Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

cyflumetofen (ISO); 2-methoxyethyl (RS) -2-(4-tert-butylphenyl)-2-cyano-3-oxo-3-(α,α,α-trifluoro-o-tolyl)propionate

EC Number: -
CAS Number: 400882-07-7

CLH-O-0000001412-86-183/F

Adopted
5 December 2017

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CYFLUMETOFEN (ISO); 2-METHOXYETHYL (RS)-2-(4-TERT-BUTYLPHENYL)-2-CYANO-3-OXO-3-(A,A,A-TRIFLUORO-O-TOLYL)PROPIONATE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: cyflumetofen (ISO); 2-methoxyethyl (RS)-2-(4-tert-butylphenyl)-2-cyano-3-oxo-3-(α,α,α-trifluoro-o-tolyl)propionate
EC number: -
CAS number: 400882-07-7
Dossier submitter: Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2017	Germany		MemberState	1
Comment received				
Based on the presented data and information, the proposed classifications for human health hazards are supported. We do not agree with the proposal of none classification for environmental hazards. We propose classification and labeling for long-term aquatic hazard with category Chronic 1; H410.				
Dossier Submitter's Response				
Thank you for your support. Please see comment number 36 in regard to the classification for environmental hazards.				
RAC's response				
Noted. See RAC response to comment 36.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	2
Comment received				
The manufacturer supports the CLH report as prepared by the dossier submitted, Bureau REACH, except for the part on the carcinogenicity evaluation of the thyroid findings. This relates to page 8 and pages 113 to 115 of the CLH report of cyflumetofen. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential				

attachment Cyflumetofen attachement - confidential.zip
Dossier Submitter's Response
Noted. See response to comment 5.
RAC's response
Noted.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	3
Comment received				
Leydig cell tumours page 112-113: - Even though, F344 rats have a high spontaneous Leydig cell tumour incidence, there is a significant increased incidence ($p \leq 0.01$) at 6000 ppm compared to control group. - The historical control data are not in line with CLP guidance recommendations, i.e.: the historical data should be contemporary to the study being evaluated (e.g. within a period of up to around 5 years of the study). - Potential mechanism has not been investigated. It is therefore not possible to conclude on the human health relevance of those tumours. Based on the above consideration, FR is of the opinion that those tumours should not be disregarded for classification with regard to carcinogenicity. C-cell carcinoma page 113-114: The potential mechanism underlying thyroid tumours by UGT induction, reported page 113, is not appropriate. Indeed, thyroid tumours in rodent mediated by UDP glucuronyl-transferase induction concern follicular cell adenoma/carcinoma. While cyflumetofen induced C-cell carcinoma and C-cells are not involved in T3 and T4 synthesis but in calcitonin synthesis. Conclusion on classification page 115: FR agrees with RMS that classification for carcinogenicity Carc. Cat2 H351 is warranted.				
Dossier Submitter's Response				
Thank you for your support. With regard to the Leydig cell tumours: -We agree that despite the already high incidence of Leydig cell tumours in the control group, there is a significant increase in the top dose group, which normally would indicate a substance-specific effect. - Historical control data are provided of the period of 5 years before the study, and longer ago. The data can therefore be compared to only the most recent 5 years and indeed the incidence of Leydig cell tumours in the top dose group is exceeds the historical control data. - We agree that the mechanism of Leydig cell tumours is not investigated and that a mechanism relevant for humans cannot be excluded. However, it is generally accepted that "data on LCTs generated in Fisher rats or other rat strains having comparably high spontaneous LCT rate are considered normally not informative." (ECBI/08/04Add 4, 2004). This is supported by the fact that no indications for Leydig cell tumours are observed in other rat strains or species. Nevertheless, even if the Leydig cell tumours are taken into account for classification, they would maximally result in a Carc, Cat 2 classification, which is already warranted because of the C-cell carcinomas.				

With regard to the C-cell carcinomas: We agree, that the UGT induction based mode of action can be relevant for follicular cell adenomas/carcinomas, but not for C-cell carcinomas and that relevance for humans cannot be excluded.

RAC's response

In relation to the Leydig cell tumours (LCT), RAC agrees with the DS. The background incidence in F344 rats for this neoplasm is well documented and its incidence and variability in aged rats of this strain make any assessment of these specific tumours one with little to no human relevance. Indeed, if we examine the incidence in the studies summarised in the CLH report, we find the following data:

Incidence of F344 rat interstitial cell tumours, numbers of animals affected.

Dose in mg/kg bw/day	**0_1**	**0_2**	**4.9**	**16.5**	**49.5**	**220**
All animals examined	43/50	38/50	42/49	43/48	46/50	**48/50****

1. Yoshida 2004 study; 2. Takahashi 2013 study; ** $p \leq 0.01$ (Fisher's exact probability test)

At all doses the incidence equals the upper bound limit of the supplied historical control data or exceeds it. The published literature gives even higher incidences for this tumour type in this rat strain. This makes interpretation of the high dose data for a carcinogenic effect non robust. What is indicative of a possible effect is the increased incidence of Leydig cell hyperplasia – there is an early onset of hyperplasia (at the high dose in the 1-year chronic study – 19/20) which is increased over the historical (incidence of 12 month Leydig cell hyperplasia within the last five relevant years at IET is 2/20 – 1/20 – 0/20 – 9/20) and concurrent controls (6/20). However, in this strain of rat because of the large background incidence of LCT, RAC does not consider that the Leydig cell tumour incidence provides reliable evidence of a carcinogenic effect by Cyflumetofen.

RAC also notes FR comment on thyroid tumours by UGT induction and agrees with the MSCA.

RAC supports the DS' conclusion that Carc. 2 classification is warranted based on the C-cell carcinomas.

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2017	Spain		MemberState	4

Comment received

Based on the available mutagenicity tests, the mechanism for the carcinogenic effect of cyflumetofen is probably non-genotoxic.

An increased incidence in Leydig cell tumour with statistical significance and outside the range of recent (5-year) historical controls was observed in Fischer F344 rats. Leydig cell tumours are observed with a high spontaneous tumour incidence in male Fischer F344 rats (according to section 3.6.2.2.6-a of the CLP Guidance). The rat leydig cell is extremely sensitive to slight changes in circulating luteinizing hormone (LH) levels. Among rat strains, the F344 rat is particularly susceptible to this process and is not considered a relevant model for studying LCT. The data with cyflumetofen supports this species and strain-specific

effect on the Leydig Cells. Therefore, the increase in LCTs should not be taken into account for classification for carcinogenicity.

An increased incidence in thyroid C-cell carcinoma was observed in male Fischer F344 rats. The increased incidence was not statistically significant, but clearly exceeded the recent (5y) historical control values. Further, a statistically significant increased incidence in thyroid C-cell carcinoma/adenoma was observed in male Fischer F344 rats, which was also above the incidences of historical controls.

The increase in thyroid C-cell carcinoma/adenoma could be due to stimulation of the high spontaneous rate of these tumours in this strain of rats. However, this is not shown. It is known that some mechanisms for carcinogenicity as observed in test animals are considered not relevant for humans. Certain thyroid tumours in rodents mediated by UDP glucuronyltransferase (UGT) induction are considered not relevant for humans (according to section 3.6.2.3.2 of the CLP Guidance). For cyflumetofen, mechanistic studies investigating the cyflumetofen induced thyroid tumours are not available and this specific mechanism (i.e. UGT induction) is therefore not demonstrated.

Given that the evidence of carcinogenicity is restricted to a single experiment and the fact that there is limited evidence for carcinogenic effects (no information is available regarding the mechanism of the spontaneous C-cell tumours), the Spanish CA consider that it cannot be excluded that the observed thyroid tumours are relevant for humans and therefore a classification for carcinogenicity as Carc. 2 (H351: Suspected of causing cancer) is required.
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Dossier Submitter's Response
Thank you for your support.
RAC's response
Agreed.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	5

Comment received

The manufacturer OAT Agrio Co. Ltd. (OAT) agrees with the data submitter's position with regard to the findings in Leydig cells in the carcinogenicity study in rats.
OAT would like to comment to pages 113 to 115 of the CLH report. The manufacturer does not agree with the dossier submitter's proposal to classify cyflumetofen as a Carc. Cat. 2, based on the c-cell tumours or the thyroid.

Therefore, OAT submits a detailed position paper (CRL, 2017, separate attachment) and additional investigations performed recently that have not been reviewed as they were not available in time for preparation of the CLH report of cyflumetofen (Retrospective analysis of cell proliferation in the thyroid gland, 2017, separate attachment).

The increased incidence in the high dose males could not be predicted from any of the other experiments performed before. In none of the rat studies from 28-day up to 2-year treatment were any lesions of the thyroid recorded, neither a weight change nor a histopathological effect. The same is true for all other species Cyflumetofen was tested in. To elucidate possible mechanisms behind the increased tumour incidence, expert statements have been provided by a consultant (see Annex I and II of the attachment). The

author concluded that the increased incidence in C-cell carcinomas is most likely not treatment related but spontaneous in nature. This is corroborated by the following observations:
1. Statistical significance was not seen for the increase in C-cell carcinoma itself. Only for the combined incidence a very weak significance was attained if the animals not surviving until terminal kill were added.
2. A dose-dependency was not observed; the increased incidence was only seen in the high dose study. Thus, there is no proof of a treatment relation by a dose-dependent increase.
3. C-cell tumours occur frequently in the Fisher F344 rat with a tendency to increased values in the performing laboratory. The concurrent control had an incidence at the upper border of the historical range which may hint to an increased spontaneous incidence in the animals used for the study. While the incidence of C-cell carcinoma alone exceeds the historical control range, the combined incidence, the only parameter with weak statistical significance, is only just above the historical controls (57 vs 50%). In addition, the incidence for C-cell adenoma shows large variations in this strain. It is notable that the F344 strain used at the performing laboratory has the highest incidence of C-cell carcinomas observed. This may have contributed to the incidence of C-cell carcinomas in the study on Cyflumetofen.
4. No increased incidence in proliferative precursor lesions (hyperplasia, adenomas) was seen in any of the rat studies while any agent or chemical that directly or indirectly increases C-cell carcinomas would be expected to increase the incidence of focal C-cell hyperplasia and C-cell adenomas at early or late time points.
5. Effects are observed in male rats only but not in females without a relevant sex specific difference in exposure.
6. C-cell carcinomas are not seen in mice treated up to 2-years at limit dose. No thyroid effects are seen in dogs treated up to 1-year at limit dose.
7. There is no indication from any other study that the thyroid is a target organ of Cyflumetofen as indicated by missing effects on thyroid weight.
8. As a genotoxic mechanism was excluded, there is no dose-dependency, the incidence was just outside the historical control range, there is no sex specific difference and there are no precursor lesions, there is no scientific argumentation or basis to perform a mechanistic study. The mechanistic assay on UGT-induction mentioned by the dossier submitter in the CLH dossier is not related to C-cell tumours but to follicular tumours and thus not suitable for Cyflumetofen.

Additional immunohistopathological investigations of animals treated with Cyflumetofen for 14 and 53 weeks (not yet included in the CLH dossier, Retrospective analysis of cell proliferation in the thyroid gland, 2017, separate attachment) did not reveal any proliferative events in C-cells stained with Ki67/calcitonin, thus implying that C-cell tumour formation is an event occurring only in ageing rats, which can be considered further proof of the sporadic nature.

Overall, a mode of action for the formation of C-cell carcinomas in male rats cannot be identified based on the data available for cyflumetofen. There is no possible mechanistic study design available that would help to further elucidate the mode of action. Based on a weight-of-evidence the increased C-cell carcinoma incidence is considered sporadic in nature and does not warrant any classification according to criteria of EC1272/2008.

In the CLH report page 113 the dossier submitter notes "For cyflumetofen, mechanistic studies investigating the cyflumetofen induced thyroid tumours are not available and this specific mechanism (i.e. UGT induction) is therefore not demonstrated." UDP-glucuronyl transferase (UGT) plays a role in follicular cell homeostasis and is thus a mechanism related

to thyroid tumours of follicular cell origin but is not known to be related to C-cell tumours. Therefore, assays on UGT-induction are not considered helpful in case of cyflumetofen, where a weak increase of C-cell tumours but no increase of follicular cell tumours is seen.

In the CLH report page 113 the dossier submitter notes "Based on the mutagenicity tests, the mechanism for the carcinogenic effect of cyflumetofen is probably non-genotoxic". We do not understand the word "probably" in this sentence. Based on the mutagenicity studies with Cyflumetofen an in vivo genotoxic potential can be clearly excluded as confirmed on page 91 of the CLH report and thus also a genotoxic mechanism of tumour formation.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip

Dossier Submitter's Response

We agree that the indications for induction of thyroid C-cell tumours is not very strong, because they are observed

- Only in rats and not in mice or dogs,
- Only in males, whereas kinetic studies do not indicate a higher systemic concentration in males,
- Without dose response,
- Without an increase in pre-neoplastic lesions or increased C-cell proliferation as a.o. indicated by the calcitonin/Ki-67 double staining in thyroid glands after 14 and 53 weeks
- Only a significant increase in adenomas and carcinomas combined, and only when all animals (also dead and killed in extremis) are taken into account.

In addition, we agree that the background incidence in C-cell carcinomas in the F344 strain is relatively high and seems to have increased in the last years. However, the increases observed in high dose animals (carcinomas and tumours combined) are outside historical control values, which point to a substance-based effect. Although we agree that the number of adenomas and carcinomas in the historical control groups seem to have increased in the last years, we do not agree 'that the concurrent control of the Cyflumetofen high dose study performed in 2011-2013 yielded an incidence that forms the upper border of the range'. Incidences of combined adenomas/carcinomas in the control group were 41 and 38% for scheduled kill and all animals examined respectively, compared to 20-48% and 26-50% in the historical control values from IET studies between 2005 and 2013. In contrast, the incidences of combined adenomas/carcinomas in the top dose group were 58 and 57% respectively, i.e. they clearly exceeded the historical control values.

With regard to the UGT based mechanism: We agree, that the UGT induction based mode of action can be relevant for follicular cell adenomas/carcinomas, but not for C-cell carcinomas.

With regard to the non genotoxic carcinogenic mechanism: The mutagenicity and genotoxicity data available (as described in the chapter on germ cell mutagenicity) provide no indication on a genotoxic potential of cyflumetofen. It is therefore not likely that the carcinogenic mechanism is genotoxic, however, such a mechanism can never be completely excluded.

We also agree that due to the absence of early effects on the thyroid, it is difficult to perform mechanistic studies.

Nevertheless, taking all information together, we agree that it is questionable whether there is sufficient evidence based on the C-cell carcinomas to classify cyflumetofen as carcinogenic category 2.
RAC's response
RAC supports the DS proposal for classification and considers there is sufficient evidence (taking into account all the uncertainties and lack of expected supporting data for hyperplasia → adenoma → carcinoma) to propose Carc. 2; H351.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	6

Comment received

We agree with the dossier submitter's opinion that the increased incidence in Leydig cell tumors in F344 Fisher rats is not relevant for classification based on the high spontaneous rate seen in this strain of rats.

We do not agree with the dossier submitter's proposal to classify Cyflumetofen as Carc. Cat 2 based on C-cell tumors of the thyroid. The increased incidence seen is considered sporadic in origin and not related to treatment with Cyflumetofen.
Therefore, we are providing a detailed position paper (see Meurer 2017; BASF DocID 2017/1053919; separate attachment) and additional investigations performed recently that have not yet been reviewed as they were not available in time for preparation of the CLH-report (see Marxfeld 2017, BASF DocID 2017/1051529; separate attachment).
For a weight-of-evidence assessment the following needs to be considered:
In male rats treated with a high dose of 6000 ppm Cyflumetofen for a time span of two years an increased incidence of C-cell carcinomas of the thyroid was observed that was not statistically significant but above the concurrent and historical control data. There was no increase in either C-cell hyperplasia or C-cell adenoma at this dose. Statistical significance was obtained only for the combined incidence of C-cell adenomas/carcinomas and was only based on a difference of one animal of this group.
A statistical evaluation of C-cell proliferative lesions (not included in the CLH-report) was performed on the combined incidence of C-cell hyperplasia, C-cell adenoma, and C-cell carcinoma. This evaluation is considered informative regarding the overall proliferative status of the animals. No increase in overall proliferative C-cell lesions was observed for any of the treatment groups compared to the concurrent controls (see attached document Meurer 2017).

The increased incidence in the high dose males could not be predicted from any of the experiments performed before. In none of the previous rat studies from 28-day up to 2-year treatment were any lesions of the thyroid recorded, neither a weight change nor a histopathological effect. The same is true for all other species cyflumetofen was tested in.

To elucidate possible mechanisms behind the increased tumor incidence, expert statements have been provided by Thomas J. Rosol (see Appendix I and II). The author concluded that the increased incidence in C-cell carcinomas is most likely not treatment related but spontaneous in nature. This is corroborated by the following observations:

• No significant difference in C-cell adenoma, carcinoma or adenoma/carcinoma incidence was seen in male rats treated with 6000 ppm and surviving until terminal kill. Only when the animals killed in extremis are added (n=2 in control and n=3 in treated animals) statistical significance was just attained (p-value=0.04378) and the combined incidence

adenoma/carcinoma (57%) is still only slightly above the upper border of the historical control range (50%).
• No increased C-cell tumor incidence was seen in an earlier 2-year rat study at doses up to 1500 ppm. C-cell tumors do only occur at a high dose in rats at an exposure level not relevant for humans based on the use pattern of the plant protection product.
• No increased incidence in proliferative precursor lesions (hyperplasia, adenomas) was seen in any of the rat studies while any agent or chemical that directly or indirectly increases C-cell carcinomas would be expected to increase the incidence of focal C-cell hyperplasia and C-cell adenomas after 6 months or later. This is underlined by the absence of an increase in the combined incidence of C-cell hyperplasia/adenoma/carcinoma in the 2-year carcinogenicity studies in rats.
• The absence of proliferative events was confirmed by a retrospective staining of thyroid tissue with the proliferative marker Ki67. No increased proliferation was observed for animals treated 3 months or 1 year with 6000 ppm of Cyflumetofen. This implies that tumor formation in the C-cells is indeed a very late response occurring only in ageing rats which can be considered further proof of the sporadic nature.
• A shift in historical control incidences for C-cell carcinomas was seen in the recent years at the performing lab and the concurrent control of the high dose study showed an incidence at the upper border of this control range. In addition, the incidence for C-cell adenoma shows large variations in this strain. It is notable that the F344 strain used at IET (Japan) has the highest incidence of C-cell carcinomas observed. This may have contributed to the incidence of C-cell carcinomas in the study on Cyflumetofen.
• There is no difference in the unilateral vs bilateral occurrence of C-cell carcinoma between control and treated animals (control: 7 of 9 males with C-cell carcinoma had unilateral tumors; high dose: 12 of 15 males with C-cell carcinoma had unilateral tumors). If a chemical or drug induced C-cell carcinomas in rats, then it might be expected to increase the incidence of bilateral C-cell carcinomas depending on sample size of the groups and the overall incidence of C-cell carcinoma.
• Effects are observed in male rats only but not in females without a relevant sex specific difference in internal dose as shown in ADME studies with Cyflumetofen.
• C-cell carcinomas are not seen in mice treated up to 2-years at limit dose.
• No thyroid effects are seen in dogs treated up to 1-year at limit dose.
• Cyflumetofen is not genotoxic in vivo.

Overall, a mode of action for the formation of C-cell carcinomas in male rats cannot be identified based on the data available for cyflumetofen. Based on a weight-of-evidence approach and as confirmed by independent experts, the increased C-cell carcinoma incidence is considered sporadic in nature. There is no possible mechanistic study design available that would help to further elucidate the mode of action. Based on the spontaneous nature of the tumors the results are not considered to warrant any classification according to the criteria of EC1272/2008.

Additional remark: 2 factual errors were found in the CLH-report section on carcinogenicity
1. In the CLH report page 113 the dossier submitter notes "For cyflumetofen, mechanistic studies investigating the cyflumetofen induced thyroid tumours are not available and this specific mechanism (i.e. UGT induction) is therefore not demonstrated." UDP-glucuronyl transferase (UGT) plays a role in follicular cell homeostasis and is thus a mechanism related to thyroid tumors of follicular cell origin but is not known to be related to C-cell tumors. Therefore, assays on UGT-induction are not considered helpful in case of cyflumetofen, where a weak increase of C-cell tumors but no increase of follicular cell tumors is seen.
2. In the CLH report page 113 the dossier submitter notes "Based on the mutagenicity tests, the mechanism for the carcinogenic effect of cyflumetofen is probably non-genotoxic.

We do not understand this sentence. Based on the mutagenicity studies with Cyflumetofen an in vivo genotoxic potential can be clearly excluded as confirmed on page 91 of the CLH report and thus also a genotoxic mechanism of tumor formation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx
Dossier Submitter's Response
Noted. See response to comment 5.
RAC's response
RAC supports the original proposal by the DS. RAC also agrees with the company that cyflumetofen does not exhibit a genotoxic potential.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	7
Comment received				
No comment				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	8
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	9
Comment received				
We agree with the dossier submitter's proposal not to classify for mutagenicity. ECHA note – An attachment was submitted with the comment above. Refer to public				

attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx
Dossier Submitter's Response
Thank you for your support.
RAC's response
RAC agrees with the DS proposal.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	10
Comment received				
Fertility effects page 134: While no effects on reproductive and fertility index are observed in the 2-gen study, delay in sexual maturation possibly related to changes in steroidogenesis is observed in both sexes in the absence of systemic toxicity (no effect on bodyweight in all tested groups of any generation, only effects on adrenals are reported in mid and high dose groups probably also related to changes in steroidogenesis). Indeed, delayed vaginal opening in mid-dose and high dose F1 females correlated with hormonal changes is observed. Since those effects are statically significant and dose related it is questionable to disregard them based on HCD. Statistically significant prolongation of the oestrous cycle length and increase in ovary interstitial vacuolation in high dose F1 females are also reported. Furthermore effects on the ovary are observed in repeated dose toxicity studies (at dose levels of 69 mg/kg bw/day and above). Finally statistically significant delay in balano-preputial separation is also observed in high dose F1 males in the 2-generation study. Based on those effects, cyflumetofen may trigger classification for reproduction Repr. Cat2 H361f.				
Dossier Submitter's Response				
We agree that some slight effects, probably related to the exposure to cyflumetofen, are observed in the 2 generation study. These include a delay in sexual maturation in males and females, a prolongation of the oestrous cycle length and an increase in ovary interstitial vacuolation. Although statistically significant, the time to sexual maturation and the oestrus cycle length are still within historical control values. This indicates that he effects that are induced are not toxicologically relevant. They may become so at higher dosages, however, higher dosages also induce parental toxicity. Because of this, these effects do not warrant classification.				
RAC's response				
RAC supports the DS position.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	11
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip				

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip
Dossier Submitter's Response
Thank you for your support.
RAC's response
RAC agrees with the DS proposal.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	12
Comment received				
We agree with the dossier submitter's proposal not to classify for reproductive toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	13
Comment received				
No comment				
Dossier Submitter's Response				
noted				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	14
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	15
Comment received				
We agree with the dossier submitter's proposal not to classify for respiratory sensitisation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	16
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	17
Comment received				
We agree with the dossier submitter's proposal not to classify for acute toxicity. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	18
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	19
Comment received				
We agree with the dossier submitter's proposal not to classify for skin corrosion/irritation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	20
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agreed.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	21
Comment received				
We agree with the dossier submitter's proposal not to classify for serious eye damage/eye irritation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Agreed.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	22
Comment received				
FR agrees with proposal for skin sensitisation category 1A: H317				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with FR and the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2017	Spain		MemberState	23
Comment received				
The Spanish CA considers that the proposed classification for skin sensitization, as Skin Sens. 1A; H317 – May cause an allergic skin reaction, is warranted for cyflumetofen. The results in the maximization test fulfil the criteria, as a sensitizing effect was observed in 100% of the animals after an intradermal induction dose of 1%.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with ES and the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2017	Sweden		MemberState	24
Comment received				
The Swedish CA supports classification of cyflumetofen as Skin Sens 1A based on the results from a GPMT study where 100% of the animals had positive skin reactions using an				

intradermal induction dose of 1%. A SCL is set if ≥ 60% of the animals have positive reactions at ≤ 0.1% intradermal induction. SE agrees with the decision not to set a SCL for cyflumetofen, but would like to point out that the need to do so cannot be evaluated based on the available data since the number of animals having positive reactions when using a 1% intradermal induction was so high (100%). Hence, there is no evidence that the substance is not an extreme sensitizer. It is possible that testing with intradermal induction ≤ 0.1% cyflumetofen would result in positive reactions in ≥ 60% of the animals.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Noted. RAC agrees with SE and the DS proposal.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	25
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	26
Comment received				
We agree with the dossier submitter's proposal not to classify for skin sensitisation. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
It is noted that we proposed a classification for skin sensitization as Skin Sens. 1A; H317. However, we assume that the comment made by BASF contains a typing error and that they agree with the proposed classification.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	27
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	28
Comment received				
We agree with the dossier submitter's proposal not to classify for STOT SE. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
09.03.2017	Spain		MemberState	29
Comment received				
Increased adrenal weight and vacuolation of adrenal cortical cells was observed in all three species investigated after semi-chronic oral administration of cyflumetofen, with rat being the most sensitive species. In rat, ovarian interstitial cell vacuolation was also seen. In long term toxicity studies and carcinogenicity studies with rat also vacuolation and hypertrophy of the adrenal cortex was seen. In a mechanistic study in rats, the vacuoles seen in the adrenals and ovaries were shown to consist of lipid droplets. The vacuolation of adrenal cortical cells and vacuolation of interstitial ovary cells after repeated exposure to cyflumetofen might be due to cholesterol and cholesterylester deposition as a result of a reduced activity of hormone-sensitive lipase (HSL). Decreased levels of HSL in the presence of adrenal weight increase and adrenal				

cortical cell vacuolation were not accompanied by a change in serum ACTH (adrenocorticotropic hormone) or corticosterone for either sex, indicating that adrenal function was not affected. In the absence of any indication for functional disturbance, toxicologically relevant morphological changes or significant impact of health in any of the toxicity studies, it can be concluded that the cyflumetofen-induced vacuolation of adrenal cortical cells or vacuolation of the ovary cells, is not related to significant or severe toxicity. Therefore, the Spanish CA agrees with dossier submitter that the observed adrenal and ovary effects do not meet the CLP criteria for STOT RE classification.
Dossier Submitter's Response
Thank you for your support.
RAC's response
Agreed.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	30
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	31
Comment received				
We agree with the dossier submitter's proposal not to classify for STOT RE. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Aspiration Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	32
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the proposal for no classification for aspiration hazard.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	33
Comment received				
We agree with the dossier submitter's proposal not to classify for aspiration hazard. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the proposal for no classification for aspiration hazard.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
16.03.2017	France		MemberState	34
Comment received				
We agree not to classify cyflumetofen for aquatic and chronic hazards.				
Dossier Submitter's Response				
Thank you for your evaluation and support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2017	Belgium		MemberState	35
Comment received				
BE CA agrees with your conclusion that Cyflumetofen is not rapidly degradable, has a low potential to bioaccumulate and show no toxicity up to the water solubility. Therefore				

Cyflumetofen does not meet the classification criteria for environmental hazards.

It is mentioned in the CLH report (e.g. on p.184 : acute toxicity of B2 to Daphnia magna) that in case of rapid hydrolysing substances it is considered justified to base the toxicity endpoint on the measured initial concentration.
For unstable substances however CLP guideline (I.4.1) recommend to consider, for classification purposes, the geometric mean concentration at the start and the end of test when measured data are available for these time points, which is usually the case for Daphnia and algae tests.

Dossier Submitter's Response

Thank you for your evaluation and support. You are correct in pointing out the recommended expression of test concentration results for unstable substances, in this case the geometric mean. The intention behind the statement you pointed out was to highlight the difficulty at maintaining a constant level for the metabolite B-2 under test conditions because of its hydrophobicity and half-lives.

Summarizing the available information of the metabolite B-2 for acute toxicity study in *Daphnia*:
Static test design with B-2: Analysis of the sample taken from the limit concentration at the start of the test showed a measured concentration of 0.039 mg/L. During the exposure of the period the measured concentration decreased below the LOD (i.e. below 0.002 mg/L).

Flow-through design: One and 2 days after the start of the flow-through system, the measured concentration represented 14-24% and 11-17% of nominal, respectively. Seven days after the start of the system, the concentration of B-2 was below the limit of detection. It was concluded that it is technically impossible to perform an acute toxicity study in Daphnia magna with B-2 under flowthrough conditions in which the exposure levels can be maintained at a constant level.

A geometric mean of > 0.009 mg/L is obtained if one uses the values of the acute toxicity study unde static conditions, 0.039 mg/L and 0.002 mg/L, respectively start and end concentrations. This value is in the same range as the LOD.

RAC's response

Indeed, for unstable substances, however CLP guideline Version 5 – July 2017 (I.4.1) recommends to consider *where measured data are available for the start and end of test (as is normal for the acute Daphnia and algal tests), the L(E)C_{50}, for classification purposes, may be calculated based on the geometric mean concentration of the start and end of test. Where concentrations at the end of test are below the analytical detection limit, such concentrations shall be considered to be half that detection limit.*
For the metabolite B-2, the DS indicated that the *concentration of the start is 0.039 mg/L and at the end of test the concentration resulted below the analytical detection limit (0.002 mg/L).* In this case, *the L(E)C_{50},* should be calculated based on the *geometric mean concentration* of 0.039 mg/L and the *half that detection limit* (0.002/2 =0.001 mg/L). As a consequence, the results should be = 0.0062 mg/L, as reported in the DAR (Sept 2011) instead of the value 0.009 mg/L, reported in the DS comment.

Date	Country	Organisation	Type of Organisation	Comment number
23.03.2017	Germany		MemberState	36

Comment received

P. 167 the results and discussion of the water/sediment study by Noorloos van B., and J. de Mol (2007) and p. 145 Summary of relevant information on degradation: In Tab. 143 and Tab. 123 the stated DT50 of cyflumetofen (B-ring-label) in the sediment of the Schoonrewoerdsewiel water/sediment system is 0.6 d, according to the DAR of cyflumetofen Volume 3 B8 (revised Sept. 2011) this value should be 1.6 d (SFO excl t=0.7, $\chi 2$=2.78, r2=0.962)

Page 174 point 5.4 Aquatic Toxicity:
Table 147: there is a relevant chronic toxicity study of Cyflumetofen to fish missing, which was reported in EFSA Journal 2016; 14(11):4635 at Section Ecotoxicology and by the RMS as confirmatory data in 2015: Salinas, E. (2011) ELS test over 34 days under flow through conditions with Pimephales promelas according to OECD 210 with NOEC (survival, hatching, growth) of 0.0292 mg a.s./L (mean measured). This study was run as a "Limittest" with only one test concentration and without solvent (100 % saturated solution). The RMS stated the study is valid and acceptable.

Page 187 point 5.5 Comparison with criteria for environmental hazards:
The summary of the chronic toxicity data and conclusion on long-term aquatic hazards should be completed and amended, as follows:
The NOEC of 0.0292 mg/L (at test conditions of 24-26°C and pH 6) from the ELS-study of Salinas, E. (2011) without any solvent should be the lowest NOEC value from long-term studies, instead of the NOEC of 0.0396 mg/L from algae.
Because the lowest NOEC (without any solvent) is equal to the water solubility of 0.028 mg/L (at 20°C and pH 7), we propose classification and labeling for long-term aquatic hazard with category Chronic 1; H410.

Dossier Submitter's Response

Thank you for you evaluation and comments.

<u>Degradation</u>
The correction regarding, the DT50 of cyflumetofen (B-ring-label) in the sediment of the Schoonrewoerdsewiel water/sediment system, is noted.

<u>Aquatic Toxicity</u>
Thank your for making us aware of the Salinas, E. (2011) study and we agree that this study is relevant and valid. However, we believe that this information does not change the proposed classification of no classification for chronic toxicity. Below you will find our reasoning using the new information.

The lowest water solubility of Cyflumetofen is 0.028 mg/L (at 20°C and pH 7). If the 34-d NOEC value of 0.0292 mg/L for fish is valid, then it would be considered as the lowest NOEC value (mean measured, growth/survival/hatching). We would like to point out that the toxicity value reported by EFSA Journal is ≥ 0.0292 mg/L. It was also mentioned that under the conditions of the study exposure over 34 days resulted in no effects (to hatching success, survival or growth of the fathead minnow) at the tested concentration which should be regarded as close to the water saturation level (EFSA Journal, 2016). This is based on the EFSA Confirmatory data addendum, B.9, Ecotoxicology, B.9.2.1.2, Chronic toxicity to fish ELS study by (2011).

In addtition, there is a report that indicates a problem caused by the low solubility during the study (EFSA Confirmatory data addendum, B.9, Ecotoxicology, B.9.2.1.2, Chronic toxicity to fish ELS study by (2011)).
"The measured concentrations on day 22 were 148% of the nominal and vastly exceeded the water solubility of the test substance. It was suggested that this may have been due to aeration of the test systems causing organic matter with adsorbed test material to become suspended. It is therefore questionable whether this value should have been used in the calculation of the mean measured concentrations which were used to express the endpoint. In the end, it was considered more appropriate to remove the measured concentrations which exceeded the water solubility in the calculation of the exposure value. However, this does not affect the overall conclusion of the study i.e. that there were no effects at the tested concentration which should be regarded as close to the water saturation level. Ideally a footnote could be added to the LoEP to indicate that the quantified endpoint is not completely reliable."

It also worth noting that the NOEC value for algea of 0.0396 mg/L should be expressed as > 0.0396 mg/L.
In conlusion, the new information does not change the long-term aquatic hazard classification for cyflumetofen. No toxicity is recorded at levels close and at levels in excess of the water solubility, therefore the NOEC for classification purposes may be considered to be greater than the measured water solubility.

RAC's response

Aquatic Toxicity
The relevance of additional information on fish should be evaluated for the possibility to affect the environmental classification.

In particular the additional study original of Salinas, 2011 should be considered in the ODD.

On public EFSA web site, the documents on peer review of the pesticide risk assessment (EFSA Journal, 2016) and on the outcome of the consultation on confirmatory data EFSA supporting publication 2016/EN/997 are available.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	37

Comment received

OAT Agrio Co. Ltd. agrees with the data submitter's proposal.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip

Dossier Submitter's Response

Thank you for your support.

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	38
Comment received				
We agree with the dossier submitter's proposal not to classify for environmental hazard. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Ozone Layer

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	39
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	40
Comment received				
We agree with the dossier submitter's proposal not to classify for environmental hazard. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Netherlands	OAT Agrio Co. Ltd.	Company-Manufacturer	41
Comment received				
OAT Agrio Co. Ltd. agrees with the data submitter's proposal. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Cyflumetofen attachements_sanitized.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Cyflumetofen attachement - confidential.zip				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal for no classification.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2017	Germany	BASF SE	Company-Downstream user	42
Comment received				
We agree with the dossier submitter's proposal not to classify for physical hazards. ECHA note – An attachment was submitted with the comment above. Refer to public attachment BASF sanitized.zipx ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment BASF confidential.zipx				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC agrees with the DS proposal for no classification.				

PUBLIC ATTACHMENTS
1. Cyflumetofen attachements_sanitized.zip [Please refer to comment No. 2, 5, 8, 11, 14, 16, 18, 20, 25, 27, 30, 32, 37, 39, 41]
2. BASF sanitized.zipx [Please refer to comment No. 6, 9, 12, 15, 17, 19, 21, 26, 28, 31, 33, 38, 40, 42]

CONFIDENTIAL ATTACHMENTS
1. Cyflumetofen attachement - confidential.zip [Please refer to comment No. 2, 5, 8, 11, 14, 16, 18, 20, 25, 27, 30, 32, 37, 39, 41]
2. BASF confidential.zipx [Please refer to comment No. 6, 9, 12, 15, 17, 19, 21, 26, 28, 31, 33, 38, 40, 42]