Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

clopyralid (ISO); 3,6-dichloropyridine-2-carboxylic acid

EC Number: 216-935-4
CAS Number: 1702-17-6

CLH-O-0000007365-71-01/F

Adopted

14 February 2023

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ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CLOPYRALID (ISO); 3,6-DICHLOROPYRIDINE-2-CARBOXYLIC ACID

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during 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 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 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. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: clopyralid (ISO); 3,6-dichloropyridine-2-carboxylic acid
EC number: 216-935-4
CAS number: 1702-17-6
Dossier submitter: Finland

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Denmark	Corteva Agriscience International Sàrl	Company-Manufacturer	1
Comment received				
As the sole notifier for the EU renewal of clopyralid according to Regulation (EC) 1107/2009 Corteva Agriscience hereby submit our comments to the proposed harmonised classification and labelling of clopyralid. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Corteva comments CLH report clopyralid dec2022.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Corteva position on the proposed R2 classification_final dec2022.pdf				
Dossier Submitter's Response				
Thank you for your comments. Please see our responses to comments no. 3 and 6.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
31.10.2022	Sweden		Individual	2
Comment received				
This substance causes serious problems in the environment due to it's persistance and effects on plants. We used a soil product fertilized with manure from animals, which had been given food where clopyralide was used. All of our tomato and chili plants died or was seriously damaged, compared to a reference with another soil product. This substance must be stopped!				
Dossier Submitter's Response				
Thank you for your comment.				

RAC's response
Noted.

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Denmark	Corteva Agriscience International Sàrl	Company-Manufacturer	3

Comment received

Corteva Agriscience disagree with the statement made under point 10.10.5 Short summary and overall relevance of the provided information on adverse effects on development of the CLP report (p.41-42) Please find Corteva Agriscience's comments in the enclosed position paper "Corteva position on the proposed R2 classification_final dec2022.pdf".

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Corteva comments CLH report clopyralid dec2022.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Corteva position on the proposed R2 classification_final dec2022.pdf

Dossier Submitter's Response

Comment 1: Indeed, microphtalmia and anophtalmia were observed in the 2-generation reproductive toxicity study F1 pups.

Comment 2: It is true that malformations distributed across multiple litters are of a greater concern than those that are observed in a single litter, as single-litter observations are more likely to represent spontaneous findings. Moreover, the incidence numbers are close to histrorical control incidences. Even though the incidences are higher than for HCD (phase 1 and 2 calculated separately) it is not possible to explicitly conclude that this is a treatment related effect because polydactyly was seen only in one litter and in Phase II it was not observed at all. However, the possibility of substance relation of these findings cannot be completely ruled out.

Comment 3: Examination of the fetuses from rabbits in the 25Omg/kg/ day dose group revealed evidence of fetotoxicity and teratogenicity. However, administration of clopyralid at this dose level also produced severe maternal toxicity. Maternal body weight gain at 250 mg/kg/ day was also significantly depressed during the treatment period, and maternal body weight was significantly lower at the end of treatment. As Germany states, this will significantly lower the value of the developmental findings at this dose level. Because hydrocephaly occurred only in pups from dams exhibiting severe weight loss, this may have been secondary to the severe maternal stress. Regardless, the authors of the study could not rule out the possibility of a direct effect of clopyralid.

Comment 4: In the rabbit study, concerning the minor alterations and delays in skeletal ossification, statistically significant increases in the incidence of delayed ossification of the bones of the skull were present in the 50 and 110 mg/kg/ day dose groups, and an increased incidence of delayed ossification of the sternebrae was observed at 110 mg/kg/day. Because there were no significant increases in the incidence of delayed ossification at the highest dose (250 mg/kg/ day), and the incidence of delayed ossification of the skull and sternebrae at 50 and 110 mg/kg/ day were within the range of historical control, the differences in the lower dose groups could be considered a reflection of the normal variability of these parameters in this species.

RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Germany		MemberState	4

Comment received

The proposed classification as Repr. 2 (H361d) is in line with the recommendations of the EU peer review process under PPPR and supported. Still, we would like to provide some comments on the proposal.
The proposal Repr. 2 (H361d) for Clopyralid is mainly based on two studies:
1) on an prenatal developmental toxicity study in F344 rats (dRAR B.6.6.2, 1981) and
2) on an prenatal developmental toxicty study in NZW rabbits (dRAR B.6.6.2, 1990).

Ad 1)
We would appreciate if the Dossier Submitter would supply numerical data for all dose groups regarding body weight, body weight gain, food consumption, and liver weight for the dams. Only on the basis of numerical data, a clear evaluation of maternal toxicity is possible. Descriptive information such as „significant decrease" or „significant reductions" are less valuable for the evaluation.

We agree that the occurrence of the malformation „polydactyly" can principally constitute a basis for classification as developmental toxicant. Admittedly, the incidence was low in the high-dose group (250 mg/kg bw/d) of „Phase I" – namely 3/243 fetuses (1.2%) – but we note at the same time that the concurrent control group was devoid of this malformation and that other skeletal anomalies were also slightly increased in the same experiment:
☐ Hemivertebra: 0, 0, 0, 0.4% at 0, 15, 75, 250 mg/kg bw/d.
☐ Unfused thoracic centra: 0.7, 0.5, 0.9, 1.6% at 0, 15, 75, 250 mg/kg bw/d.

Moreover, in the „Phase II" experiment the occurrence of „unfused sternebrae" was increased: 0.5, 2.1% at 0, 250 mg/kg bw/d. And in the teratogenicity study in rabbits (dRAR B.6.6.2, 1990), „atlas, fused" was observed (N° fetuses (N° litters)): 0 (0), 0 (0), 1 (1), 2 (2) at 0, 50, 110, 250 mg/kg bw/d. These findings together may indicate that the developing skeletal system constitutes a target for Clopyralid. This would support its classification as developmental toxicant.

However, there are also observations which would rather contradict a classification for developmental toxicity:
☐ Polydactyly occurred in fetuses from the same litter and was not distributed over different litters;
☐ Polydactyly was not observed in the offspring of a 2-generation study in F344 rats treated with Clopyralid via the diet at even higher concentrations (0, 82.5, 275, 825 mg/kg bw/d) and with two matings in each generation (dRAR B.6.6.1, 1983). (We assume that polydactyly would have been discovered as external alteration.)

Ad 2)
In the high-dose group (250 mg/kg bw/d), 32% of the dams (11/34 animals) were moribund or found dead. Almost half of these cases (5/11 animals) were attributed to preceding intubation errors. Without these cases, maternal mortality still accounted for 21% (6/29 animals). According to CLP Regulation 3.7.2.4.4. one may conclude that due to the excessive maternal mortality rate (i.e. >10%) fetal findings from the high-dose group should be disregarded as a whole. This option has not been broached by the

Dossier Submitter in the CLH report.

However, CLP Regulation 3.7.2.4.4. also states that „an increased incidence of mortality among the treated dams over the controls shall be considered evidence of maternal toxicity if the increase occurs in a dose-related manner and can be attributed to the systemic toxicity of the test material." In this regard the Dossier Submitter concluded that rabbit lethalities were caused by the irritative nature of Clopyralid on the stomach mucosa (see CLH report 10.13.2, p.65). Hence, mortality in dams was attributed to the local toxicity of the test substance.
It will be interesting to hear from the upcoming discussions if it makes a crucial difference whether the dams died through systemic or local toxic effects and thus whether fetal findings at maternal mortality rates >10% can be considered for classification at all.

Conclusion:
There is some data which could justify a classification for Repr. 2 (H361d) but there are also considerations which could argue against a classification. It will be interesting to hear how RAC will balance pros and cons in the upcoming discussions.

Dossier Submitter's Response

Ad 1:
Oral teratogenicity study in F-344 rats:
Phase 1 maternal body weight (g) on gestation day from control to high dose (0, 15, 75, 250 mg/kg, corresponding number of dams: 29 22 25 26):

GD 6 203±8 199±6 199±7 201±8
GD 10 211±9 208±7 206±9 204±11c
GD16 231±11 229±8 226±11 219±11c
GD21 268±18 267±14 261±20 257±16

Maternal body weight gain (g)
GD 6-9 8±6 9±3 7±5 2±7c
GD 10-15 20±4 21±4 19±6 15±9c
GD16-20 37±10 38±8 36±11 38±10
Total 6-20 65±16 67±12 62±17 56±14

Maternal liver weight on gestation day 21 ((0, 15, 75, 250 mg/kg)
Absolute 10.45±0.86 10.36±0.94 9.84±0.89c 9.67±0.80c
Relatived 3.91:0.28 3.89:1:0.29 3.77±0.24 3.77±0.2

c = Significantly different from the control value by Dunnett's Test, $p<0.05$

Similar values were seen in the phase 2 of the study.

Ad 2: Examination of the fetuses from rabbits in the 25Omg/kg/ day dose group revealed evidence of fetotoxicity and teratogenicity. However, administration of clopyralid at this dose level also produced severe maternal toxicity. Maternal body weight gain at 250 mg/kg/ day was also significantly depressed during the treatment period, and maternal body weight was significantly lower at the end of treatment. As Germany states, this will significantly lower the value of the developmental findings at this dose level. Because hydrocephaly occurred only in pups from dams exhibiting severe weight loss, this may have been secondary to the severe maternal stress. Regardless, the authors of the study could not rule out the possibility of a direct effect of clopyralid.

RAC's response
Noted.

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Denmark	Corteva Agriscience International Sàrl	Company-Manufacturer	5
Comment received				
Corteva Agriscience have no comments. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Corteva comments CLH report clopyralid dec2022.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Corteva position on the proposed R2 classification_final dec2022.pdf				
Dossier Submitter's Response				
Thank you, noted.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Denmark	Corteva Agriscience International Sàrl	Company-Manufacturer	6
Comment received				
Corteva Agriscience disagree with the conclusion on classification and labelling for STOT RE, point 10.13.3 in the CLH report (p. 65). Please find our comment in enclosed position paper "Corteva position on STOT RE proposal_final dec2022.pdf". ECHA note – An attachment was submitted with the comment above. Refer to public attachment Corteva comments CLH report clopyralid dec2022.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Corteva position on the proposed R2 classification_final dec2022.pdf				
Dossier Submitter's Response				
Thank you for your comments. We agree that the evidence strongly points toward a local irritative/corrosive effect on the stomach as a cause of lethality both in the rabbit and the rat. Unfortunately, the reporting of the rat gavage study is very poor: no necropsy procedures or findings are reported, it is only stated that the cause of death could not be ascertained upon gross pathologic examination. Therefore, we decided to propose classification of clopyralid for STOT RE 2 based on lethality in the rat. RAC should carefully consider whether this classification is warranted or is there sufficient certainty for a local irritant effect as a cause of lethality.				
RAC's response				
The study on the rats with respect to lethality in the rats was finally not indicated as the key study (marked as "acceptable") by the DS, but as "supportive". Instead, the study on rabbits concerning lethality after short term oral gavage and considered as "acceptable" is giving the same classification conclusion (STOT RE 2). Nevertheless, RAC considers all the eight oral dietary studies in its weight of evidence assessment. RAC concludes that				

clopyralid does not warrant classification as STOT RE.

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Germany		MemberState	7
Comment received				
The proposed classification as STOT RE 2 (H373) is in line with the recommendations of the conclusions of the EU peer review process under PPPR. However, in both species (rat and rabbit), the reported effects (concerning erosions and ulcers in the stomach mucosa as well as lethality) could perhaps be attributed to an irritant effect, rather than toxicity after repeated administration. If the critical effects can be identified as secondary to GI lesions with sufficient certainty, we would prefer classifying and labelling for the local effect.				
Dossier Submitter's Response				
Thank you for your comments. We agree that the evidence strongly points toward a local irritative/corrosive effect on the stomach as a cause of lethality both in the rabbit and the rat. Unfortunately, the reporting of the rat gavage study is very poor: no necropsy procedures or findings are reported, it is only stated that cause of death could not be ascertained upon gross pathologic examination. Therefore, we decided to propose classification of clopyralid for STOT RE 2 based on lethality in the rat. RAC should carefully consider whether this classification is warranted or is there sufficient certainty for a local irritant effect as a cause of lethality.				
RAC's response				
RAC includes eight oral dietary studies in its weight of evidence assessment, and concludes that clopyralid does not warrant classification as STOT RE.				

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Germany		MemberState	8
Comment received				
We agree with the proposed classification. Remark: in 11.1.1 (Ready biodegradability) a pass level of 60% of the theoretical value after 28 is given, whereas in 11.1.5 (Conclusion on rapid degradability) a pass level >70 % mineralisation after 10 days is given for the ready biodegradation study (OECD TG 301B – Modified Strum Test).				
Dossier Submitter's Response				
Thank you for your support and comment. Indeed, there are mistakes in the sections. A pass level for the $ThCO^2$ should be 60%, which have to be reached in a 10-d window within the 28-d period of the test.				
RAC's response				
Thank you for your comment. The support of DS proposal for classification of the substance as Aquatic Chronic 1, M-factor=10 is noted by RAC. RAC agrees. Mistakes are noted.				

Date	Country	Organisation	Type of Organisation	Comment number
16.12.2022	Denmark	Corteva Agriscience International Sàrl	Company-Manufacturer	9
Comment received				
Corteva Agriscience have no comments. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Corteva comments CLH report clopyralid dec2022.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment Corteva position on the proposed R2 classification_final dec2022.pdf				
Dossier Submitter's Response				
Thank you.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
15.12.2022	France		MemberState	10
Comment received				
Environmental hazards: FR agrees with the assessment and the approach performed by FI to reach the following hazard class and category for Clopyralid: Aquatic Chronic Hazard Category 1, M-factor = 10.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
Thank you for your comment. The support of DS proposal for classification of the substance as Aquatic Chronic 1, M-factor = 10 is noted by RAC. RAC agrees.				

Date	Country	Organisation	Type of Organisation	Comment number
12.12.2022	United Kingdom	Health and Safety Executive	National Authority	11
Comment received				
clopyralid (CAS: 1702-17-6) We note that a toxicity to Lemna gibba study is available. While the study and presented endpoints are based on 14-days duration, please can you confirm if preferred 7-day endpoints are available or able to be calculated? We note that 7-day study controls should also be considered against relevant test method criteria .				
Dossier Submitter's Response				
Thank you for your comment. 7-day endpoints were not available in the study. However, the study report included mean values for fronds and plants on day 6 and 9, so we calculated endpoints for those days using the same method as for the 14-day endpoints (linear regression, mean measured concentration) to get approximations of the 7-day toxicity:				

	Plants		Fronds	
	day 6	day 9	day 6	day 9
EC10 (mg/l)	24	19	23	19
EC50 (mg/l)	118	97	116	97

As the endpoints are based on mean values, we could not calculate confidence intervals nor do any additional statistical analysis with the results. The 7-day toxicity endpoints would be somewhere between the 6-day and 9-day endpoints.

The study fulfilled the validity criteria for OECD TG 221. The doubling time for frond number in the controls was < 2.5 for days 0 – 6 and 0 – 9.

Considering that the validity criteria is fulfilled, and the study is not the most critical regarding the classification, we consider that the presented endpoints are sufficient to show that *Lemna gibba* is not the most sensitive species for herbicide clopyralid.

(We noted that for day 14, the EC10 was not reported in the CLH-report. The 14-day EC10 was 17 (0-50) mg/l and 18 (0-43) mg/l for fronds and plants, respectively.)

RAC's response

Thank you for your comment. Noted.

PUBLIC ATTACHMENTS
1. Corteva comments CLH report clopyralid dec2022.zip [Please refer to comment No. 1, 3, 5, 6, 9]

CONFIDENTIAL ATTACHMENTS
1. Corteva position on the proposed R2 classification_final dec2022.pdf [Please refer to comment No. 1, 3, 5, 6, 9]