Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

imidacloprid (ISO); (*E*)-1-(6-chloropyridin-3-ylmethyl)-*N*-nitroimidazolidin-2-ylidenamine

EC Number: 428-040-8
CAS Number: 138261-41-3

CLH-O-0000001412-86-282/F

Adopted

13 June 2019

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON IMIDACLOPRID (ISO); (*E*)-1-(6-CHLOROPYRIDIN-3-YLMETHYL)-*N*-NITROIMIDAZOLIDIN-2-YLIDENAMINE

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: imidacloprid (ISO); (*E*)-1-(6-chloropyridin-3-ylmethyl)-*N*-nitroimidazolidin-2-ylidenamine
EC number: 428-040-8
CAS number: 138261-41-3
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Germany	Bayer AG	Company-Manufacturer	1
Comment received				
no general comment ECHA note – An attachment was submitted with the comment above. Refer to public attachment Bayer comments sanitized.7z ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Bayer comments.7z				
Dossier Submitter's Response				
The proposed classification for acute oral toxicity (Category 3) is clearly justified by a valid study in the mouse providing sufficient evidence that this species is more sensitive than the rat. Therefore, our proposal is not amended. We agree with Bayer that the current guidance document does not say that a certain species would not be relevant. If valid studies in more than one species are available, the result obtained in the most sensitive species should be used as the basis. We also agree with Bayer that human data (i.e., the information from poisoning incidents) should not have an impact on classification and labelling in this case.				
RAC's response				
RAC agrees with the dossier submitter's (DS) response. In addition, RAC wants to clarify that according to the CLP Regulation the minimum classification was introduced for certain hazard classes, including acute toxicity, as for those hazard classes the classification according to the criteria in Directive 67/548/EEC does not correspond directly to the classification in a hazard class and category under the CLP Regulation. Based on a classification as R22; Xn according to Directive 67/548/EEC, it is not possible to explicitly				

allocate to Category 4 or 3 according to CLP Regulation. By default, such substances were put in Category 4 with an asterisk indicating the minimum classification. The CLP Regulation further states that based on the actual data the correct classification to either of the categories shall be applied, either by self-classification by industry or in the course of harmonised classification, via a CLH dossier, as is the case here.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Germany	Bayer AG	Company-Manufacturer	2

Comment received

Bayer comments on the topic are provided in the attached document M-638137-01

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Bayer comments sanitized.7z
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Bayer comments.7z

Dossier Submitter's Response

Comment on use of a SL formulation instead of technical active substance:

Van den Brink et al. (2016) performed acute studies using technical imidacloprid with the same test organisms that were used by Roessink et al., but using overwintering generations. A comparison of the respective results is given below (LC_{50} values from supplemental data to the publication):

Species		SL formulation (Roessink et al. 2013)	Technical imidacloprid (van den Brink et al., 2016)	Factor
Cloeon dipterum	96h-EC50	1.0 µg/L	18 µg/L	18
	96h-LC50	26 µg/L	29 µg/L	1.11
Caenis horaria	96h-EC50	1.8 µg/L	6.0 µg/L	3.33
	96h-LC50	6.7 µg/L	28 µg/L	4.2
Chaoborus obscuripes	96h-EC50	284 µg/L	3258 µg/L	11.4
	96h-LC50	294 µg/L	5226 µg/L	17.7
Gammarus pulex	96h-EC50	18 µg/L	49 µg/L	2.72
	96h-LC50	263 µg/L	386 µg/L	1.5
Asellus aquaticus	96h-EC50	119 µg/L	78 µg/L	0.65
Plea minutissima	96h-EC50	36 µg/L	189 µg/L	5.25
	96h-LC50	37 µg/L	287 µg/L	7.7

The effect values (EC_{50} and LC_{50}) from the tests performed with *Caenis horaria*, *Gammarus pulex*, *Asellus aquaticus* and *Plea minutissima* are in good agreement, the differences can be explained by normal intra- and interlaboratory variations. Only the EC_{50} values for *Cloeon dipterum* and the EC_{50} and LC_{50} values for *Chaoborus obscuripes* differ between the two papers by a factor > 10. For *Cloeon dipterum* the difference is much smaller considering the LC_{50} values. If it would be assumed that the SL formulation is more toxic than the

technical active substance, the results for all species would show significant differences. As this is not the case, our conclusion is that the effect values from Roessink et al. (both acute and chronic) can be considered for the classification of imidacloprid. Furthermore, the acute M factor of 100 is also supported by the result from van den Brink for *Caenis horaria* using technical imidacloprid (96h-EC50 = 6.0 µg/L).

Comment on reliability of the Roessink study:

We refer to our response to comment 6 below.

EFSA conclusion

You state that EFSA has considered the publication by Roessink to be not sufficiently reliable for regulatory use. However, the EFSA conclusion is much more differentiated:

The following paragraphs are cited from EFSA (2014):

p.4: "In view of an evaluation carried out by the Netherlands based on a recent study on the toxicity of imidacloprid on aquatic organisms (Roessink et al., 2013), a new chronic toxicity threshold regarding aquatic organisms was derived for imidacloprid. Following the review of the article by the rapporteur Member State Germany it was proposed that the new study can be considered useful for regulatory purposes."

p.4: "The conclusions laid down in this report were reached on the basis of the evaluation of the existing studies that were submitted by the applicant in support of the original approval of imidacloprid, the recent study on the toxicity of imidacloprid on aquatic organisms (Roessink *et al.,* 2013) together with its evaluation undertaken by the Netherlands (EFSA, 2014b)."

p.8: "Nevertheless, as it was agreed at the meeting, in the absence of further data, EFSA considered that the endpoints from Roessink *et al*., (2013) can be used for risk assessment as a conservative approach."

For both, the acute and chronic risk assessment, the results from Roessink et al. (2013) were considered for the derivation of a SSD in Tier 2.

The overall conclusion in EFSA (2014) was:

"Definitive Regulatory Acceptable Concentrations (RACs) to be used for the acute and chronic chronic risk assessment for aquatic organisms could not be established [….]. The tier-2 RACs cover the species that according to the scientific information available were more sensitive. However, they can only be considered as provisional due to the qualitative and quantitative limitations of the data set. No tier-3 RACs could be derived. In the absence of further data, the provisional tier-2 RACs should be considered as the most suitable approach for risk assessment for the representative uses. It was acknowledged at the meeting that further field investigations on Ephemeroptera are currently ongoing. When available, the RAC derivation can be reconsidered."

From this it can be concluded, that the results from Roessink et al. are also suitable for classification and labelling.

Comment on analytical monitoring of test substance concentration:

You are right, that for the acute tests only the concentrations in the dosing solutions were measured, as described in the study summary (A 7.4.1.2_05). Unfortunately, this is stated

incorrectly in the CLH report. The correct procedure as cited from the paper was as follows: "Samples were taken from the dosing solution to confirm imidacloprid concentrations. Exposure concentrations at the start of the acute and chronic tests were characterized using the measured concentrations in the dosing solution, the amount of dosing solution applied and the amount of receiving test volume. During the chronic tests water samples from the control and the highest treatments were collected for residue analysis at the end of each test week." "Concentrations of imidacloprid measured in the dosing solutions were, on average, 97.5 % (± 7.1, n=10) and 95.5 %(± 4.3, n=7) of the intended concentration for the acute and chronic tests, respectively".

Considering the mean measured concentrations from the chronic test (highest concentration) they were in the range of 84.9 % (± 4.5) for nominal 1 µg/L and 97 % (± 1.1) for nominal 100 µg/L (highest test concentration). These data show that a correct dosing of test substance concentration was performed and that the test substance concentration was > 80 % of the nominal concentrations at the end of the 7 day exposure period (semi-static test system). Therefore, it is the view of the dossier submitter that it can be concluded, that for the acute tests with a duration of 4 days the test substance concentration was also > 80 % of nominal concentration. This conclusion is also plausible considering the physico-chemical properties as well as the degradation behavior of imidacloprid.

Comment on stage of test organisms:

The following information on the test organism is given in the part "materials and methods":

"Macrocustecean juveniles and early larval insect instars were used for the studies except for P. minutissima which was tested using adults". The information from this section of the publication is considered more reliable than the title.

Concerning your statement that invertebrates could not be evaluated for their developmental stage and age, this is just a statement for which there is not indication in the publication.

Comment on the lack of rubustness of the chronic endpoints for regulatory purposes:

See excerpt from EFSA conclusion above.

Comment that mayflies are unususal test species:

Your comment that the test protocol was not adapted to to the test species and that non-optimal conditions may explain low endpoints cannot be proven by any information from the publication. All physico-chemical paramters (dissolved oxygen, pH, temperature and conductivity) did not significantly change over the exposure period for mayflies. The results from the control replicates also indicate that the test conditions were adequate for the species tested.

Comment on method for assessing immobility:

You criticize that immobility in this study is defined as lack of voluntary movement within 20 seconds instead of using an external stimulus. However, please note that also the immobility in the controls was determined by the same definition and the control replicates differ significantly from the test substance replicates related to immobility. This means, that the test organisms were generally able to move without an external stimulus under the

conditions of examination and your statement that no or very limited movement under light conditions is shown by the test species seems not to be comprehensible.
RAC's response
RAC notes the DS response providing additional detailed information and agrees with the DS evaluation.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Finland		MemberState	3
Comment received				
FI CA supports the conclusions that imidacloprid is considered neither as rapidly degradable nor as potentially bioaccumulative for the classification purposes. There are adequately of toxicity test data available for classification purposes of aquatic hazards. According to studies listed, the most sensitive trophic level is invertebrates. The key data for this proposal was acquired from a non-guideline study using different species of mayflies. The study is considered reliable and using the data for classification appropriate because freshwater macroinvertebrate species may be considered a non-target aquatic species for unexpectable exposure of an insecticide via input from leaching for example. Test results from several aquatic insect species would result in more severe classification of imidacloprid compared to the data available from the standard species and test methods. The lowest toxicity values by far are from studies performed with Cloeon dipterum and Caenis horaria. The acute toxicity EC50 value for Cloeon dipterum is between 0.001-0.01 mg/l and the chronic toxicity NOEC10 value for Caenis horaria is between 0.00001-0.0001 mg/l, and thus, resulting in classification of Aquatic Acute 1 and Aquatic Chronic 1 with M-factors of 100 and 1000, respectively. Based on the available information and the classification criteria, FI CA supports the proposed classification of Aquatic Acute 1, H400 with M-factor of 100 and Aquatic Chronic 1, H410 with M-factor of 1000 for imidacloprid.				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	Germany	Bayer AG	Company-Manufacturer	4
Comment received				
Bayer comments on the topic are provided in attached document M-642211-01 ECHA note – An attachment was submitted with the comment above. Refer to public attachment Bayer comments sanitized.7z ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Bayer comments.7z				

Dossier Submitter's Response
Thank you for your attention. We confirm the theoretical need of the proposed correction concerning the transcription errors and inconsistencies as to metabolites formation in Table 11. However, please not that the CLH-report is not revised at this stage of the CLH-process. Regarding the provided Ka values in section 5.2.1 we used for the CLH report the same values as summarised in the Competent Authority Report (CAR 2010) in the framework of approval as biocidal active substance. These values are provided by Bayer Environmental Science (see documents Doc IIIA 7.1.3/01 to 04-15 Adsorption onto / desorption from soils (revised November 2006)). A renewed comparative examination showed that there are slight inconsistencies to values provided by Bayer Environmental Science in Doc IV level (original studies). Taking into account the values provided in Doc IV level this might lead to minor difference in the arithmetic mean of adsorption coefficients, but this will have no impact on overall conclusion for imidacloprid classified as being moderately mobile in soil.
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
06.12.2018	United Kingdom		MemberState	5

Comment received
Imidacloprid (ISO); (E)-1-(6-chloro-3-pyridylmethyl)-N-nitroimidazolidin-2-ylideneamine (EC: -; CAS: 138261-41-3) We agree that mayflies are a relevant test species and where available, reliable data should inform hazard classification. The proposed aquatic classification for imidacloprid is based on aquatic ecotoxicity endpoints from academic literature (Roessink et al, 2013) which were not conducted to GLP. The CLH proposal includes some study details which indicate the study followed modified OECD 202 and 211 test guidelines but we feel further information should be considered to support the study reliability when determining M-factors. This includes details on the following: - Test item purity. - Test item media and exposure treatment preparation. - Consideration of invertebrate standard duration 48h acute endpoints if observations are available. - Acute and chronic raw data to assess differences between exposure treatment replicates and numbers of animals remaining when emerged animals were removed over the chronic timescale. - Acute and chronic toxicity dose-response curves – this is most relevant to acute EC50 endpoints which are close to the lowest exposure treatment concentration.
Dossier Submitter's Response
The following information is available from Roessink et al. (2013) as well as from van den Brink (2016): Test item: SL formulation containing 200 g/L imidacloprid. In a subsequent publication (van den Brink 2016) some experiments were also performed with technical grade imidaloprid

(purity not given) (see response to comment 2). For *Caenis horaria* (overwintering generation) a 96h-EC_{50} of 6 µg/L is reported, that supports the EC_{50} of 1.77 µg/L and would result in the same M factor. Therefore, it can be concluded that the use of the SL formulation instead of pure imidacloprid would not influence the test results.

Test item media: Copper-free water, 1.5 L jars with 1 L copper-free media. Stainless steel meshes were introduced to the test system to serve as substrate.

Exposure treatment preparation: Immediately after the animals were transferred into the test jars containing test water, an appropriate volume of imidacloprid stock solution was spiked using a capilettor.

48h effect values: This information is not available from Roessink et al. However, from a subsequent publication (van den Brink et al. 2016) supplemental data are available also for the experiments by Roessink et al. The following data are given for *Cloeon dipterum*:

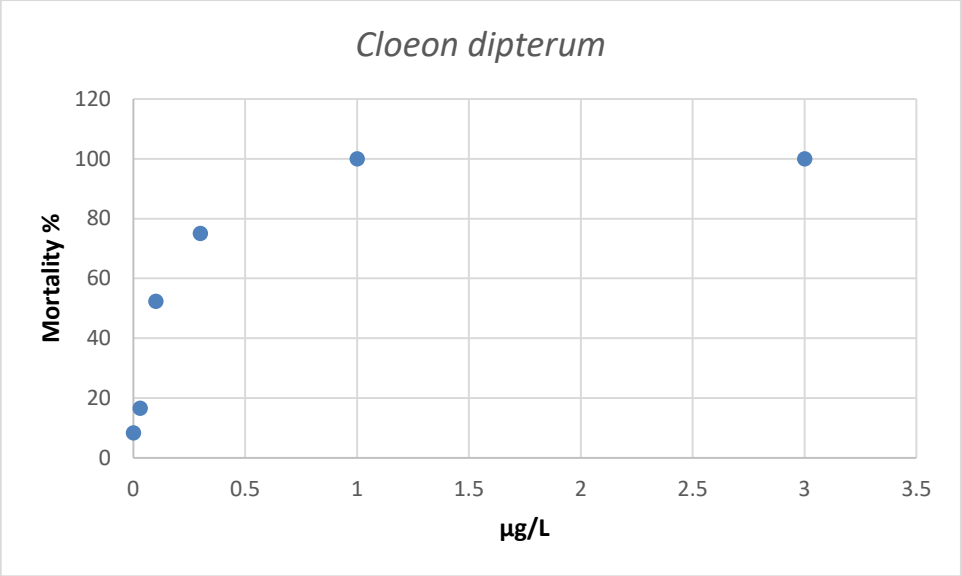
Exposure time	EC50 [µg/L]
24 h	72
48 h	2.7
72 h	1.7
96 h	1.0

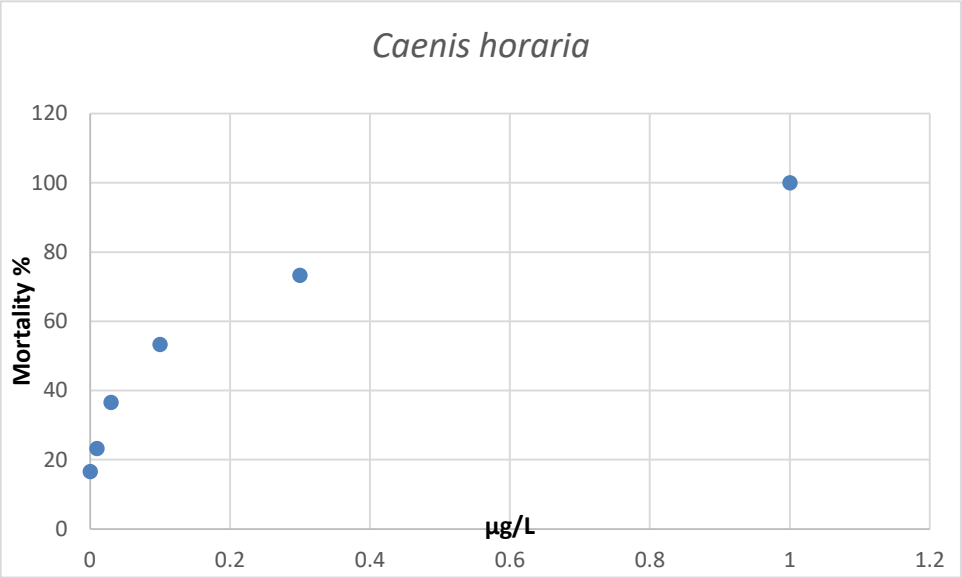
These data indicate that even if the "standard test duration" of 48 h is considered, the classification proposal would not change.

Acute and chronic raw data: Raw data for the acute tests are not available. Raw data for the chonic tests (obtained as confidential information from the author) indicate that in the 28d-experiment with *Caenis horaria* no emergence of test animals occurred. In the 28d-experiment with *Cloeon dipterum* the number of emerged animals was between 0 (highest test concentration with 100 % immobility) and 6 (in one replicate of the lowest test concentration). Average emergence over all replicates and test concentrations was 2. Emerged animals were counted as missing in the statistical analysis.

Concerning the difference between the replicates in the chonic tests, for both *Cloeon dipterum* and *Caenis horaria* the replicates of the single test concentrations are in good agreement.

Acute and chronic toxicity dose-response curves: Dose-response curves are not given in the publication. For the acute tests the slope of the dose-response function is given with 1.29 for *Caenis horaria* and 0.944 for *Cloeon dipterum*. For the chronic studies the slope is given as 1.32 for *Caenis* and 1.67 for *Cloeon*. From the raw data available for the chonic studies the following dose-response curves were derived by the dossier submitter:





RAC's response
RAC notes the DS response providing additional detailed information and agrees with the DS evaluation.

Date	Country	Organisation	Type of Organisation	Comment number
05.12.2018	France		MemberState	6
Comment received				
Page 37 to 48: FR agrees with the classification and M factors (acute and chronic) proposed in the CLH report based on the endpoints reported. The key studies that provide data, which determines the classification proposal and M factors (acute toxicity study on Cloen dipterum: Roessink et al. (2013), CAR: A7.4.1.2/05, and chronic study on Caenis horaria: Roessink et al. (2013), CAR: A7.4.1.2/05) are issued from literature (Roessink et al. (2013). A brief summary is available in CLH report for this literature study. It can be noted that this study of Roessink et al. (2013) was peer reviewed at EU level under regulation 1107/2009 and was considered not fully reliable (see EFSA Journal 2014;12(10):3835 Conclusion on the peer review of the pesticide risk assessment for aquatic organisms for the active				

substance imidacloprid) and it is also reported in CLH report that those studies evaluated by the competent authority in the framework of the authorisation of imidacloprid as biocidal active substance (CAR – Competent Authority Report revised version 2015) have a reliability score of 2. Could you please include more details on the assessment of Roessink et al. (2013) for its use and relevance under CLP based on these remarks (i.e list of criteria fulfilled and not fulfilled to conclude on reliability score of 2)?

Dossier Submitter's Response

For further information on the study as well as on the EFSA conclusion, please refer to our responses above. Concerning the derivation of the reliability score of 2, the following issues according to the Klimisch score were taken into account:

Information on test substance: SL formulation containing 200 g/L imidacloprid, no further information available. In a subsequent publication (van den Brink 2016) some experiments were also performed with technical grade imidaloprid (purity not given). For *Caenis horaria* (overwintering generation) a 96h-EC_{50} of 6 µg/L is reported, that supports the EC_{50} of 1.77 µg/L and would result in the same M factor. Therefore, it can be concluded that the use of the SL formulation instead of pure imidacloprid would not influence the test results.

Test organisms: Taxonomic identity of the organisms used in the study are sufficiently described including genus and species. Origin of test organism is also sufficiently described.

Test setup: Test system is adequately described in terms of testing procedure, origin and acclimation of the test organisms, test conditions (temperature, dissolved oxyven, pH, lighting), test duration, type of exposure, test concentrations, number of replicates, number of test organisms per replicate, analytical monitoring of test substance concentration, control mortality/immobilization, statistical method for derivation of effect values.

In addition the validity criteria of OECD 202 (Daphnia acute test) were fulfilled for the acute tests (control mortalitiy not above 10 %, oxygen content >= 3 mg/L and validity criteria of OECD 211 (Daphnia reproduction test) (control mortality not above 20 %) was fulfilled for the chronic tests.

Considering the available information, it seems appropriate to give the study a reliability score of 2.

RAC's response

RAC notes the DS response providing additional detailed information and agrees with the DS evaluation.

Date	Country	Organisation	Type of Organisation	Comment number
07.12.2018	Denmark		MemberState	7

Comment received

Please take (more) into consideration, that the test performed by Roessink et al., (2013) is not according to a guideline (e.g. OECD 202). Please elaborate on the fact, that the immobilisation test has been performed for 96 h instead of 48 h. Is the longer exposure time expected to have an impact on the various invertebrates?! Why, why not?! The study may not be appropriate (enough) for the purpose of classification.

Dossier Submitter's Response
Please refer to our answer to comment 5 and the information given there on the 48h-EC_{50}.
RAC's response
RAC notes the DS response providing additional detailed information and agrees with the DS evaluation.

PUBLIC ATTACHMENTS
1. Bayer comments sanitized.7z [Please refer to comment No. 1, 2, 4]

CONFIDENTIAL ATTACHMENTS
1. Bayer comments.7z [Please refer to comment No. 1, 2, 4]