been reported in the present CLH report (in the table 5.7.1-1: Summary of carcinogenicity data). It has not been taken into account in our proposal of classification because it didn't achieve statistical significance.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		this is not "supportive" evidence of carcinogenicity. All pathologists who have looked at this data subsequently have concurred with that assessment (Butler 1991). Statistical analyses of adenoma/hyperplasia or carcinoma incidence showed no significant differences between control and treated groups (the significance level for trend test in pair-wise comparisons did not achieve a value of $p<0.01$). The incidence was generally low, and the marginally higher value for mice dosed at levels exceeding the MTD is incidental and unrelated to treatment. Also, the study duration was 6 months longer than the standard study (24 months vs. 18 months) meaning animals were not just exposed to 33% more chemical but were also senescent. The absence of similar findings with bifenthrin in rats, or in female mice, or with other pyrethroids, supports the conclusion that these neoplasms are irrelevant with respect to classification of bifenthrin. Thus, there is no evidence of treatment-related liver tumors and even in a study conducted under extreme conditions. **ECHA PROPOSAL FOR CLASSIFICATION AND LABELING WITH REGARD TO CARCINOGENICITY:**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		COMPARISON TO GUIDELINE CRITERIA **According to the guidelines for a Carcinogenicity Category 3 classification requiring R40 labelling, the following consideration is relevant [EU Directive 67/548/EEC 4.2.1.2 (b)]: "For a distinction between category 3 and no classification arguments are relevant which exclude a concern for man:** **-a substance should not be classified in any of the categories if the mechanism of experimental tumor formation is clearly identified, with good evidence that this process cannot be extrapolated to man."** **As discussed, an independent panel of pathologists have clarified that lesions in the mouse originally denoted as tumors are in fact submucosal mesenchymal lesions (SMLs) with low malignancy potential and no relevance to man. Therefore, the criterion for distinguishing between a Carc. Cat. 3 and no classification have been met, and no classification should be made.** **According to the more recent CLP guidelines for a Cat. 2 – H350 classification [Classification, Labelling and Packaging (CLP) Regulation EC**		

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		1272/2008], carcinogenicity is defined as follows (3.6.1): **"A substance or mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumors in well-performed experimental studies on animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumor formation is not relevant for humans."** **Furthermore, the following consideration also is relevant [3.6.2.2.3 (b)]:** **"Sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumors in both sexes of a single species in a well-conducted study, ideally conducted under GLP, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity**		

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		when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumor or age at onset, or when there are strong findings of tumors at multiple sites." **The CLP criteria further indicate some additional important factors that may be taken into consideration, when assessing the overall level of concern (3.6.2.2.6), including tumor type and background incidence; multisite responses; progressions of lesions to malignancy; reduced tumor latency; whether responses are in single or both sexes; and whether responses are in a single species or several species.** **Clearly bifenthrin does not meet these CLP criteria. Lesions in the mouse originally denoted as tumors are in fact submucosal mesenchymal lesions (SMLs). Even if the lesions were tumors, they are only seen in a single study, and are only seen in male mice. Additionally, the effects observed were seen in very senescent animals only at the highest dose, which actually exceeded the MTD. The lymphosarcoma and leukemia in females were age-related and not treatment-related, as these effects are not different from the control, and are only observed in senescent females at**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		the high dose which exceeded the MTD. There was no statistically significant increase in adenoma and carcinoma at any dose level, and no dose related trend and no progression from adenoma to carcinoma was observed. Therefore, there was no carcinogenic effect observed in mice, and a classification of Category 2-H350 according to CLP criteria would be inappropriate. **OVERALL CONCLUSIONS** **The case against regulating bifenthrin as a carcinogen is strong, given that the oncogenicity potential of bifenthrin has been extensively studied. There is sufficient evidence available to classify bifenthrin as negative with respect to its potential carcinogenicity with little uncertainty. The oncogenicity of bifenthrin has been addressed in the rat and mouse in chronic dietary studies along with a suite of in vitro and in vivo genotoxicity studies. These studies have all been found acceptable to US and EU regulators. Findings in the original rat and mouse oncogenicity reports, as well as by an independent panel of pathologists (the Pathology Working Group, or PWG), indicate that bifenthrin should not be considered oncogenic in humans based**		

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		on EU criteria. Specifically, comparing the bifenthrin data with both the older and newer EU CLP guidelines: **1. There is no evidence of carcinogenicity in guideline rat studies.** **2. The genotoxicity database for bifenthrin is uniformly negative.** **3. Bladder lesions** **a. Lesions observed in the male mouse that were originally denoted as urinary bladder tumors (leiomyosarcomas) are currently referred to by the pathology community as submucosal mesenchymal lesions (SMLs) with low malignancy potential and no relevance to humans.** **b. A Pathology Working Group (PWG) determined that the incidence of these lesions was not significantly different from controls at any dose level, including 600 ppm (p=0.068).** **c. The SMLs were only nominally elevated in male mice at a dose (600 ppm) that exceeds the MTD; therefore, the lesions have limited relevance for risk assessment purposes. Females did not show an increase in bladder lesions at any dose level, and the MTD was not exceeded for females.** **d. The issue of whether the occurrence of SMLs warrants a carcinogenicity classification has been debated, with**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		experts agreeing that SMLs in mouse urinary bladder are not neoplastic, and they have no relevance to humans. **e. The same issue of SMLs arose more recently for benalaxyl, and was reviewed by a PWG; the RMS (Portugal) withdrew classification of benalaxyl as a carcinogenic category 3. The European Chemicals Bureau agreed that benalaxyl should not be classified as a carcinogen.** **4. The incidence of hepatocellular adenomas and adenocarcinomas in male mice dosed with bifenthrin was not significantly different than the incidence in controls and was not considered to be treatment related.** **5. Lymphosarcoma and leukemia in females are age-related and not treatment-related, as their incidence is not different from the controls, and are observed only in mice receiving a dose level that exceeds the MTD.** **6. Bifenthrin does not cause statistically significant incidences of lung tumors at any dose.** **7. The evidence from extended exposure to doses near the maximum tolerated dose (MTD) did not result in lesions or other responses that could be viewed as evidence of a dose-related carcinogenic effect in mice induced by bifenthrin. Carcinogenicity determinations should not be based on**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		evidence from a dose that exceeds the MTD in senescent animals. **8. The duration of the study was 24 months, or 33% longer than the 18-month guideline study typically used in carcinogenicity assessments. The fact that mice were 33% older than usual is a confounding factor in relying on the high dose for a carcinogenic assessment. . There is no evidence of bifenthrin treatment-related tumor occurence, even under extreme study conditions where the MTD is exceeded and animals are senescent.** **All required data are available; no study provides evidence of carcinogenicity; and the EU CLP criteria have not been metTherefore, it is reasonable to conclude that bifenthrin should not be classified as a carcinogen.** **REFERENCES** **Boobis, A.R., Cohen, S.M., Dellarco, V., McGregor, D., Meek, M.E., Vickers, C., Willcocks, D. and Farland, W. (2006). IPCS framework for analyzing the relevance of a cancer mode of action for humans. Crit. Rev. Toxicol. 36:781-792.** **Butler, W.H. 1991. FMC 54800**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Technical. Oncogenicity lifetime feeding study in albino mice. Histopathological review of selected sections of liver, lung and urinary bladder. BIBRA Toxicology International, Surrey, UK. Report date 28 May 1991. Revision dates 3 June 1991 and 16 July 1991. Dossier reference point – Doc IVA, A6_7_02addB. **Butler, W.H. 1991. FMC 54800 Technical. Oncogenicity lifetime feeding study in albino mice. Histopathological review of selected sections of liver, lung and urinary bladder - addendum. BIBRA Toxicology International, Surrey, UK. Report date 13 November 1991. Dossier reference point – Doc IVA, A6_7_02addC.** **Butler, W.H., Cohen, S.H. and Squire, R.A. 1997. Mesenchymal tumors of the mouse urinary bladder with vascular and smooth muscle differentiation. Toxicol. Pathol. 25(3):268-274**.		

Mutagenicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 26ff** **The German CA supports not to classify bifenthrin for mutagenic hazard.**	FR: Thank you for your support	Noted.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 30 : We agree with the proposed classification.**	FR: Thank you for your support	Noted.

Toxicity to reproduction

Date	Country/ Person/Organisation/ MSCA	Comment	Response	RAC comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 34ff** **The German CA supports not to classify bifenthrin for reproductive or developmental hazard.**	FR: Thank you for your support	Noted.
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 37: We agree with the proposed classification.**	FR: Thank you for your support	Noted.

Respiratory sensitisation

Date	Country/ Person/Organisation/ MSCA	Comment	Response	RAC comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 19** **The German CA supports not to classify bifenthrin for respiratory sensitising hazard.**	FR: Thank you for your support	Noted.
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**No comments**	FR: Thank you for your support	Noted.

Other hazard classes - Environment

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 10ff** **The German CA agrees with the proposal for environmental classification and labelling of Bifenthrin. We would suggest the**	FR: The CLH report has been amended.	Noted and confirmed

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		addition of Pictogram GHS09 and signal word: Danger. **Additional remarks ref. chapter 4 environmental fate properties, point 4.3 Bioaccumulation:** **Measured bioaccumulation data (3 references) are summarized which indicates a high potential for bioconcentration of Bifenthrin in fish.** **The results of the BCF study with common carp (Shigeoka and Saito, 1993) has to corrected to BCF 1290 L.kg-1 (related to total measured radioactivity) as measured data (instead of 1082 L.kg-1). Additionally the BCF should be corrected for lipid content of test fish (3.2%) to BCF 2016 L.kg-1 (lipid normalized to 5% lipid content).** **The results of the BCF study with bluegill sunfish (Surprenant, 1985) could not be corrected for lipid content of test fish, because there are no data for lipid content of fish in the report. The relevant BCF is 6090 L.kg-1(related to total measured radioactivity).** **The results of the BCF study with bluegill sunfish (Gries, 2006) could not be evaluated. The original study (with raw data) is not yet available for authorities in Germany.** **Nevertheless the BCF 1414 L.kg-1**	FR: The CLH report has been amended.	Noted, one calculation error corrected: lipid normalised BCF for Gries (2006) study should read 2142 (instead of 2016).

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		related to Bifenthrin (parent) should be corrected for lipid content of test fish (3.3%) to BCF 2016 L.kg-1 (lipid normalized to 5% lipid content).		
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Photolysis in water:** **Page 10: Please specify the identity of the degradation product TFP acid. For the sake of completeness, please specify the degradation products formed in the second photolysis experiment (Currey, 2006) as presented in Document I (Assessment report for Bifenthrin Product-type 18 (insecticide) under Directive 98/8/EC concerning the placing biocidal products in the market, September 2009).**	FR: The CLH report has been amended.	Noted
		Simulation tests: **Page 11: Please specify that the reported DT50s for both water/systems studies are related to the total system. The presented DT50 values at 12 ºC do not fully correspond with the range given in Document I, please check.**	FR: The DT50 values at 20°C and 12°C has been checked and corrected.	Noted
		In order to allow for a good evaluation of the simulation studies, we suggest that the rapporteur include information on mineralization, bound residues, and metabolites found in water and sediment phase.	FR: the information about mineralization, bound residues and metabolites has been added.	Noted
		Summary on persistency: **Page 11: We agree on conclusion:**	FR : Thank you for your support	Noted – for classification purposes, the

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		Based on the results from biodegradation screening test (not readily biodegradable) and limited information from the simulations studies Bifenthrin is considered not readily biodegradable for purposes of classification and labelling.		decisive criterion is **rapid** degradation.
		Bioaccumulation: **Page 12: To provide more information on the validity of the BCF values provided (especially the high values) it will be useful to include the evaluation of the B-criterion of the Technical Committee for PBT assessment.**	FR: we consider it is not the purpose of a classification dossier to include conclusions on the B criterion and we prefer not to add this point.	Noted and agree. In the CLH process, conclusions on PBT criteria are not mandated.
		We propose to delete § 4.3.2. As no measured data for earthworm are available, this paragraph has no added value.	FR: we accept to delete this part of the report which is not used for classification..	
		Overall, we agree that the BCF is > 500 which is indicative of the potential to bioconcentrate for classification purpose.		
02/04/2010	**Belgium / Frederic Denauw / MSCA**	**Bifenthrin is a poorly soluble substance (watersolubility < 1µg/l)** **Based on the results of the aquatic acute toxicity test on the most sensitive species (96hEC50fish = 0.1 µg/L), the fact that the substance is not readily biodegradable and that the substance shows potential to bioaccumulate in fish and earthworm (log Kow >6), it is**		

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		justified to classify as Aquatic Acute 1 and Aquatic Chronic 1. **Based on the classification and labelling criteria in accordance with dir. 67/548/EEC, Bifenthrin should be classified as N, R50/53. Application of the translation table of annex VII of the CLP regulation 1272/2008, results in the corresponding classification as Aquatic Acute 1 and Aquatic Chronic 1.** **In view of the proposed classification and the toxicity band between 0.00001mg/l and/ or equal to 0.0001mg/l, a M-factor of 10 000 could be assigned.**		Noted. See also additional M-factor suggested for H410 after implementation of the 2nd ATP of the CLP Regulation.
		In conclusion : we agree with the proposed environmental classification by the FR MSCA.	FR: Thank you for your support.	Noted
		comments: **General remark : It would be useful to mention always the guidelines according to which the tests were performed**		
		Biodegradation - simulation tests : guideline?, temperature? Specification of DT50 (water, sediment, whole system)	FR: this information has been added;	Noted
		p.47 7.6 conclusion : **Acute toxicity to invertebrates 48H-**	FR: it has been corrected.	Noted

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		EC50=0.11µg/l instead of >		
08/04/2010	**UK / Daniel Merckel / MSCA**	**- Classification for the Environment: we agree with the proposal to classify the substance N: R50/53 (according to Directive 67/548/EEC) and Aquatic Acute I (H400) and Aquatic Cronic I (H410) (according to regulation EC 1272/2008) based on the data in the dossier.**	FR: Thank you for your support.	Noted
		-M-factor (page 5 and page 41): The M factor of 10,000 is based on the result with the freshwater fish Oncorynchus mykiss (LC50 of 0.1 ug/l). We agree with this factor. **The freshwater invertebrate result with Daphnia magna is very similar (EC50 0.11 ug/l).** **[NB The assignment of the M factor is correct as the regulation states values "equal to or greater than" 0.0001 mg/l are given an M factor of 10,000. (It is unfortunate that the fish result sits right on the cut-off value, as it may be that reanalysis of these data with greater accuracy, depending on the accuracy of the analytical method, or with a different method, could give a result just above the quoted result and so an M factor of 1,000).]**	FR: The fish-EC50 of 0.1 µg/l is based on the mean measured concentration varied from 0.086 – 0.12µg/l. We propose to add this confidence interval.	Noted. See also additional M-factor suggested for H410 after implementation of the 2nd ATP of the CLP Regulation. Noted. The range of measured values added as footnote to table 18. Indeed, the decisive fish test result (0.1 µg/L, Suprenant 1985c) matches exactly the borderline to the next higher SCL and lower M-factor, respectively. However, with a view to the range of measured concentrations in both neighboured categories, and to significantly lower effect thresholds in chronic fish and invertebrate tests, selection of the stricter SCL and M-factor appears to be additionally confirmed (while formally still correct).
		-page 11, 4.1.2.3 biodegradation in	FR: it has been corrected.	Noted

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		water/sediment systems, first line: please add "radio" to "labelled". Details of the type and position of the radiolabel would be useful.	FR: this information has been added.	Noted
		-page 11, 4.1.2.3, biodegradation in sediments and in soils: it would be useful to list the types of sediment and the four types of soil used in the study.	FR: it has been added.	Noted
		-page 11, 4.1.3: the summary should refer to all forms of degradation, not just biodegradation, and compare these against the criteria in CLP and DSD (as has been done for bioaccumulation and ecotoxicity).	FR: a short conclusion on hydrolyse and photolysis has been added.	Noted
		-page 11, 4.2.2: it might be useful to refer to bifenthrin's estimated Henry's Law constant and its implications for volatilisation from surface waters, for completeness.	FR: complementary information on volatilisation has been added.	Noted
		-page 12, section 4.3.1.1: in the first paragraph the BCF is predicted from the equation of Binstein et al using a log Kow of 6.6. Why was this value chosen (log Kow given as >6) - as a worst case? Please justify the selection of 6.6 rather than some other value that is >6. (eg KOWWIN estimates a log Kow of 8.15).	FR: it has been amended	Noted
		-page 12, section 4.3.1.2: hardly any	FR: a table of summary of	Noted, see also general comment with

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		detail is given for the four studies put forward here. What were the conditions of the test, what concentrations in water were tested, how long were the uptake and depuration phases, what are the bases for results (analysis for parent compound or radioactivity, any comparison of results from radio analysis with parent compound analysis in the Full life cycle study, etc)?	bioaccumulation studies has been added.	headline '<u>Limited details</u>', above.
		-Page 13, section 4.3.2: the TGD equation (Jager, 1998) for estimating bioaccumulation in the earthworm is applicable to substances in the range log Kow 3 – 8, but has been shown to perform poorly for substances with log Kows above about 4 – 5 (see for example Brooke D N and Crookes M J, 2007 Verification of bioaccumulation models for use in environmental standards. Part B: Terrestrial models. Science Report SC030197/SR3. Environment Agency. ISBN: 978-1-844320-756-0). Please consider adding some comment on the uncertainty in the predicted value here, although we recognise that this information is not used for classification.	FR: the chapter concerning the bioaccumulation on earthworm has been delete as no test data are available. See also comment from Netherlands.	Noted
		<u>Minor Comments - Typos etc</u>	FR: it has been corrected.	Noted

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		- page 6, 1.2: "The cis-Z isomer pair are the predominant compounds" **- page 11, 4.1.2.3, third paragraph: can delete "at least" here.**		
08/04/2010 **Confidential claim on the comments removed since 12 August 2010**	**Belgium / FMC Chemical sprl / Company-Manufacturer** **(ECHA: Same comment was sent several times)**	**Environmental Fate Properties: Bioaccumulation** **p 13 it is concluded that 'bifenthrin have a potential to bioaccumulate in fish.** **To address this the conclusion of the TC NES Sub-Group meeting of 20th November 2007 is submitted. The conclusion of this meeting was that bifenthrin did not bioaccumulate. In addition an overview paper is submitted, in which it is concluded that bifenthrin will not bio-accumulate in either the terrestrial or aquaitc compartments.**	FR: we consider it is not the purpose of a classification dossier to include conclusions on the B criterion and we prefer not to add this point.	Noted and agree. In the CLH process, conclusions on PBT criteria are not mandated.

Other hazard classes – Acute toxicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 14ff** **The German CA supports to classify bifenthrin for acute oral and inhalative toxicity (Acute tox. cat 3: H301 and H331; Toxic: R23 and R25). Oral LD50 and inhalative LC50 are within the ranges for the respective categories.**	FR: Thank you for your support	Noted. But see final proposal for acute toxicity (Acute Tox.2-H300)

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 17: We agree with classification as 'toxic' with the risk phrase R25 - Toxic if swallowed according to the Directive 67/548/EEC criteria. However, the oral LD50 values from the second study (42.5 mg/kg bw for female mice and 43.5 mg/kg bw for male mice) require classification as Acute Tox.2-H300 instead of Acute Tox.3-H301 according to the CLP criteria. According to paragraph 3.1.2.3.2 of the Guidance on the application of the CLP criteria, in general the lowest ATE in the most sensitive species is used, unless expert judgment leads to another ATE value. However, the use of another ATE requires a robust justification.** **In addition, it is noted that following dermal exposure, rats exhibited staggered gait. Is it considered to classify for STOT-SE based on these effects?**	FR: We agree with your comment concerning the classification as Acute Tox. 2_H300 instead of Acute Tox.3_H301. The CLH report has been amended. FR: Critical effects (tremors) are not observed during the study. The dermal DL_{50} value is greater than 2 000 mg/kg bw, therefore a classification as STOT SE. is not relevant for dermal route.	Noted. Noted. Rapporteur accepts not to classify for acute dermal toxicity (see background document).
02/04/2010	**France / Antony Fastier / AFSSA**	**We agree with the proposal classification of Bifenthrin:** **Based on Directive 67/548/EEC criteria:** **Xn ; Carc. Cat 3; R40** **T; R23/25** **Xi; R43** **Based on CLP criteria:** **Carc.2 – H351** **Acute Tox. 3 – H331** **Acute Tox. 3 – H301** **Skin Sens. 1 – H317**	FR: Thank you for your support	Noted. But see final proposal for acute toxicity (Acute Tox.2-H300)

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		(ECHA: copied from General comments)		

Other hazard classes – Skin sensitisation

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 19** **The German CA supports to classify bifenthrin as a skin sensitiser (Skin sens. cat. 1: H317; Xi: R43). In the respective study 8 of 9 tested animals showed signs of sensitisation upon challenge.**	FR: Thank you for your support	Noted.
02/04/2010	**France / Antony Fastier / AFSSA**	**We agree with the proposal classification of Bifenthrin:** **Based on Directive 67/548/EEC criteria:** **Xn ; Carc. Cat 3; R40** **T; R23/25** **Xi; R43** **Based on CLP criteria:** **Carc.2 – H351** **Acute Tox. 3 – H331** **Acute Tox. 3 – H301** **Skin Sens. 1 – H317** **(ECHA: copied from General comments)**	FR: Thank you for your support	Noted.

Other hazard classes – Repeated dose toxicity

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
26/03/2010	**Germany / Jan Averbeck / MSCA**	**Page 20ff** **Specific target organ toxicity repeated exposure / damage to health by prolonged exposure:** **The German CA does not support to classify bifenthrin with STOT-RE / R48. We consider the observed signs of neurotoxicity (tremors) not to be a major functional change which would necessitate C&L. This is in line with C&L for other pyrethroids.** **We support not to classify bifenthrin for any other hazard (i.e., skin and eye irritation, STOT-SE). No effects to support such additional classification were described in the report.**	FR: According to the CLP criteria "*target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included."* (§ 3.9.1.1 of the 1272/2008/EC regulation). Furthermore, a classification STOT. Rep. 1-H372 can be proposed when *"significant functional changes in the peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses"* are observed (§ 3.9.2.7.3.b). Therefore, FR maintains its proposal for classification as STOT Rep. 1-H372.	Rapporteur checked the comments and considerations on RDT. See background document for a detailed discussion on the adequacy of the RDT classification. RAC finally concluded to classify bifenthrin for RDT.
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**Page 26 : According to Directive 67/548/EEC criteria, the longest studies per species should be used for classification for repeated dose toxicity. Therefore, please also include the 52 week studies (dog) (and the 90 day study in dogs) in the argumentation for classification, in which delayed tremors are also observed at low(er) doses. Since these studies also indicate that classification as Xn; R48/22 (or STOT-RE 1 – H372) is required, we do agree**	FR: We agree with your comment. The CLH report has been amended.	Rapporteur checked the comments and considerations on RDT. See background document for a detailed discussion on the adequacy of the RDT classification. RAC finally concluded to classify bifenthrin for RDT.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		with the proposed classification. **In the dermal study, staggered gait and exaggerated hindlimb flexion were observed at 100 mg/kg bw. From the results it is not clear whether these results are acute effects or if they are caused by repeated exposure. If the effects are caused by repeated exposure, classification for repeated dermal exposure is also needed (limit for classification according to 67/548/EEC is 428 mg/kg bw [90/21*100]). Thus, more detailed information from the dermal repeated dose study is necessary.**	FR: In the dermal study, staggered gait and exaggerated hindlimb flexion were observed at the beginning of the study (from day 1 day 4). These effects are not caused by repeated exposure, so classification for repeated dermal exposure is not relevant. Detailed information has been added to the CLH report. The target organ (nervous system) has also been added.	
02/04/2010	**France / Antony Fastier / AFSSA**	**Comments from AFFSA (French Food Safety Agency) on the CLH REPORT** **<u>Column 1:</u> Reference to assessment report** **<u>Column 2:</u> Comment** **(2) 5.5.3 Summary and discussion of repeated dose toxicity: Classification Xn, R48/22(directive 67/548/CE) and STOT Rep 1-H372(regulation 1272/2008/CE) is not justified.** **In the CLH report of bifentrin, a classification Xn, R48/22, according to the directive 67/548, and STOT Rep 1-H372, according to the CLP criteria, are proposed based on tremor (2/15**	FR: According to the CLP criteria "*target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to substance or mixture. All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included."* (§ 3.9.1.1 of the 1272/2008/EC regulation). Furthermore, a classification STOT. Rep. 1-H372 can be proposed when *"significant functional changes in the peripheral nervous systems or other organ systems, including signs of central*	Rapporteur checked the comments and considerations on RDT. See background document for a detailed discussion on the adequacy of the RDT classification. RAC finally concluded to classify bifenthrin for RDT.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		males and in 3/10 females) observed at 100 ppm (≈ 8 mg/kg/d) on a 90-day rat study. However, this clinical sign appeared early in the study (within day 3 to day 5 in male rats and day 3 to 16 in female rats) and then after disappeared till the end of the study. This effect hasn't exhibited a potential of accumulation or exacerbation of the toxicity with repeat exposure. Besides, bifenthrin has not exhibited any treatment-related effect on the nervous system, including the sciatic nerve, at histopathological examination. **Further more, tremors were also observed in all toxicity study either after a single or a repeated dose regardless the route of administration of bifenthrin. Tremor is one of the most consistent neurobehavioral signs following exposure to Bifenthrin/pyrthroid, which is a tremorgenic/neurotoxic substance belonging to type I pyrthroid insecticide (T-syndrome- tremor). Bifenthrin as other pyrthroid act on voltage-sensitivity sodium channel, calcium, chloride channels and perhaps the potassium channel.** **Thus it can be concluded that tremor is essentially an acute, in such case classification Xn, R48/22 and STOT Rep 1-H372 are not appropriate.**	*nervous system depression and effects on special senses"* are observed (§ 3.9.2.7.3.b). Therefore, FR maintains its proposal for classification as STOT Rep. 1-H372. We however recognise that these effects are transient at doses relevant for classification but this is not in contradiction with criteria for STOT Rep. Besides, they are observed in repeated-dose studies at lower doses than in acute studies and we consider that it justifies an additional classification.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		(ECHA: transferred from General comments)		
02/04/2010	**Belgium / Frederic Denauw / MSCA**	**Xn; R48/22 (STOT Rep.1 – H372):** **- 28-day oral rat: clonic convulsions and tremors, followed by death of all animals by day 15 at 400 ppm (34.5/32.6 mg/kg bw/d), clonic convulsions and tremors + mortality (6/10M and 1/10 F) at 300 ppm (21.9/21.6 mg/kg bw/d)** **- 90-day oral rat: tremors at ≥100 ppm (≥7.5/8.5 mg/kg bw/d)** **Carc. Cat.3; R40 (Carc. Cat.2 – H350):** **- not genotoxic** **- not carcinogenic in rats** **- in mice, tumors were observed in:** **- the urinary bladder (dose related increase of hemangiopericytoma in M, statistically significant at high dose, the relevance of these lesions for humans is questionable),** **- the lung (stat. signif. increase of bronchio-alveolar adenoma and adenocarcinoma in F, neither dose related nor showing dose trends),** **- the liver (dose-related increase of adenoma and adenocarcinoma in M, not statistically significant, based on the historical controls they were considered unlikely to be treatment related) and** **- lymphoblastic lymphosarcoma and leukemia (in F, stat. signif. at high**	FR: Thank you for your support	Noted.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		dose). **Without robust mechanistic data it cannot be excluded that these effects are relevant to humans.** **(ECHA: transferred from General comments)**		
08/04/2010	**UK / Adrea Caitesn / MSCA**	**Page 18 Parathesia** **As a class, pyrethroids can induce parathesia in humans following dermal exposure, but the CLH dossier only refers to this effect briefly in the repeat dose section (page 25). It could be useful to include a short paragraph discussing this potential hazard in more detail.** **A specific S phrase (S24) was available under Directive 67/548/EEC for parathesia, but there is no equivalent under CLP. For bifenthrin it is not a problem as skin exposure should be avoided due to the classification for skin sensitisation.** **(ECHA: transferred from General comments)**	FR: a short paragraph has been added to the CLH report. FR: the specific S phrase S24 has been added.	Noted. Noted and accepted.
08/04/2010 **Confidential claim on the comments removed since 12**	**Belgium / FMC Chemical sprl / Company-Manufacturer** **(ECHA: Same comment was sent**	**Human Health Hazard Assessment: p 26 for the conclusion on Bifenthrin (CAS 862657-04-3) regarding STOT Rep.1 - H372.** **The CLH report for bifenthrin (pp. 26) proposes classification as Xn; R48/R22 (Danger of serious damage to health by**	FR: According to the CLP criteria "*target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to substance or mixture. All significant health effects that can impair function, both reversible and irreversible,*	Rapporteur checked the comments and considerations on RDT. See background document for a detailed discussion on the adequacy of the RDT classification. RAC finally concluded to classify bifenthrin for RDT.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
August 2010	**several times)**	**prolonged exposure, with the route of exposure being 'if swallowed', e.g. by the oral route). The basis for this classification is that "Overall, tremors are considered as a major functional change". In considering classification, per the STOT on repeated exposure, consideration of both human and animal data is required.** **In the animal data, the CLH reported that there was no histological damage of the nervous system observed, and there was no change in the morphology of the nervous system. This is also the view of the RMS (France) for the review of bifenthrin under Directive 91/414/EEC (Draft Assessment Report; pp. 177), where it was concluded that "The nervous system is the target system for toxic effects of bifenthrin and there was no evidence of damage to the nervous tissues at the microscopic level. No significant non-neoplastic adverse effects were identified which were clearly related to ingestion of bifenthrin." Tremors seen on repeated dosing of all pyrethroids are reversible in animals. Thus, FMC believes that tremors should not be considered as a major functional change.** **Concerning human data, information**	*immediate and/or delayed are included."* (§ 3.9.1.1 of the 1272/2008/EC regulation). Furthermore, a classification STOT. Rep. 1-H372 can be proposed when *"significant functional changes in the peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses"* are observed (§ 3.9.2.7.3.b). Therefore, FR maintains its proposal for classification as STOT Rep. 1-H372. We however recognise that these effects are transient at doses relevant for classification but this is not in contradiction with criteria for STOT Rep. Besides, they are observed in repeated-dose studies at lower doses than in acute studies and we consider that it justifies an additional classification.	

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		from adverse affects reporting in the US, and Bifenthrin active substance and formulation plant experiences indicated that the primary affects in humans is parasthesia. Parasthesia reactions are also reversible and disappear within a few hours.		

Other hazard classes

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
30/03/2010	**Netherlands / Bureau REACH / MSCA**	**<u>Toxicokinetics</u>** **Page 14: Elimination: Please include the dose and the exposure route in the metabolism study.** **Distribution: Please include the species, the dose and the exposure route in the bioaccumulation study.** **Distribution: Please include the doses used in the developmental neurotoxicity study.** **(ECHA: transferred from General comments)**	FR: The CLH report has been amended.	Noted.
08/04/2010	**UK / Adrea Caitesn / MSCA**	**<u>Respiratory tract irritation</u>** **Page 19** **There are indications in the CLH dossier that bifenthrin can induce respiratory tract irritation in humans (reports of chest pain, throat irritation, nasal irritation/stuffy nose, respiratory**	FR: we do not dispose of sufficient detailed and specific information regarding the ability of bifenthrin to cause irritation to the respiratory tract. The only available information concerned few human cases reports on pyrethrins. Therefore, we do not propose a classification for this end-point.	Noted. French proposal is accepted by the Rapporteur because of the scarcity of data.

Date	Country/ Person/Organisation/ MSCA	Comment	Response	Rapporteur's comment
		irritation and shortness of breath). However, the authors conclude that it is not a respiratory tract irritant. Taking into consideration the CLP criteria for STOT-SE 3 (respiratory tract irritation) the conclusion for this section should included an explanation of why it does not meet the criteria for classification, or amend the classification accordingly. **(ECHA: transferred from General comments)**	The CLH report has been amended with this explanation.	

LIST OF ORIGINAL DOCUMENTS RECEIVED AS COMMENTS

FROM FMC: ZIP FILE

HTTPS://CIRCA.EUROPA.EU/MEMBERS/IRC/SECUREECHA/NEWRAC/LIBRARY?L=/NON-CONFIDENTIAL/PROCESSES_SUBSTANCES/HARMONISED_CLASIFICATION/BIFENTHRIN/CARCINOGENICITY/ATTACHMENTS_CONFIDENTIAL&VM=DETAILED&SB=TITLE

APP 1-PP RELEVANCE R40 CLASSIFICATION BIFENTHRIN
BIFENTHRIN-CASE AGAINST REGULATING AS CARCINOGEN_EU_08APR2010 (FINAL)
ARES(2009)131692_RESULT PBT WG NOVEMBER 2007 ON BIFENTHRIN
BUTLER W H ET AL (1997)
HALLIWELL ET AL (1998) HASEMAN J K (1990)IARC (1991)
KARBE E (1999)
LOPRIANA & DONCISTIAN (1992)
MOUINS (1991)
PC-0518 LEGGETT 15DEC09
RUDOLPHIE & DEN TONKELAAR (1996)
WELLS M Y (2006)
TABLE 1
TABLE 2
TABLE 3
TABLE 4