COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that the comments displayed below may have been accompanied by attachments which are not published in this table.

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Last data extracted on 26.03.2019

Substance name: acetamiprid (ISO); (1E)-N-[(6-chloropyridin-3-yl)methyl]-N'-cyano-N-methylethanimidamide; (E)-N1-[(6-chloro-3-pyridyl)methyl]-N2-cyano-N1-methylacetamidine
CAS number: 135410-20-7;160430-64-8
EC number: -
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France	<confidential>	Company-Downstream user	1
Comment received				
The public consultation on CLP classification for acetamiprid let the possibility to comment the proposed CLP classification. Please, find the comments below.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
13.03.2019	Germany		MemberState	2
Comment received				
Agreement with the proposal that Acetamiprid should be classified as Carc. 2, H351 based on an increased incidence of mammary gland adenocarcinoma in connection with increased incidence of mammary gland hyperplasia. The proposed classification agrees also with the Conclusion on Pesticide Peer Review EFSA Journal 2016; 14(11):4610.				

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	United Kingdom	Nisso Chemical Europe GmbH	Company-Manufacturer	3
Comment received				
Please see uploaded document reference 1007618.UK0-9906, which includes formatted figures and tables. We disagree the CLH proposal as Carc Cat 2. No classification should apply. The proposal is based on an increased incidence of mammary tumours in female rats. The increased incidence of mammary tumours was 29 tumour-bearing animals in a group size of 60 rats (29/60), vs 24/59 in controls. In pairwise comparison, the groups were not statistically different. The data owner notes that similar (or greater) incidences of mammary tumours have been assessed at RAC on occasions within the recent past, and anticipates that these data for acetamiprid shall receive equal treatment.				

Mammary Gland Histopathology
Dose (ppm) HCD
0 160 400 1000
Fibroadenoma 17/59 15/60 10/60 15/60
Adenoma 1/59 0/60 4/60 3/60
Benign (adenoma or fibroademoma) 18/59 15/60 14/60 18/60
Adenocarcinoma 10/59 11/60 16/60 17/60
(28.3%) 13.3 – 28.6%
Total mammary tumour-bearing animals 24/59 21/60 24/60 29/60

Hyperplasia (1-year interim sacrifice) 3/10 1/10 2/10 2/10
Hyperplasia (terminal sacrifice) 5/23 10/26 10/29 18/29**
Hyperplasia (total) (a) 17/59 13/60 16/60 26/60 0 – 58%
** p <0.01 in comparison with control by Fisher's exact test
(a) Sourced from XXXXX(1999). A report by XXXXX et al (2001) mis-states the statistical significance and did not re-analyse the results reported in XXXXX(1999).

The CLH report notes a continuum between increased mammary gland hyperplasia (statistically significant) at terminal sacrifice, and increased mammary gland adenocarcinoma (not statistically significant). However, the continuum is not continuous as there was no increase in the incidence of (intermediate) adenoma. Further, it must be suspected that the proposed classification is based not on tumour incidence, but on the statistically-significant increased incidence of hyperplasia predominantly in the sub-population surviving to terminal sacrifice. Hyperplasia is not a neoplastic change, is not evidence of carcinogenicity, and is not appropriate for carcinogenicity classification. The incidence of hyperplasia was highly variable between studies at the test facility and there was no treatment related change in the incidence of hyperplasia at the 1-year interim kill. Further, mammary gland hyperplasia was not observed in in any other studies in rats, mice or dogs.

Mammary tumours are a common finding in Sprague-Dawley female rats, and the incidence of mammary tumours in this study remained within the historical control range of this specific test facility, and further within historical control ranges of comparable facilities with this strain of rat. The high incidence typical of female Sprague-Dawley rats is specifically noted in the "Guidance on the Application of the CLP Criteria", where "even a statistically significant increase within the historical control range may not be providing reliable evidence of treatment-related carcinogenicity". The incidences in this study do not achieve (pairwise) statistical significance. There was no change in tumour latency (the time of first appearance of these tumours in rats is readily detected by palpation).

No mode of action is evident for mammary hyperplasia/ carcinogenicity. Acetamiprid is not genotoxic. An increase in mammary gland hyperplasia in female rats might be taken to imply some form of estrogenic influence. However, acetamiprid shows no estrogenic activity in the US EPA ToxCast ER bioactivity model. This model meets EFSA/ECHA requirements for "sufficiency" of testing for estrogenicity under the 2018 Joint EFSA/ECHA "Guidance for the identification of endocrine disruptors".

(US EPA EDSP21 Dashboard. Available at: https://actor.epa.gov/edsp21/

In summary, there is inadequate evidence to support a treatment-related increase in the incidence of mammary tumours in female rats with acetamiprid. Acetamiprid should not be classified for carcinogenicity.

Reference:
XXXXX et al (2001) Biological and statistical analysis of mammary gland findings in the chronic rat study on acetamiprid. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX., Unpublished report No.: RD-00994

XXXXX(1999) Two Year Dietary Toxicity and Oncogenicity Study in Rats. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX., Unpublished report No: RD-99104.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Acetamiprid CLH Consultation - Supporting docs - NON CONFIDENTIAL.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Acetamiprid CLH Consultation - Supporting docs - CONFIDENTIAL.zip

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France	<confidential>	Company-Downstream user	4
Comment received				
The proposed CLP classification "Carcinogenicity Category 2" for Acetamiprid is based on 2 observations in the long-term oral/carcinogenicity on rats (1999e), knowing that a long-term oral/carcinogenicity on mice (1999a) concludes to "no carcinogenic effects observed". (CLH report pages 12 to 23) The 2 observations highlighted for classification are: significant hyperplasia at high dose and increase of adenocarcinoma in the mammary gland. 1/ Hyperplasia is mainly observed at the 2 higher doses of 400ppm and 1000ppm that stands for doses upper to 17.5 mg/kg bw/d (see Table 16 – page 12 of CLH report). For both doses, toxicity to rats is expected, considering the NOAEL of 14.8 mg/kg bw/d determined in the supportive sub-chronic 90 days study on rats (1997d - CLH report page 45). Hyperplasia can be so considered as one of the toxicity signs at these doses. Moreover, as hyperplasia is not a neoplastic change, it is not an evidence of carcinogenicity and so is not a justification of carcinogenicity classification. 2/ The increase of adenocarcinoma in the mammary gland does not appear statistically significant in terms of incidence, considering also the fact that no change in tumor latency are observed (possible observation by palpation). Moreover, the overall weight of evidence from the in vitro and in vivo studies indicates that acetamiprid is not genotoxic. (CLH report page 12). Consequently, the proposed CLP classification "Carcinogenic Category 2" for Acetamiprid is based on observations that do not fulfil CLP criteria for this classification.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	5
Comment received				
Agreement with the RAC opinion, this is in accordance with the EFSA Conclusion.				

Date	Country	Organisation	Type of Organisation	Comment

				number
22.03.2019	Germany	<confidential>	Company-Downstream user	6
Comment received				
10.9 CARCINOGENICITY ECHA note – An attachment was submitted with the comment above. Refer to public attachment Evergreen_Expert Statement on C2R2 classification Acetamiprid_final_san.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Evergreen_Expert Statement on C2R2 classification Acetamiprid_final.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2019	France		MemberState	7
Comment received				
FR: Page 12: In one of the two carcinogenicity conducted studies, evidence of carcinogenic effects at high doses, in female rats have been shown. Considering that there was a continuum between hyperplasia (significant at high dose) and increased incidence of adenocarcinoma, FR agrees on the classification proposal: Carc 2, H351 Suspected of causing cancer.				

Date	Country	Organisation	Type of Organisation	Comment number
15.03.2019	Spain		MemberState	8
Comment received				
The dossier submitter considers that based on the increase incidence in adenocarcinoma of mammary gland in rats the acetamiprid should be classified as Carc. 2. The increase in adenocarcinoma of the mammary gland in female SD rats was significant in a trend test, but not in a pair-wise comparison with the controls. No decrease in latency period was observed and no excessive toxicity was observed at this highest dose. No carcinogenicity was observed in the mice study. Mammary tumors in female SD rats are known to occur with a high spontaneous incidence (CLP guidance 5.0). In such cases the CLP guidance suggests a comparison with the historical control data. The observed incidence in adenocarcinoma in the highest dose (28.3%) was just within the available historical control range of the performing laboratory of 14.0% - 28.6% (n=6, same laboratory and same period). Overall, the Spanish CA considers that the increase incidence in adenocarcinoma of the mammary gland of female SD rats doesn´t provide reliable evidence of treatment related carcinogenicity and it is rather part of a biological variability in a strain which have a propensity to develop a particular type of tumour spontaneously with potentially high incidence. Therefore, in our opinion, acetamiprid does not meet the criteria for classification for carcinogenicity.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
13.03.2019	Germany		MemberState	9

Comment received
We agree with the data submitter that "there is some evidence from animal studies on adverse effects on development…". Pub survival was decreased at parental toxic doses. Furthermore, the startle response was decreased in the developmental neurotoxicity study at doses of 45 mg/kg bw and 10 mg/kg bw/day. Therefore, the proposal of the dossier submitter to classify Acetamiprid as Repr. 2, H361d might be agreed. However, it is not that clear if the described effect on startle response is really adverse with regard to further development. It is proposed to report the data on startle response and postnatal mortality in the developmental neurotoxicity study in a table in the CLH report to verify the submitted conclusions and to discuss possible adversity.

Date	Country	Organisation	Type of Organisation	Comment number
20.03.2019	United Kingdom	Nisso Chemical Europe GmbH	Company-Manufacturer	10

Comment received
Please see uploaded document reference 1007618.UK0-9906 and supporting document, Li, A.A. (2015). CLH Report (p49): There is some evidence from animal studies on adverse effects on development resulting in classification as Repr. Cat. 2 H361d. General summary of comment: Effects in offspring of both the DNT study and both generations of the 2-generational study occur only in the presence of significant maternal toxicity, characterised by body weight losses and/or markedly decreased body weight gains (up to 60 %) and food intake (up to 16 %). Marked maternal toxicity on both studies occurs at pertinent times for offspring survival and development, particularly post-parturition, and at levels in excess of those reported in many publications documenting the effects of marked maternal toxicity on post-natal development (1, 3, 4, 5, 6, 10, 11, 12, 16), rather than the Carney publication cited in the CLH report, of which methodological differences reduces its relevance to the acetamiprid studies (2, 7, 8, 9). Furthermore, high doses on all generations of both studies were a substantial fraction (up to 70%) of the acute toxicity oral LD50 dose levels; maternal toxicity is therefore consistent with excessive toxicity seen with acetamiprid. The changes seen in survival of the offspring on both studies constitute a secondary, nonspecific, consequence of maternal toxicity and not a direct effect of the substance. We support the view that there is no adverse effect at 10 mg/kg bw/day on the DNT study. The precautionary lowering by EFSA of the NOAEL to 2.5 mg/kg bw/day, was due to variability of the other neurodevelopmental data, since unfounded by HCD, and does not constitute evidence of adversity. The isolated change in startle response amplitude at 10 mg/kg bw/day, was not statistically different from Controls; remained within both laboratory and industry HCD ranges; had no associated change in the reflex time or habituation to the stimuli; nor any concomitant functional or physical indications of neurodevelopmental toxicity. This substantiates the EFSA opinion that (despite disputing the NOAEL), acetamiprid is not sufficiently toxic as for reproduction Category 2. A recent publication examining the potential of different neonicotinoid insecticides as neurodevelopmental toxicants, including acetamiprid, also corroborates this view (14). We consider that no classification for developmental toxicity is warranted. Specifically: Question: Are effects on post-natal survival secondary to maternal toxicity or a direct effect of acetamiprid? CLH Report: Evidence of effects of food restriction and maternal body weight on post-natal

mortality are inconsistent due to the publication by Carney et al (2004).
Comment: In contrast to the Carney publication (2), there is a large body of evidence which acknowledges the effect of reduced maternal body weight on post-natal survival and development (1, 3, 4, 5, 6, 16) which is also exacerbated intergenerationally (10). Furthermore, differing from many feed-restriction studies, and those on the DNT and 2-generational studies, animals in the Carney publication did not have ad libitum access to food. Differences in feeding regimen causes different effects on body weight gain, circadian hormonal patterns and maternal behaviour patterns, even when total food intake is similar (7 and 8), with many contradictory findings of calorie restriction studies attributable to methodological differences (9). These differences in study design methodology reduce the relevance of the findings in the Carney publication to those identified in the DNT and 2-generational studies.

By using a weight of evidence approach, there are far more publications which recognise the impact of maternal toxicity on the maternal behaviours necessary for offspring to thrive, compared with this single publication which raises doubt, particularly when the feeding methodologies are different.

CLH Report: Changes in maternal body weight of females given the highest doses acetamiprid are of only limited effect.
Comment: Comparing maternal toxicity for the total gestation or lactation periods severely underestimates different vulnerabilities within these periods, as reflected by changing nutritional demand with normal feeding behaviour and known adversity to perturbation in maternal behaviour, particularly affecting the neonatal period (5, 11, 16). Changes in excess of 20 % reductions in body weight gain and any body weight losses are recognised industry-wide to constitute excessive maternal toxicity (12). The 2-generational study with acetamiprid achieved up to 44 % less weight gain over Days 0 to 4 of the parental lactation period and actual body weight loss over the same period of the F1 lactational phase. The F1 generation also had 60 % less body weight gain from Lactation Days 14 to 17. Changes in body weight were pursuant of decreases in food intake (16 % and 14 % less over Days 0 to 4 of the parental and F1 generation, respectively). On the DNT study 16 % less body weight was gained during gestation and considering the individual data of the litters with all offspring lost, up to 36 % less weight was gained in comparison to the mean Control. Furthermore, 39 % less food was eaten during gestation Days 6 to 9.

The differences in body weight and food intake seen on both the DNT and 2-generational studies are of a magnitude which constitute significant maternal toxicity which had a secondary consequence on post-natal survival and, as such, do not constitute a direct effect on development. On this basis, classification of acetamiprid for development is not warranted. This interpretation is in concordance with the EFSA Conclusion, as documented in the peer review of the pesticide risk assessment which stated that acetamiprid 'is not as toxic for reproduction category 2' (13).

Question: Are the changes in startle response at 10 mg/kg bw/day related to treatment with acetamiprid?
CLH Report: there was a decrease in startle response in the developmental neurotoxicity study at 10 mg/kg bw/day, enough to constitute an adverse effect justifying a precautious lowering of the NOAEL to 2.5 mg/kg bw/day
Comment: We disagree with the CLH proposal that there was a treatment-related decrease in startle response at 10 mg/kg bw/day. It should be understood that the startle response measured reaction time as a measure of neuronal function, and subsequent habituation to

repeated startle, as an indicator of learning and memory. "Amplitude" is the force with which the animal responded. At 10 mg/kg bw/day, the startle response amplitude (i.e. how strong the response was to the stimuli) appeared decreased but the startle time (Tmax) and habituation was not. The biological and toxicological relevance of this putative change in amplitude, in the absence of any effect on Tmax or habituation, is questionable. In addition, the difference in startle amplitude was not statistically different from concurrent Controls and remained within both the laboratory's historical Control data range, and within the variability seen in Control data compiled by the US EPA from numerous subsequent DNT studies, submitted to the US EPA after the acetamiprid DNT study (14). In addition, there were no concomitant neurodevelopmental delays in any of the other functional assessments at 10 mg/kg bw/day (motor activity, learning and memory assessments), nor any changes in the brain neuropathology or morphometry at any dose level. This change in the amplitude of the startle response is within normal biological variability seen in laboratory animals and should therefore be concluded not to be treatment related.

CLH Report: the DNT study conducted for acetamiprid misses certain study data (motor activity, learning and memory assessments) to enable a change in startle amplitude to be contextualised.
Comment: The DNT study conducted did not miss any guideline compliant data and included temporal assessments of acetamiprid effects on motor activity, learning and memory acquisition. On initial review, US EPA initially deferred decisions on whether acetamiprid affected these parameters due to uncertainty on the extent of variability in these data and whether the data set was sufficiently robust for assessment. This uncertainty was incorporated in the later EFSA opinion, where the NOAEL was on a precautionary basis set to 2.5 mg/kg bw/day until further data was available. US EPA has since compiled a wider database of Control data for these end points, demonstrating that these biological data are inherently variable and that the acetamiprid data are in fact, normal in their variability. US EPA has subsequently concluded that the neurodevelopmental data set is complete for acetamiprid, with robust, guideline compliant studies for developmental neurotoxic assessments (15).

As further weight of evidence, a comprehensive review has subsequently been published since the initial EFSA and EPA opinions were generated on potential of acetamiprid for developmental neurotoxicity (14). This review evaluates whether the neonicotinoid insecticidal class is a neurodevelopmental toxicant comparing data from 6 neonicotinoid insecticides (including acetamiprid). The publication concludes that the neonicotinoids do not selectively affect the developing nervous system, with no common DNT effects or findings associated with the neurodevelopmental effects of nicotine. Instead, findings at higher doses were secondary to systemic toxicity, as demonstrable with acetamiprid.

We conclude that the isolated observation of an apparent decrease in startle amplitude at 10 mg/kg bw/day, which is within background Control data ranges, with no concomitant changes in startle time, changes in startle habituation, motor activity, learning or memory acquisition, or brain neuropathology or morphometric differences, does not demonstrate convincing evidence of neurodevelopmental toxicity and is instead within the normal biological variability for animals at these ages. Accordingly, we concur with the EFSA opinion that acetamiprid is not sufficiently toxic as to justify classification as Repro Cat. 2 and disagree with the CLH Report proposal of Repr. Cat. 2 H361d.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Acetamiprid CLH Consultation - Supporting docs - NON CONFIDENTIAL.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Acetamiprid CLH Consultation - Supporting docs - CONFIDENTIAL.zip

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	France	<confidential>	Company-Downstream user	11
Comment received				
The proposed CLP classification "Reprotoxic Category 2" for Acetamiprid is based on the observations in 2 different studies on rats (CLH report pages 46 and 47): 1/ In the developmental neurotoxicity study (2008), at the higher dose of 45mg/kg bw/d: a decrease in postnatal survival and a startle response in the developmental neurotoxicity are observed but both are linked to a significant toxicity observed for mothers (including body weight changes during the test). 2/ In the Two-generation reproduction study (1999d), at the higher dose of 800ppm (i.e. 51mg/kg bw/d): a decrease in postnatal survival is observed for the F2 pups but also linked with a significant decrease of body weight gain and food consumption for mothers. This lets guess a certain toxicity to mothers. In the supportive sub-chronic 90 days study on rats (1997d - CLH report page 45), the NO Adverse Effect Level (NOAEL) is obtained at 14.8 mg/kg bw/d with no evidence of neurotoxicity and confirms that maternal toxicity is expected for the higher doses of the 2 previous studies, respectively 45mg/kg bw/d and 51mg/kg bw/d. It is the reason why, due to maternal toxicity, Reprotoxicity is thus highly difficult to be assessed in the same time. Consequently, the proposed CLP classification "Reprotoxic Category 2" for Acetamiprid is based on observations that do not fulfil CLP criteria for this classification.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	12
Comment received				
DK finds the observed effects (despite maternal toxicity) relevant for classification as Repr 2, and thus agrees with the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Germany	<confidential>	Company-Downstream user	13
Comment received				
10.10 REPRODUCTIVE TOXICITY ECHA note – An attachment was submitted with the comment above. Refer to public attachment Evergreen_Expert Statement on C2R2 classification Acetamiprid_final_san.pdf ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Evergreen_Expert Statement on C2R2 classification Acetamiprid_final.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2019	France		MemberState	14
Comment received				

FR: Page 23:
Based on the main adverse effects observed in the 2-generation rat study (i.e. in utero and postnatal growth decrease), FR agrees on the classification proposal: H361d.

Date	Country	Organisation	Type of Organisation	Comment number
15.03.2019	Spain		MemberState	15
Comment received				
Fertility The Spanish CA agrees with the dossier submitter that the available data do not warrant classification for effects on sexual function and fertility. Development The most adverse developmental effect is the reduced post-natal survival of the pups as observed in the F2 pups of the 2-generation study and in the developmental neurotoxicity study but not in the F1 pups of the 2-generation study. These developmental effects were observed in the presence of maternal toxicity including reduced maternal body weight (gain) and food consumption. We agreed with the dossier submitter that it is considered unclear whether the developmental effects are secondary to the maternal toxicity. Therefore, classification in Repr. Cat. 2 (H361d) is warranted based on the reduced post-natal survival observed.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	16
Comment received				
Agreement with the RAC opinion, this is in accordance with the EFSA Conclusion.				

Date	Country	Organisation	Type of Organisation	Comment number
15.03.2019	Spain		MemberState	17
Comment received				
Acute toxicity - oral route The lowest calculated LD50 value in the studies using ion-exchanged water is 146 mg/kg bw. The lowest calculated LD50 value in the study using corn oil as vehicle is 140 mg/kg bw. As both lowest calculated LD50 values are 50-300 mg/kg bw, acetamiprid should be classified as Acute Tox 3, H301 "Toxic if swallowed".				

Date	Country	Organisation	Type of Organisation	Comment number
13.03.2019	Germany		MemberState	18
Comment received				
Agreement with the proposal that Acetamiprid should be classified as Acute Tox. 3, H301 based on the lowest calculated oral LD50 values in the range 50-300 mg/kg bw/day.				

Howev-er, an according ATE should be discussed and harmonised.

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2019	France		MemberState	19
Comment received				
FR: Acute Toxicity Page 7: Following the addition of the two acute oral toxicity studies (1998 and 2002), FR agrees on the classification proposal: H301 instead of H302.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
21.03.2019	United Kingdom		MemberState	20
Comment received				
Acetamiprid (EC: N/A; CAS: 135410-20-7/160430-64-8) Chronic toxicity to Daphnia manga: Please can you clarify if the quoted 21-day semi-static Daphnia magna NOEC (Suteau, 1997) is based on mean measured concentrations of fresh solutions or does it reflect measured fresh + expired concentrations? We note the mean measured values are very close to the nominal concentration range which appears unusual if based on analytical measurement of fresh and expired test solutions given observations in other ecotoxicity tests. In addition, the study endpoint appears to be significantly less chronically sensitive than the chronic endpoint for Chironomus despite the two species having acute endpoints in close proximity. Chronic toxicity to Chironomus: The proposed chronic endpoint (28-day EC10 0.000235 mg/l) for Chironomus (McElligott, 1999 and Dossier submitter calculation) is based on concentrations calculated using estimated kinetic regressions. For 3 out of the 4 treatments the kinetic regressions are based on 1 or 2 data points above the LOQ. We are therefore unclear if these regressions and estimated concentrations <LOQ are reliable. We note that significant effects were only observed in the highest treatment. While 3 analytical data points >LOQ are available for this treatment, we are unclear how reliable the overall dose-response curve is and think 95% CI should be presented to aid interpretation. We also think it would be useful to present endpoints (NOEC and EC10 if appropriate) using the standard geometric mean measured calculation for analytical periods and ½ the LOQ where <LOQ is reported. This information is relevant as the RAR text indicates endpoints using this method would be in the 0.001 to 0.01 mg/l classification range indicating M = 10. Finally we note, using the valid acute toxicity to Chironomus endpoint and the surrogate approach would results in Aquatic Chronic 1, M=10.				

Date	Country	Organisation	Type of Organisation	Comment number
22.03.2019	Denmark		MemberState	21
Comment received				
Agreement with the RAC opinion.				

Date	Country	Organisation	Type of Organisation	Comment

				number
13.03.2019	Germany		MemberState	22
Comment received				
Proposed harmonised classification and labelling (Table 6): We agree with the proposal of classification for environmental hazards as Aquatic acute 1 (H400), Aquatic chronic 1 (H410) and acute/chronic M-factor of 10/100.				

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2019	France		MemberState	23
Comment received				
FR: Thank you for this very clear document. We agree with the Aquatic Acute 1 (H400; M-factor=10) and Aquatic Chronic 1 (H410; M-factor=100) classification proposal.				

PUBLIC ATTACHMENTS
1. Evergreen_Expert Statement on C2R2 classification Acetamiprid_final_san.pdf [Please refer to comment No. 6, 13]
2. Acetamiprid CLH Consultation - Supporting docs - NON CONFIDENTIAL.zip [Please refer to comment No. 3, 10]

CONFIDENTIAL ATTACHMENTS
1. Evergreen_Expert Statement on C2R2 classification Acetamiprid_final.pdf [Please refer to comment No. 6, 13]
2. Acetamiprid CLH Consultation - Supporting docs - CONFIDENTIAL.zip [Please refer to comment No. 3, 10]