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.

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

Last data extracted on 13.09.2019

Substance name: dimoxystrobin (ISO); (2E)-2-{2-[(2,5-dimethylphenoxy)methyl]phenyl}-2-(methoxyimino)-N-methylacetamide; (E)-2-(methoxyimino)-N-methyl-2-[a-(2,5-xylyloxy)-o-tolyl]acetamide
CAS number: 149961-52-4
EC number: -
Dossier submitter: Hungary

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	France		MemberState	1
Comment received				
FR: In the table 1.2, please indicate that the active substance has no relevant impurity.				

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	Germany		MemberState	2
Comment received				
The classification with Acute Tox. 4, H332 and H362 (May cause harm to breast-fed children) is supported. The data base is insufficient to conclude that the harmonised classification with Repr. 2, H361d is not justified. With regard to STOT RE2 the comparison with guidance value is currently focused on doses that did not clearly evoke significant/severe effects as requested by the CLP Regulation.				

Date	Country	Organisation	Type of Organisation	Comment number
19.08.2019	Germany	<confidential>	Company-Manufacturer	3
Comment received				
Page 27; Sperm parameters investigated in the 2-generation toxicity study: In top dose F0 parental males, percentage of normal sperm and sperm motility were decreased below the HCD range. When evaluating the individual values, one F0 high dose animal #118 with reduced testis and epididymides sizes and oligospermia in epididymides was mainly responsible for the decreased mean sperm motilities and increased number of abnormal sperm. Similar pathology was also seen for control animal #1, which showed epididymidal aspermia and no sperm were detectable (for %normal and abnormal sperm and motility), thus only 24 animals were evaluated. Also, one F1 animal from the 50 ppm dose group (#444) showed aspermia in the pathological investigation and no sperm could be measured (for %normal and abnormal sperm and motility). When the high dose animal #118 was excluded from the calculation all values were within the normal range, and the standard deviation was smaller. The absence of effects in the F1 males further confirms,				

that spermatogenesis is not affected by treatment with dimoxystrobin. However, these parameters were not affected and within the historical range, when assessed in the F1 males. An updated table on the sperm parameters ("Sperm parameters of males administered dimoxystrobin") - with added information on standard deviations, historical control data, and number of animals investigated - is provided in the documents sent to EFSA in the context of the AIR III Peer-Review Process. These additional documentation and data is also provided to ECHA via e-mail at the 19th of August.

Page 28, Tables 16 and 17 (mean number of implantations in the 2-generation toxicity study):
The mean number of implantations was statistically significantly reduced in the F1 females and not in the F0 females. The F1 females but not the F0 females had considerably reduced body weights during the premating and the gestation phase. From public literature, there is evidence, that lower body weights (induced by feed restriction) in can induced lower number of implants in rats.
In Terry et al. study (2005) (reference is added), dams with restricted food access that showed a body weight decrease of about 15% during pre-mating and of about 26% during the first gestation week also revealed statistically significantly decreased numbers of implantations.
In this publication access to food was restricted during the pre-mating phase (PMD 8 and 15) and the first week of gestation (GD 7) leading to body weight reductions of -15 to -30%. Body weight was recorded at premating days 8 and 15 (PMD 8 and 15) and gestation day 7 (GD 7) (see Table 14 below). The animals receiving 15 and 10 g food/day, showed reduced body weights between -12 to -26% in the 15 g/day group and -18 to -42% in the 10 g food/day group compared to controls. These two treatment groups had statistically significant lower numbers of implants and numbers of corpora lutea (see Table below):

Table 14: Comparison of selected fertility parameters in animals with restricted access to food (taken from Terry et al., 2005)

Parameter	Feed administration			
	Ad libitum	20g/day	15g/day	10g/day
Mating phase no.	20	20	20	13
Body weight PMD 1	256 +/- 13	Within 1% of ad libitum group		
Body weight PMD 8	Control	-6%*	-12%*	-18%*
Body weight PMD 15	Control	-6%*	-18%*	-29%*
Body weight GD 7	Control	-15%*	-26%*	-42%*
No. copulation positive	20	20	20	8
Pregnancy rate [%]1)	85	85	95	50
No. corpora lutea [mean (SD)]	15.9 (1.4)	16.3 (2.4)	13.2 (1.9)*	12.0 (0.0)*
No. implants [mean (SD)]	15.7 (1.6)	15.8 (2.4)	12.2 (3.4)*	9.5 (3.7)*
No. viable [mean (SD)]	14.2 (2.4)	15.2 (2.4)	11.5 (3.3)*	6.0 (4.9)*
No. dead	0	0	0	0
No. early resorptions [no (SD)]	1.5 (1.8)	0.6 (0.9)	0.7 (0.9)	3.5 (5.7)
Pre-implantation loss [mean % (SD)]2)	1.5 (3.7)	3.2 (5.6)	8.1 (22.0)	20.8 (30.8)
Post-implantation loss [mean % (SD)]3)	9.4 (11.5)	3.7 (5.9)	5.2 (6.6)	29.6 (47.2)

* $p<0.05$
1) pregnancy rate = (no. gravid/no. copulation positive) x 100
2) pre-implantation loss (per litter, %) = (corpora lutea – implantation sites/corpora lutea) x 100
3) post-implantation loss (per litter, %) = [(implantation sites – viable fetuses)/implantation sites] x 100

The body weight data of the 15 g food/day group are comparable to the females F1 animals dosed with 1200 ppm dimoxystrobin. The adult female F1 body weights during the pre-

mating phase of the 2-generation toxicity study were -16 to -34% during the premating phase and -16 - -19% during gestation compared to controls, which gives evidence, that the observed numbers of implants are secondarily related to impaired body weight development, and not a specific indication for a specific effect on reproduction. This is further supported by the fact, that F0 females showed only marginally lower body weights (-3 to -5% in the premating phase and the first week of gestation) and no difference in numbers of implantation compared to concurrent controls were seen in F0 females.
A more detailed description of the body weight effects induced by dimoxystrobin treatment is provided in the documents sent to EFSA in the context of the AIR III Peer-Review Process. These additional documentation and data is also provided to ECHA via e-mail at the 19th of August.

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Terry et al 2005_feed restriction and fertility.pdf

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	Germany		MemberState	4

Comment received

Adverse effects on development
Based on current knowledge, there are insufficient mechanistic data to clearly demonstrate that the dose dependent incidence of cardiomegaly in the 2-generation study in F1- and F2-offspring is due to the iron deficiency of the lactating dams.

According to the DS Hungary cardiomegaly in pups has been observed in the 2-generation reproductive toxicity study only transiently, because this effect occurred only on day 21 p.n. but neither on day 7 p.n. nor in adults. However, it remains unclear how many pups have been examined on day 4 p.n. The same applies to adult animals. Therefore, the dossier should provide sufficient information on the number of examined pups/adults to come to a clear conclusion on this point.
Whether the cardiomegaly was actually induced by the iron-deficient milk remains uncertain, since there is no information on the iron content in the milk of dimoxystrobin exposed rats. According to Zhang, P. et al, (The effect of serum iron concentration on iron secretion into mouse milk, J Physiol. 2000 Feb 1; 522(Pt 3): 479-491), at least in the mouse milk the iron content is threefold higher than in the serum.
Another possible explanation of the transiently observed cardiomegaly would be that the pups themselves ingest the active substance when start eating other than milk at the age of 12-16 days.
In the cited publication by Roth & Smith (1988), uptake of sodium nitrite during pregnancy and lactation in drinking water induced iron deficiency in lactating dams and in the second week p.n. in offspring. Depending on the dose level of sodium nitrite, following effects were observed in pups: hypochromic microcytic anaemia, reduced growth and mortality. Strong anaemic offspring showed e.g. fatty livers, chylous serum lipaemia and decreased haematopoiesis in the spleen. Except anaemia, these effects were not observed in pups exposed to dimoxystrobin. According to Roth & Smith no defined cardiomegaly was observed, but increased cardiac weights in offspring and dams. In contrast, an increase in heart weights was apparently not observed in adult animals after administration of dimoxystrobin in repeated dose studies.
In two developmental toxicity studies in rabbits, ventricular septal defects were described. In the first study this finding was not clearly dose-dependent (0/0, 3/3, 2/2 and 0/0) (Schilling et al., 2001). However, it should be noted that at maternal toxic dose level of 100 mg/kg bw/d) the post-implantation loss was nearly twice that of the control and therefore

ventricular septal defects could have been undetected. In the second study (Schneider et al., 2001) at maternal toxic dose level of 75 mg/kg bw/d both pre- and post-implantation losses were increased and septal defects were observed in 3 animals out of 3 litters (control 1/1). Although these values are within the HCD, the current control groups should not be disregarded, especially since the heart was also identified as a target organ in the 2-generation study.

Conclusion:
In both developmental toxicity studies (rabbit) and the 2-generation reproductive toxicity study (rat) the target organ was the heart. The conclusion of DS Hungary that observed cardiomegaly has been induced during lactation in the 2-generation study is not excluded on our part, but additional data are considered necessary for a clear assessment, e.g. cross-fostering studies as well as the determination of iron and dimoxystrobin in rat milk.

Remark:
In the summary table 24 (p. 31/32) the description of the two-generation reproductive toxicity study appears not correct. The effects at 500 ppm and 150 ppm which occurred in F1 dams and F2 offspring are missing. Furthermore it can be taken from the summary table 24 that at 150 ppm 'impaired body weight and body weight gain' was observed in F1 pups. However, in table 35 (p. 44) there is no statistically significant effect on bw in F1 pups, but there is an effect on bw of F2 pups at 150 ppm (table 16, p. 46).

Adverse effects on or via lactation
In table 16 (p. 46) a statistically significant reduced in bw of F2 pups (150 ppm) was observed on PND 7 which cannot be explained by self-feeding which is argued to start at PND 12. Such an effect was not observed at PND 1 and 4 and also not in F1 dams. Thus, an effect mediated by lactation should be considered.
With reference to the CLP Regulation (criterion b) the transfer in the milk or adverse effects on the quality of the milk have to be taken into account.

Transfer in the milk:
The milk of lactating goats (up to 288 ppm or 10.3 mg/kg bw/d, 5 days) and cows (up to 25 ppm or 0.64 mg/kg bw/d, 30 days) did not contain dimoxystrobin (or metabolites) or very low amounts only. It is argued in the CLH report that the applied doses were very low, however the highest dose applied to goats was in the dose range inducing effects on e.g. body weight in rats. The transfer of dimoxystrobin (or metabolites) into the milk has not been measured in rats. Therefore, and due to known species differences in milk composition, no reliable statement is possible.

Quality of milk:
Decreased iron concentration in milk was observed as consequence of an induced iron deficiency in lactating rats (Roth & Smith, 1988; Anaokar, 1981). Dimoxystrobin decreased iron levels in serum and offspring. Thus, it is considered plausible, that the quality of milk is affected via a decreased iron level. This could explain the above mentioned effect on bw of F2 pups at PND 7. However, determination of iron in rat milk has not been provided.

Conclusion:
Based on the statistically significant reduced body weight observed in pups on PND 7 the additional classification with H362 (may cause harm to breast-fed children) is considered justified.

Date	Country	Organisation	Type of Organisation	Comment number
29.08.2019	Netherlands		MemberState	5

Comment received
The NL MSCA agrees with the proposed 'no classification' for adverse effects on sexual function and fertility. It is noted that in the 2-generation study: - a significant decreased number of implantations in the high dose group of F1 dams was observed. As no lab historical control data were available, HC data from literature were used to neutralize this statistically significant observation; - effects on the ovarian follicle were observed (increases F0 and statistical significant decreases in F1) and these effects were regarded to be within the biological variability, but no HC data for this parameter were given. With respect to the removal of the Repr. 2 classification for adverse effects on development and the addition of the Lact. classification, there are some uncertainties. The following is noted: - As described in the CLH-report, current Repr. 2 (H361d) classification is apparently based on effects on body weight, heart (cardiomegaly) and blood (anemia), with an assumed higher susceptibility of offspring compared to adults for these effects. - The results of the prenatal developmental toxicity study in rat do not provide an indication for adverse effects on development. In the rabbit prenatal developmental toxicity, some adverse effects on development are noted. However, these were observed at the high dose only, and at incidences that were within the HCD range, showing no dose-response or not attaining statistical significance. Moreover, the high dose levels were clearly maternally toxic. So, it is agreed that also the prenatal developmental toxicity studies in rabbit do not warrant classification. - When looking at the multigeneration studies, dimoxystrobin treatment resulted in adverse effects on development in both the 2-generation study and the modified one-generation study. No developmental toxicity occurred in the extended one-generation study, though noticing that in this study dimoxystrobin was tested at relatively low dose levels, and that these levels hardly, if at all, induced general toxicity. - Iron-deficient anemia can be considered a general effect of dimoxystrobin, also observed in the repeated dose studies. It is noted that the enhanced one-generation study presented similar NOAELs for anemia for both parental as well as offspring. This was however the highest dose tested (4.3 mg/kg bw/d). Therefore, the true NOAEL can be higher and a difference in true NOAELs between parental animals and offspring is possible. - A reduction in pup body weight was noted postnatally with consistency seen over two generations in the 2-generation study and, additionally, also seen in the modified one-generation study. The pup body weight effects were absent at birth. Further, these body weight effects occurred, at least partly, during a time period where milk is the only nutrition source for pups. It is however noted that maternal toxicity was also present during the lactation period in both studies. It may be questioned whether the pup body weight effects should be considered as direct or indirect effects, and thereby affecting the proposed Lact. Classification for this type of effect.

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2019	Germany	<confidential>	Company-Manufacturer	6
Comment received				
Dimoxystrobin is currently under the EFSA pesticide peer review process for reregistration. During the commenting period of the Draft Assessment Report of dimoxystrobin (which is the basis for the Annex I to the CLH Dossier of dimoxystrobin), the notifier/manufacturer was asked to provide additional tabulated summaries/information/data relevant for the assessment of the reproduction toxicity studies (generation toxicity studies in rats and prenatal developmental toxicity studies in rats and rabbits). As these information are also				

relevant for classification of dimoxystrobin and as EFSA has asked the notifier/manufacturer to provide all information relevant for classification of dimoxystrobin to ECHA, the following additional attachments are provided by the notifier/manufacturer. This is submitted in this way, as the size limitation of the Zipfile of 10 MB was exceeded.
- Historical control data rabbit prenatal developmental toxicity studies April 1999 - November 2003 (DocID 2013/1421980) - are submitted in the Zip File 2
- Historical control data rabbit prenatal developmental toxicity studies April 1997 - April 2002 (DocID 2019/2044955 - are submitted in the Zip File 2
- Historical control data rabbit prenatal developmental toxicity studies May 1994 - October 2000 (DocID 2019/2044956 - are submitted in the Zip File 2

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ECHA-25 August2019-2.zipx

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2019	Germany	<confidential>	Company-Manufacturer	7

Comment received

Dimoxystrobin is currently under the EFSA pesticide peer review process for reregistration. During the commenting period of the Draft Assessment Report of dimoxystrobin (which is the basis for the Annex I to the CLH Dossier of dimoxystrobin), the notifier/manufacturer was asked to provide additional tabulated summaries/information/data relevant for the assessment of the reproduction toxicity studies (generation toxicity studies in rats and prenatal developmental toxicity studies in rats and rabbits). As these information are also relevant for classification of dimoxystrobin and as EFSA has asked the notifier/manufacturer to provide all information relevant for classification of dimoxystrobin to ECHA, the following attachments are provided by the notifier/manufacturer:
- Compiled document with the additional tabulated summaries/information/data relevant for the assessment of the reproduction toxicity studies (generation toxicity studies in rats and prenatal developmental toxicity studies in rats and rabbits) (containing additional tables on body weight, body weight developments, food consumption, result tables including all relevant historical control data, additional individual data and information to assess sperm parameters, female reproduction and entry into puberty) and acute toxicity studies (DocID 2019/2047163)
- Historical control data rabbit prenatal developmental toxicity studies April 1999 - November 2003 (DocID 2013/1421980) - are submitted in the Zip File 2
- Historical control data rabbit prenatal developmental toxicity studies April 1997 - April 2002 (DocID 2019/2044955 - are submitted in the Zip File 2
- Historical control data rabbit prenatal developmental toxicity studies May 1994 - October 2000 (DocID 2019/2044956 - are submitted in the Zip File 2
- Historical control data rat prenatal developmental toxicity studies January 1994 - June 1999 (DocID 2019/2044957
- Historical control data pup necropsy observations from reproduction toxicity studies January 2008 - December 2014 (DocID 2019/2046312)
- Benchmark Dose Calculations on body weight effects in dams and offspring of the 2-generation toxicity study (DocID 2015/1172904)
- Benchmark Dose Calculations on body weight effects in dams and offspring of the 2-generation toxicity study (EPA BMDS Software 3.1.1) (DocID 2019/2046321)
- Graphical analysis of individual male entry into puberty (preputial separation - PPS) data correlated with body weight (1200 ppm dimoxystrobin dose vs control) (DocID 2019/2044949)
- Graphical analysis of individual male entry into puberty (preputial separation - PPS) data correlated with body weight (500 ppm dimoxystrobin dose vs control) (DocID 2019/2044950)

- Graphical analysis of individual female entry into puberty (Vaginal opening - VO) data correlated with body weight (1200 ppm dimoxystrobin dose vs controls) (DocID 2019/2044951)
- Graphical analysis of individual female entry into puberty (Vaginal opening - VO) data correlated with body weight (500 ppm dimoxystrobin dose vs controls) (DocID 2019/2044952)
Publications:
- Terry et al 2005 (DocID 2019/2045629)
- Da Silva Faria et al 2004 (DocID 2019/2045813)
- Carney et al 2004 (DocID 2004/1041034
- Chernoff et al 2009 (DocID 2009/1132002)
- Melching-Kollmuss et al 2014 (DocID 2014/1326033)

ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ECHA-25 August 2019-1.zipx

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
25.08.2019	Germany	<confidential>	Company-Manufacturer	8
Comment received				
A more detailed summary of the acute toxicity studies has also been provided during the EFSA pesticide peer review process and is submitted with the word document (DocID 2019/2047163) included in the zip file. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment ECHA-25 August 2019-1.zipx				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	Germany		MemberState	9
Comment received				
The comparison with the guidance value (p. 72/73) is focussed on haematological effects of the modified one-generation reproduction toxicity study at 500 ppm (57 mg/kg). It should be noted that the small reduction in MCV and MCH in males occurred only at day 29 and not at day 98 (table 18 (p. 47/48)). The small reduction in MCH and MCHC in females was only observed at day 100 (not at day 29). A STOT RE-classification needs significant or severe effects which are not clearly given here. It is furthermore argued in the CLH-report (p. 73) that the anaemia was not completely reversible after a recovery period. This was observed in rats receiving a higher dose of 4500 ppm (3 w treatment, 2 w recovery). The calculated dose was 232 mg/kg (p. 34). In parallel a further group received 4500 ppm for 5 w (calculated dose: 264 mg/kg). The observed haematological were pronounced and are described as severe anaemia in the CLH-report. The guidance value (STOT RE 2) for a 4 w study is 30 < C ≤ 300 mg/kg. Adjusting the dose of the 5 w group (264 mg/kg) to 4 w a dose of 330 mg/kg is calculated slightly above the guidance value. Adjusting the dose of the 3 w group (232 mg/kg) to 4 w a dose of 174 mg/kg results well in the range of the guidance value. Conclusion: With regard to STOT RE 2 the comparison with guidance value is currently focused on doses				

that did not clearly evoke significant/severe effects as requested by the CLP Regulation. It is recommended to consider not only the doses of the modified one-generation reproduction toxicity study, but also those of the other studies (e.g. short-term toxicity studies in rats, mice and dogs) in case of significant/severe toxicity.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	France		MemberState	10
Comment received				
FR agrees with the proposal of classification for environmental hazards and the proposals of acute and chronic M factors.				

Date	Country	Organisation	Type of Organisation	Comment number
27.08.2019	Germany		MemberState	11
Comment received				
The German CA agrees with the proposal of classification for environmental hazards as Aquatic Acute 1 (H400), Aquatic Chronic 1 (H410) and the acute/chronic M-factor of 100. In the chronic fish study (Anonymous 1999b, 1999/10521) there is at 0.001 mg/L a 30 % decrease in wet weight and a 13 % decrease in body length, both significantly different compared to the control. Additionally there is a 13 % lower survival of young fish in the study at 0.01 mg/L. The LOEC in the study is determined at the tested concentration of 0.001 mg/L and the NOEC at 0.000316 mg/L. This NOEC should be used for the chronic classification.				

Date	Country	Organisation	Type of Organisation	Comment number
30.08.2019	Belgium		MemberState	12
Comment received				
BE CA supports the proposal of environmental classification of Dimoystrobin: Aquatic Acute 1, H400 and M=100 Aquatic Chronic 1, H410 and M=100 Aquatic acute toxicity Even though it has no impact on the proposed M-factor because the result is in the same range of the key algae study, we don't agree that the reliable and valid acute guideline study with Crassostrea virginica cannot be used for classification purposes. In the CLP-guidance (I.3.1. Acute toxicity) it is mentioned that data on other species (than fish, crustacea and algae/aquatic plants) shall also be considered if the test methodology is suitable. The results with the highest toxicity should than be chosen. Aquatic chronic toxicity Idem for the chronic Chironomus riparius study which should not systematically be disregarded for classification purposes as mentioned in the CLH report. However, for this specific case we are of the opinion that the Dohmen G.P, 2001study which uses spiked water is not suitable for chronic classification purposes: - The test is performed under static regime. Only initially measured concentrations are given in the CLH report and annex I. Because the substance disappeared rapidly from the water phase (only 18-32% detected after 28d) to the sediment, a NOEC based on the end of test concentration (if available) would have been more preferable (CLP guidance, I.4.3).				

- furthermore, the substance has the potential to adsorb to sediment particles (Koc between 195.8-935.3 mg/L) and thus exposure via sediment (ingestion) cannot be ruled out.

Furthermore we question the 97dNOAEC of 0.001mg/L in the Anonymous, 2000/5125-study with Oncorhynchus mykiss where it is concluded that there is no statistically or biologically significant difference to the control after taking into account of the higher number of surviving fish and the total biomass and length (sum of weight and length per replicate) at 0.001 mg/L. Nevertheless without this correction a significant effect on body length was seen at 0.001 mg/L. Therefore we are of the opinion that the 97dNOEC to be used for classification and labelling should be 0.000316 mg/L instead of 0.001 mg/L. This will however not impact the proposed chronic M-factor of 100 (NRD, 0.0001<NOEC≤0.001).

Even though not a key study, it would have been more appropriate to base the results of the Lemna gibba study on the geometric mean concentration instead of the initial concentration because concentrations were not maintained throughout the test. In annex I of the CLH report it is mentioned that analysed concentration were 88.8% to 101.5% of nominal at test initiation and from 59.4% to 98.4% of nominal at test termination. It is however not stated which exposure concentration(s) dropped under the 80% of nominal.

Some editorial or/and minor comments :
- Table 39: summary of relevant information on bioaccumulation
BCF of 48 should read BCF of 84
- Table 40: summary of relevant information on acute aquatic toxicity
Difference in testing regime (static, flow through) between table and description of study
- Anonymous 1998/10601
- Anonymous 2000/5125
- Anonymous 2000/5092
- Annex 1, 4.5.2 Study 2 – Development and emergence toxicity study in Chironomus riparius
Typo : Guideline 204? However this guideline is a fish, Prolonged Toxicity Test: 14-Day Study
Table 41 of the CLH report however mentions that the study is performed according to the BBA draft guideline (1995) which mainly forms the basis for OECD 219 (sediment-water Chironomid Toxicity Testing using spiked water)

Date	Country	Organisation	Type of Organisation	Comment number
24.08.2019	United Kingdom		MemberState	13

Comment received

Dimoxystrobin (EC: -; CAS: 149961-52-4)

Chronic toxicity to fish:
The basis of the proposed Aquatic Chronic classification is the 97 d NOAEC mortality of 0.0010 mg/L for Oncorhynchus mykiss, which is expressed as a nominal concentration (Anon., 1999).
The study report determined a NOEC for fish mean body length which was 0.000316 mg/L (nominal). The CLH report cites information presented in the DAR (2005) which rejects this NOEC endpoint on the basis that the effect, while statistically significant, is minimal and there is no statistical difference when the sum of fish length is considered.
The endpoint based on 'sum of lengths' is unusual and is not in the OECD 201 test guideline. Rather, the mean or median values for the length of the fish in each test group should be statistically compared to the control according to OECD 201. Equally, it is unclear

what the sum of fish lengths approach represents because neither the raw data nor a detailed description are presented in the DAR or the CLH report.
We note that the 2017 RAR does not consider the sum of fish lengths approach and includes the NOEC for fish mean body length at 0.000316 mg/L.
We consider that the NOEC for fish length of 0.000316 mg/L based on mean body length is more appropriate than the present mortality NOEC as mean length at all test concentrations above 0.000316 mg/L with surviving fish were statistically significantly lower than the control and there is a negative concentration-response relationship.
In addition, actual concentrations ranged from 51.5-158.2% of the nominal (RAR, 2017) and therefore, geometric mean measured concentrations should be used.

Algae toxicity (Wyskiel et al., 2000):
The key endpoint for the proposed Aquatic Acute classification is a 72 h ErC50 of 0.0078 mg/L for Navicula pelliculosa based on mean measured concentrations (Wyskiel et al., 2000).
Measured concentrations ranged from 85.1-112.8% of nominal concentrations at test initiation and from 101.2-173.3% of the nominal at test termination at 120 h. The CLH report does not mention analytical measurement during the study. Therefore, we are uncertain of how the 72 hour mean measured concentrations were calculated and whether they are reliable. Please can you describe how 72 hour mean measured endpoints were calculated?
The RAR includes cell data for the 3 solvent controls and procedural controls. The initial cell concentration was less than the OECD TG 201 recommendation but we note that cell numbers did meet the x16-fold increase over 72 hours. We note that the 24 hour cell measurements are all quoted as <10000 – please can you clarify if actual cell counts were taken at this time point or if the methodology was unable to consider <10000 cells. Also, other cell counts are identical for different replicates at the same time. Whilst this may be the case, please can you provide details of the counting method and its suitability? This information is relevant to confirm the validity of the study controls.
A 120 hour NOErC of 0.0012 mg/L based on mean measured concentrations was obtained from the study. We are unsure how suitable this value is for classification purposes because the exposure period is longer than the standard 72 – 96 hour duration and we are unclear if controls met both validity criteria and exponential growth over the whole exposure period up to 120 h.
From Table B.9.2.6.2-1 in the RAR (2017), it is unclear what the 72 hour NOErC was. Please can the DS provide a 72 h NOErC and / or EC10? Depending on information to support the use of 72 hour mean measured concentrations, it may be appropriate to consider the surrogate approach using the 72 hour ErC50 from this study if a 72 hour NOErC/EC10 cannot be determined.

CONFIDENTIAL ATTACHMENTS
1. ECHA-25 August2019-2.zipx [Please refer to comment No. 6]
2. ECHA-25 August 2019-1.zipx [Please refer to comment No. 7, 8]
3. Terry et al 2005_feed restriction and fertility.pdf [Please refer to comment No. 3]