**Committee for Risk Assessment**

**RAC**

Annex 2

**Response to comments document (RCOM)**

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

# mecoprop-P (ISO) [1] and its salts; (R)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts

**EC Number: 240-539-0**
**CAS Number: 16484-77-8**

CLH-O-0000006713-73-01/F

**Adopted**

**20 September 2019**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON MECOPROP-P (ISO) [1] AND ITS SALTS; (R)-2-(4-CHLORO-2-METHYLPHENOXY)PROPIONIC ACID [1] AND ITS SALTS**

**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.

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**Substance name: mecoprop-P (ISO) [1] and its salts; (R)-2-(4-chloro-2-methylphenoxy)propionic acid [1] and its salts**
**EC number: 240-539-0**
**CAS number: 16484-77-8**
**Dossier submitter: United Kingdom**

**GENERAL COMMENTS**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Germany | | MemberState | 1 |
| Comment received | | | | |
| The German MSCA does not support the proposal of classification for environmental hazards as Aquatic chronic 3.<br>Concerning human health hazards, we agree with the proposed classification as Acute Tox. Cat. 4; H302. However it is unclear, why the CLH-Report does not mention the EFSA proposal for classification for developmental toxicity Category 2 (see specific comments). | | | | |
| Dossier Submitter's Response | | | | |
| Please see responses to individual comments. | | | | |
| RAC's response | | | | |
| Human health: see reponse to comment no 2 | | | | |

**TOXICITY TO REPRODUCTION**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Germany | | MemberState | 2 |
| Comment received | | | | |
| Pages 7 and 35<br>No classification is proposed by the dossier submitter for sexual function and fertility, development or effects on or via lactation. However, PPR meeting 151 proposed classification because of an increased incidence of late resorptions in the rabbit developmental toxicity study at 50 mg/kg bw/day. According to the EFSA conclusions on pesticides peer review (EFSA Journal 2017;15(5):4832) "mecoprop-p is proposed for classification for developmental toxicity Category 2 H361….". The dossier submitter did not mention this EFSA proposal. | | | | |

Page 30
In the rat developmental toxicity study an increased incidence of rudimentary cervical ribs was observed in the highest dose group. At the same dose level significantly lower body weight gain was seen. These observations are in line with the EFSA conclusions.

Page 20
technical comment: It is reported on page 20 on results in dose group 500 ppm that "…the viability index of this group was significantly reduced ($p<0.01$)". However, in the table on this page the results of viability index were not marked as significantly changed.

Dossier Submitter's Response

Thank you for your comments.

In Section 3 (p8) of the CLH report, it states the following:

"During the Annex I renewal process in 2017, a concern for developmental toxicity was raised at the Pesticides Peer Review Meeting. The experts proposed classification with Repr. 2; H361d based on increased late resorptions in the rabbit."

We did not feel it necessary to mention the EFSA proposal again, as we consider the CLH report to be an independent assessment of the data.

In Section 10.10.4 (p16) of the CLH report, it states the following:*Although the increased number of* late *resorptions in the rabbit at the top dose was statistically significant, the mean number of* total *resorptions per rabbit at the top dose (1.0) was close to the number in controls (0.8), indicating that the biological relevance of the increased late resorptions may be questionable. Furthermore, since there was only a minor and non-statistically significant decrease in the number of live foetuses per rabbit at the top dose compared to controls, the increased number of late resorptions is probably a statistical anomaly rather than a toxicologically significant change. Given the large variability in the values of measured parameters in this study, none of the results are considered to present evidence of a significant adverse toxicological effect.*
Also the mean number of total resorptions per rabbit in the top dose was within the historical control range presented in the report (from 329 time mated females the range of total resportions was 0.2 to 1.3).

With regards the increased incidence of rudimentary cervical ribs at the highest dose in the rat developmental toxicity study, we consider this finding to be treatment-related but of low concern. This is consistent with the ECETOC guidance, which regards cervical ribs as variations (rather than malformations) of low concern. The cervical ribs were observed in the presence of maternal toxicity, i.e., significantly lower body weight gain. In our opinion, an increased incidence of a variation of low concern, in the presence of maternal toxicity, is not sufficient for classification in Category 2.

*ECETOC Monograph No. 31 (2002) European Centre for Ecotoxicology and Toxicology of Chemicals, 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.*

Thank you for pointing out the typo on p20. This result should indeed have been flagged as significant in the table.

| RAC's response |
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| No classification vs Repr. 2 for development has been discussed by RAC. Overall, the available studies are equivocal for the assessment of adverse effects of mecoprop-P on development and RAC is of the opinion that no classification for effects on development is warranted. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 09.11.2018 | United Kingdom | | Individual | 3 |
| Comment received | | | | |
| Additional information was supplied to the RMS by the applicant (Nufarm) but this was after the first assessment. Attached is a word document where the text in grey is to be added to the CLH report on page 23 onwards. Attached is this annotated on the CLH report. Subsequent table number will have to therefore change. No impact for assessment just additional information for completeness<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Mecoprop-p_CLH Report_Comments from Nufarm.zip | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for this additional analysis, which supports our proposal for no classification for reproductive effects. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Denmark | | MemberState | 4 |
| Comment received | | | | |
| The reproductive studies available are old and do not include sensitive end-points for reproduction. For instance in the 2-generation study in rats (Hellwig, 1992) no histological examination of the female reproductive organs. Sperm parameters and oestrus cycle length, vaginal opening, preputial separation, anogenital distance and number of implantation sites were not determined in this study. Only the liver, kidney and testes were weighed. The weight of the uterus, ovary, epididymis, prostate, brain, thymus adrenals, spleen and pituitary were not determined. However, some histological information is available on these organs were determined in the short term toxicity studies. On the other hand the exposure timing is not the same. The other generation study is only one-generation and a dose range study which means less animals per dose group and the historical control data were not acceptable. Hence, the two studies cannot stand alone but should be considered in combination.<br><br>In the Rabbit developmental study (Hellwig 1993b) late resorptions were statistical significant higher in the 50 mg/kg bw/d group with no maternal tox present. It should be considered if this effect is sufficient for classification. The effect was observed in five different litters. In addition, there is a trend for reduced No. of live foetuses/rabbit, though not statistical significant. This could be considered together with the increased late resorptions. | | | | |

| Dossier Submitter's Response |
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| Thank you for your comments. In the short term toxicity studies, no adverse effects were reported in the reproductive organs. In the longer term repeated dose studies, the following histological effects were observed:<br><br>1 year study in dogs (Anonymous, 1997b): Slight focal atrophy of the prostate gland was observed in one male in each of the low, mid and high dose groups. In the absence of a dose-response relationship, this is not considered to be a treatment-related effect. At the top dose, cystic corpora lutea were observed in 3 females. This finding could be treatment-related, however on its own is not sufficient to trigger classification for reproductive toxicity.<br><br>With regards the rabbit developmental study, the apparent increase in the number of late resorptions is probably a statistical anomaly rather than a toxicologically significant change. Indeed, generally there was large variability in the values of the measured parameters in this study, and in our opinion, the results do not provide convincing evidence for an adverse toxicological effect. Therefore, classification is not supported. |
| RAC's response |
| See reponse to comment no 2 |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.12.2018 | France | | MemberState | 5 |
| Comment received | | | | |
| The NOAEL values reported in the CLH report are the RMS proposals. Some NOAEL values agreed during the peer review of the pesticide risk assessment of the active substance mecoprop-P (EFSA Journal 2017;15(5):4832) and its related List of End-Points were different.<br>In the 2-generation study (Table 12), the Parental NOAEL agreed during the peer-review 500 ppm (40 mg/kg bw/d) since the slight effect observed on kidney weight was not considered adverse. Since the Offspring NOAEL was set at 100 ppm (8 mg/kg bw/d) based on increased pup mortality on days 0 to 4 post-partum and reduction in pup body weight gain (11%) sensitivity difference is observed in young rats compared to parent.<br>As regard Reproductive NOAEL, no effect was observed in the 2-generation while in the 1-generation study a statistically significant, dose-related reduction in the mean numbers of implantation from 500 ppm onwards. As this parameter was not investigated in the 2-generation study, an overall reproductive NOAEL of 100 ppm is proposed (8 mg/kg bw/d).<br><br>In the developmental toxicity in rabbit performed with mecoprop-P: the developmental NOAEL agreed during the peer review was 20 mg/kg bw per day based on the effect on late resorptions. While the maternal NOAEL was the 50 mg/kg bw per day in the absence of maternal toxicity.<br><br>Comparison with the CLP criteria for developmental toxicity page 33<br><br>- Higher frequency of skeletal anomalies (strong increase in rudimentary cervical ribs and delayed sternebral ossification) in the presence of maternal toxicity.<br>- Increased fetal mortality (late resorption) observed in rabbit in the absence of maternal toxicity.<br>- Increased perinatal mortality in the 2-generation in the absence of maternal toxicity | | | | |

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| Taking into account the above-mentioned considerations, FR is of the opinion that mecoprop-P warrants classification for reprotoxicity Repr. Cat 2 H361d. |
| Dossier Submitter's Response |
| Thank you for providing updated NOAELs. As classification is not based on the NOAEL values, they are provided in the CLH report for information only.<br><br>We do not think there is sufficient evidence of an adverse effect to classify in Repr Cat 2 H361d. |
| RAC's response |
| See reponse to comment no 2 |

**OTHER HAZARDS AND ENDPOINTS – Acute Toxicity**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.12.2018 | France | | MemberState | 6 |
| Comment received | | | | |
| Acute toxicity - oral route<br>The proposal for classification Acute Toxicity (oral) Category 4; H302 is agreed upon. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Denmark | | MemberState | 7 |
| Comment received | | | | |
| We agree with the proposed ATE for oral acute toxicity of 431 mg/kg bw as it corresponds to the oral LD50. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Germany | | MemberState | 8 |
| Comment received | | | | |
| Pages 36-63<br>Agreement with the proposal that no classification is appropriate for Specific target organ toxicity – repeated exposure. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |

| RAC's response |
|---|
| Noted. |

**OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 07.12.2018 | Germany | | MemberState | 9 |

| Comment received |
|---|
| Page 83, Point 11.7 comparison with the CLP-criteria:<br>Actually, it is shown that aquatic plants are the most sensitive species in comparison with the organisms of the other trophic levels and algae.<br>The results of two studies with the formulation Mecoprop-P K 600 g/l shows high acute and chronic toxicity especially for Myriophyllum spicatum. (Gonsior, 2015 and Seeland-Fremer, 2015).<br>Unfortunately, there are no study results for pure Mecoprop-P with Myriophyllum spicatum available. Because of the herbicidal activity and the mode of action of Mecoprop-P the toxicity for aquatic macrophytes (Myriophyllum spicatum) should be determined for classification and labelling. |
| Dossier Submitter's Response |
| The CLH report (sections 11.5 and 11.6) notes that *Myriophyllum spicatum* appears to be more sensitive than other acute and chronic endpoints based on formulation data. However, as also noted the tested formulation includes co-formulants in addition to water. The concentrations and impact of these substances in the studies is not clear. For example one co-formulant has an environmental self-classification (Aquatic Chronic 2 and 4) and the ecotoxicity to *Myriophyllum spicatum* is unknown.<br><br>The CLH reports notes that the difference between hazard classification using the formulation data (Aquatic Acute 1, M=10, Aquatic Chronic 1, M=10) is markedly different to hazard classification based on data (*Lemna*) using the active ingredient (Aquatic Chronic 3). However, it is not straightforward to compare the formulation data to hazard classification criteria given the above uncertainties. On this basis, at present the hazard classification proposal is based on ecotoxicity data using the active ingredient.<br><br>Should ecotoxicity testing using the active ingredient and additional aquatic plants such as *Myriophyllum spicatum* become available in the future, the classification should be reassessed. |
| RAC's response |
| Agree<br>We could also notice that the trophic level triggerring the aquatic chronic self-classification of the co-formulant is not known in the dossier. Algae might be the most sensitive species that, in this case, could reinforce the argument on a potential effect of this compound toward *Myriophyllum*<br>In the PEER Review of EFSA Appendix A (https://efsa.onlinelibrary.wiley.com/doi/full/10.2903/j.efsa.2017.4832), several studies performed with Mecoprop-P K 600 g/l were quoted. Compared with the toxicity study results obtained with mecoprop-P, no significant difference was observed with the toxicity of Mecoprop-P K 600 g/l towards fish and invertebrates. For algae and duckweeds, these data were presented: |

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|---|---|---|---|---|
| *P.subcapitata* | a.s. | 72 h (static) | Growth rate: $E_rC_{50}$<br><br>($E_rC_{10}$)<br><br>[Biomass: $E_bC_{50}$<br>($E_bC_{10}$) | >729 mg a.s./L (nom)<br>145 mg a.s./L<br>270 mg a.s./L (nom)<br>35 mg a.s./L |
| *P.subcapitata* | Mecoprop-P K 600 g/L | 72 h (static) | Growth rate $E_rC_{50}$<br><br>$E_rC_{10}$<br>$E_rC_{20}$<br>(NOEC)<br><br>[Biomass $E_bC_{50}$<br><br>$E_bC_{10}$<br>$E_bC_{20}$<br>(NOEC) | >100 mg form./L (>58.7 mg a.s./$L_{(nom)}$)<br>>100 mg form./L<br>>100 mg form./L<br>12.5 mg form./L<br>>100 mg form./L (>58.7 mg a.s./$L_{(nom)}$)<br>19 mg form./L<br>38 mg form./L<br>12.5 mg form./L |
| *L.gibba* | a.s. | 14 d (semi-static) | Fronds number, $EC_{50}$ (NOEC) | 1.6 mg a.s./L (mm)<br><0.53 mg a.s./L |
| *L.gibba* | Mecoprop-P K 600 g/L | 7 d (static) | Frond number,<br>$E_rC_{50}$<br>$E_rC_{10}$<br>$E_rC_{20}$<br>(NOEC)<br>Frond number,<br>$E_bC_{50}$<br>$E_bC_{10}$<br>$E_bC_{20}$<br>(NOEC) | 59 mg form./L (34.7 mg a.s./L (nom))<br>1.9 mg form.L<br>6.2 mg form./L<br>1.0 mg prep./L<br>11 mg form./L (6.46 mg a.s./L (nom))<br>0.61 mg form./L<br>1.6 mg form./L<br>0.32 mg form.L |

For *P.subcapitata,* both results were in the same range. For *Lemna gibba*, as the exposure periods were different, it is difficult to conclude.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 04.12.2018 | France | | MemberState | 10 |
| Comment received | | | | |
| We agree with the classification proposal regarding environmental hazard. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your support. | | | | |
| RAC's response | | | | |
| Noted | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.12.2018 | Finland | | MemberState | 11 |
| Comment received | | | | |
| FI CA supports the eMSCA conclusion on the substance being rapidly degradable and having a low bioaccumulation potential for the purposes of classification. Several acute and chronic aquatic toxicity data are available for all three trophic levels. From the available aquatic toxicity data, aquatic macrophytes form the most sensitive trophic | | | | |

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| group. As mecoprop-P is an herbicide, the results from tests with aquatic plants should be taken into account and the classification should be based on the studies resulting in the most stringent outcome.<br><br>However, FI CA shares the eMSCA's concern of basing the classification on the data from Myriophyllum spicatum growth inhibition tests (OECD 239) conducted with a formulation including co-formulants as these substances might have contributed to the toxicity observed. Therefore, this data is not appropriate to be used for hazard classification. Instead, Lemna sp. growth inhibition test (FIFRA 122-2 and 122-3) with Lemna gibba should be used as the key study. According to the study, the chronic toxicity 6 and 9 day ErC10 values for mecoprop-P and its salts are in the range of 0,1-1,0 mg/l; thus, resulting in classification of Aquatic Chronic 3 for a rapidly degradable substance.<br><br>Based on the information available in the stand-alone CLH report and the classification criteria, FI CA supports the proposed classification of Aquatic Chronic 3, H412 for mecoprop-P and its salts. |
| Dossier Submitter's Response |
| Thank you for the comments and support. |
| RAC's response |
| Noted |

PUBLIC ATTACHMENTS
1. Mecoprop-p_CLH Report_Comments from Nufarm.zip [Please refer to comment No. 3]