**Committee for Risk Assessment**

**RAC**

Annex 2

**Response to comments document (RCOM)**

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

# benalaxyl (ISO); methyl *N*-(2,6-dimethylphenyl)-*N*-(phenylacetyl)-*DL*-alaninate

**EC Number: 275-728-7**
**CAS Number: 71626-11-4**

CLH-O-0000007053-82-01/F

**Adopted**

**26 November 2021**

**ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BENALAXYL (ISO); METHYL *N*-(2,6-DIMETHYLPHENYL)-*N*-(PHENYLACETYL)-*DL*-ALANINATE**

## 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: benalaxyl (ISO); methyl *N*-(2,6-dimethylphenyl)-*N*-(phenylacetyl)-*DL*-alaninate**
**EC number: 275-728-7**
**CAS number: 71626-11-4**
**Dossier submitter: Romania**

### GENERAL COMMENTS

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 1 |
| Comment received | | | | |
| The DS has proposed harmonised classification and labelling for benalaxyl in accordance with the CLP criteria. FMC submits the following comments in response to this proposal during this commenting period.<br>The complete context of FMC's comments are contained in the file accompanying this submission. The file contains tables of tumor incidences relevant to the proposed carcinogenicity classification that would not copy properly into the comment boxes below.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comments. | | | | |
| RAC's response | | | | |
| Thank you, noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 29.01.2021 | Germany | | Member State | 2 |
| Comment received | | | | |
| It is noted that the dossier submitters should review the CLH report regarding both technical (such as incorrect or contradictory information on dosing or study descriptions) | | | | |

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| and editorial issues.<br><br>Mutagenicity:<br>We would like to point out that all studies on mutagenicity in vivo (micronucleus studies) were performed with i.p. application of benalaxyl. Therefore, the biotransformation of the test substance is not adequately considered. This is of particular importance as genotoxicity was observed in one MLA study after metabolic activation. However, we agree that the available data do not trigger classification with regard to germ cell mutagenicity. |
| Dossier Submitter's Response |
| Thank you for your comment. A classification as genotoxicity is not appropriate for benalaxyl. |
| RAC's response |
| The key information in the health hazard part has been checked in full study reports or in the RAR.<br>Germ cell mutagenicity was not open for consultation and has not been evaluated by RAC. The genotoxicity data are only presented as supporting information for carcinogenicity assessment. |

**CARCINOGENICITY**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 3 |
| Comment received | | | | |
| The DS has proposed to classify benalaxyl as Car. 2, H351, suspected human carcinogen based on the occurrence of a low incidence of astrocytoma in the males in the 2-year rat study. FMC disagrees that benalaxyl meets the classification criteria for carcinogenicity.<br><br>The DS stated the following:<br>"astrocytoma was considered the most critical effect, and no HCD were available for the performing laboratory and that according to the literature, astrocytoma is a rare tumour in Sprague Dawley rats. In such cases the CLP guidance suggests a comparison with the historical control data. As discussed above, the observed incidence in malignancy is just a fact without a presence of performing laboratory historical data. Also, it is unclear whether the stated HC data for the Dossier studies include the results of the different periods of time. Therefore, comparison with the historical control is not considered conclusive. The data set from the Applicant Dossier, of those older historical controls (from 1977 to 1979) which were not reliable on, due to the lack of information about the protocol/techniques of preservation/microscopic examination as well as time of sacrifice of surviving animals. The large frequency and distribution in all mice groups from the studies, higher incidence in males than in female and the high mortality concluded a treatment related".<br><br>In addition, the DS stated that there were "19 neoplasms from 65 rats in a lifetime oral dosing studies in rats combined oncogenicity and chronic toxicity. Dose level of 100 ppm (4.42/5.64 mg/kg bw per day for male and female, respectively) is general available for the tumour's occurrence in both sexes, with an increased incidence at 1000 ppm in | | | | |

males. Benalaxyl is a chemical substance which induce tumours, increase tumour incidence and/or malignancy or shorten the time to tumour occurrence."

FMC disagrees with the assessment conducted by the DS.

The 19 neoplasms pointed out by the DS are a sum of all types of neoplasms observed in treated and untreated groups combining both males and females. Overall, there is no treatment-related increased incidence in neither males nor females (see Tables 1&2 in attached file). No statistical significance was found. All the incidences have been excluded as treatment related.

The DS considered astrocytoma noted in male rats to be the most critical effect. However, astrocytoma is known to be a spontaneous brain tumor with high incidence in SD rats. In this study, no incidence of astrocytoma was found in the females, and the incidences in the males were 3.7% (2 cases) in the 1000ppm high dose group, 1.9% (1 case) and 1.8% (1 case) in the low and mid- dose groups. These incidences are comparable to reported spontaneous incidence rates in SD rats (HCD provided below). Therefore, these tumors are unrelated to treatment.

The performing laboratory at which the 2-year rat study was conducted no longer exists. Thus, being unable to obtain further HCD from the performing laboratory, FMC has collected HCD from publicly available sources for the same strain of rats covering the period when the study was performed. These publications clearly conclude that astrocytoma is spontaneous in nature, particularly in SD rats (occurring in control animals up to ~ 7%). The incidences of astrocytoma in the 2-year rat study are within the range of HCD from all the sources.

In addition, HCD shows that the incidences of astrocytoma in male and female rats are comparable. In this 2-year rat study, the incidence in the females is zero. When males and females are considered together, there is no increased incidence of astrocytoma overall.

The following two tables are contained in the attached file which show a lack of a treatment related effect of benalaxyl on tumor incidences in rats.
Table 1. Data of all neoplasms in males of benalaxyl 2-year rat study
Table 2. All neoplasms in females of benalaxyl 2-year rat study

HCD for astrocytoma from publicly available sources are provided here. Tables containing the relevant tumor incidences are contained in the submitted file.

A. Giknis and Clifford (2004): Compilation of Spontaneous Neoplastic Lesions and Survival in Crl:CD (SD) Rats from Control Groups, Charles River Laboratories
https://www.criver.com/sites/default/files/resources/CompilationofSpontaneousNeoplasticLesionsandSurvivalinCrlCD%C2%AESDRatsFromControlGroupsMarch2013.pdf
This compilation of spontaneous neoplastic lesions shows that astrocytoma was found in the control groups of 50% of the studies, and the spontaneous incidence rate was up to 4.29%. Data were collected from 1989 to 2002.

B. Nagatani (2013): Occurrence of Spontaneous Tumors in the Central Nervous System (CNS) of F344 and SD Rats, J Toxicol. Pathol., 26(3): 263-273
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3787604/

This publication shows the incidence for astrocytoma in the males is up to 6.7%.

C. Bertrand (2014): Incidence of Spontaneous Central Nervous System Tumors in CD-1 Mice and Sprague-Dawley, Han-Wistar, and Wistar Rats Used in Carcinogenicity Studies, Toxicologic Pathology, 42:1168-1173
https://journals.sagepub.com/doi/pdf/10.1177/0192623313518114
In this paper, it is stated that malignant astrocytoma is a predominant spontaneous tumor type in SD rats. The table below shows the average incidence for malignant astrocytoma, which was up to 1.49%. There was no data on individual studies, therefore no range of incidences reported. However, since the total number of malignant astrocytoma in the males is 5 in 4 studies, indicating at least two cases in one of the studies, the incidence was comparable to that of the 2-year rat study with benalaxyl.

D. Baldrick (2005): Carcinogenicity Evaluation: Comparison of Tumor Data from Dual Control Groups in the Sprague–Dawley Rat, Toxicologic Pathology 33:283 291
https://journals.sagepub.com/doi/pdf/10.1080/019262390908371
This study summarizes results of 13 rat carcinogenicity studies, performed between 1991 and 2002, each with 2 control groups and shows a high spontaneous incidence of astrocytoma in both control groups, 4% and 5% respectively.

E. Gopinath (1986): Spontaneous brain tumors in Sprague-Dawley rats, Food Chem. Toxic. Vol. 24, No. 2, pp. 113-120
https://www.sciencedirect.com/science/article/abs/pii/0278691586903455
In this paper, it is stated that astrocytoma is the most common brain tumor in rats. The incidence range observed among the studies varied from 0/100 to 3/60 in male and 0/100 to 2/50 in female rats, which is up to 5% in males and 4% in females. In addition, the ages at death of rats bearing astrocytoma were recorded and the distribution showed that astrocytoma is a lesion of older rats. In the 2-year study with benalaxyl, the 4 male rats with astrocytoma were animals that survived to the end of the study.

F. Solleveld, et al. (1986) Brain Tumors in Man and Animals: Report of a Workshop, Environmental Health Perspectives Vol.68, pp. 155-173
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1474266/pdf/envhper00439-0150.pdf
The publication summarizes the outcome of a National Toxicology Program conference that reported the incidence of astrocytoma in female SD rats at 1.3%. No information on male SD rats was provided. It was stated that brain tumors in rats are much than more common than in mice. Data derived from lifetime studies show incidences of brain tumors up to 7.1% in Wistar AF/Han-EMD rats.

FMC agrees with the DS that the urinary bladder tumors found in 3 high dose males in the mouse oncogenicity study are not relevant to human health risk assessment. The 3 urinary bladder tumors were first considered as "transitional cell carcinoma" by the study pathologist, but a subsequent pathology working group (PWG) determined that the correct diagnosis was "submucosal mesenchymal tumour", a lesion of non-epithelial origin, unique to the mouse urinary bladder and with no counterpart in any other species including humans. Therefore, these tumors were considered irrelevant to human risk assessment.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf

| Dossier Submitter's Response |
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| The Dossier Submitter have assessed the data on Applicant's dossier considering as a large occurrence of the different kind of tumours and non-neoplasic tumours on many organs and tissues which are responsible for a classification as Carc 2. |
| RAC's response |
| Thank you for your comment and for the published historical control data on astrocytoma. None of this historical control information is directly relevant because the data come from other laboratories and were conducted beyond the 5-year time window (except for Gopinath, 1986). On the other hand, the supplier was the same (Charles River, although from different locations) and the data are quite consistent. Therefore, they have been taken into account to a limited extent.<br>The incidence of malignant astrocytoma in benalaxyl-treated male rats was 0, 1, 1, and 2 in the control, low, mid and high dose group respectively. 1 astrocytoma per group is well within the spontaneous background incidence. The incidence of 2 at the top dose may slightly exceed the normal background, but the increase is not statistically significant on a pairwise comparison, the dose-response relationship is not particularly strong, and the incidence lies within the broader (although less relevant) HCD range. RAC concluded that there is insufficient evidence of a treatment-related increase in brain tumours in rats. However, the top dose of 1000 ppm in the rat carcinogenicity study appears to be considerably below the MTD (no general toxicity; the 90-day studies testing up to 10,000 ppm without severe toxicity suggest that doses higher than 1000 ppm would have been tolerated in a long-term study). Therefore, no classification is based on inconclusive data. |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 29.01.2021 | Germany | | Member State | 4 |
| Comment received | | | | |
| The classification as Carc. 2, H351 based on the occurrence of astrocytomas in rats is supported and is in line with the current EFSA conclusion on benalaxyl (EFSA Journal 2020;18(1):5985). However, it is not clear which tumours were considered by the Dossier Submitter for Carc. 2 classification in the CLH dossier. We suggest a more detailed, specific overview of the findings considered for classification including a WoE analysis. | | | | |
| Dossier Submitter's Response | | | | |
| An WoE is difficult to be made based on the data provided by applicant but a classification as a Carc 2 is definitely clear based on occurrence of astrocytomas in rats. | | | | |
| RAC's response | | | | |
| The RAC assessment represents an independent evaluation based on full study reports. RAC agreed on no classification based on inconclusive data. For details please see response to comment 3. | | | | |

## OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 5 |
| Comment received | | | | |
| Based on the available data (ATE ~ 2000mg/kg), FMC agrees with the proposal that benalaxyl be classified for acute oral toxicity (Acute Tox Category 4, H302).<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf | | | | |
| Dossier Submitter's Response | | | | |
| Thank you! | | | | |
| RAC's response | | | | |
| Thank you. RAC agreed on Acute Tox. 4; H302 with an ATE of 1000 mg/kg bw based on mortality in female rats in the acute neurotoxicity studies. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 29.01.2021 | Germany | | Member State | 6 |
| Comment received | | | | |
| Double classification as Acute Tox. 4 and STOT SE2 is not supported - Benalaxyl should be classified either Acute Tox. 4 or STOT SE 2.<br>The reliability of a general lethal effect of benalaxyl, as reported in the range-finding acute neurotoxicity study, is debateable given that this effect was only seen in this study and not in any other, most notably the acute toxicity studies specifically designed to assess this endpoint. To be clear, we do not question a toxic effect (hence our support for STOT SE2 classification, see below), rather the lethality.<br>According to Chapter R.7a, Section R.7.4.3 of the ECHA´s Guidance on Information Requirements and Chemical Safety Assessment, it is stated that, in general "information on acute toxicity, as detailed below, can be obtained from a variety of sources including unpublished studies, databases and publications such as books, scientific journals, criteria documents, monographs and other publications". However, in section R.7.4.3.1.2 relating to testing data on acute toxicity, OECD TG 424 (acute neurotox) is not listed, rather it is listed in section R.7.5.3.1.2 relating to testing data on repeated dose toxicity. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comment. | | | | |
| RAC's response | | | | |
| Thank you for your comments. A double classification should indeed be avoided. RAC agreed on Acute Tox. 4; H302 with an ATE of 1000 mg/kg bw based on mortality in female rats in the acute neurotoxicity studies, and on no classification for STOT SE.<br>The acute neurotoxicity studies were not standard acute toxicity studies, but still provide reliable information on acute toxicity of the substance, and therefore should be taken into account in the acute toxicity classification. Higher sensitivity of the animals in the | | | | |

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| neurotoxicity studies (compared to the standard acute toxicity study) does not invalidate the studies or the observations.<br>OECD TG 424 covers both acute and repeated dose studies. |

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

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 7 |
| Comment received | | | | |
| The DS proposed STOT-SE Category 2 for benalaxyl based on the acute neurotoxicity and range-finding acute neurotoxicity studies. It was stated in the CLH report that "Although clinical effects observed after short term exposure were without histopathological correlations and a high mortality in the acute toxicity study, presumably caused by the neurotoxic effects. According to the CLP criteria mortalities observed within 72 hours after the first treatment can be considered an acute effect."<br><br>FMC does not necessarily agree that the mortality observed in the acute neurotoxicity study is specifically due to neurotoxicity. Findings in the acute neurotoxicity study are inconsistent with results from other studies where benalaxyl was administered via oral gavage. Further, there is no evidence of neurotoxicity in a 90-day subchronic neurotoxicity study. However, based on clinical and behavioral findings in the acute neurotoxicity study, FMC agrees to the proposal to classify benalaxyl STOT-SE Category 2.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for comments. | | | | |
| RAC's response | | | | |
| Thank you for your comment. The acute neurotoxicity studies provide some indications of neurotoxicity at doses below those associated with mortality. However, these are not sufficiently consistent or adverse to warrant a STOT SE classification in addition to the proposed acute oral toxicity classification (double classification should be avoided). RAC agreed on Acute Tox. 4 (ATE 1000 mg/kg bw) and no classification for STOT SE. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 29.01.2021 | Germany | | Member State | 8 |
| Comment received | | | | |
| Classification of STOT SE, H371, is proposed based on neurotoxic effects in rats such as clonal convulsions and hind limb weakness observed 2-4 hours after oral administration of at least 400 mg/kg bw/d benalaxyl.<br>We consider this classification proposal to be critical. According to the criteria, classification as STOT SE should be based on non-lethal effects. This is the case here with the clonic convulsions. The authors report that in the acute toxicity studies, after | | | | |

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| administration of benalaxyl, clonic convulsions and death were observed in the experimental animals. In the report, it is not clear whether the death of the animals was a consequence of the convulsions or simply concomitant with the convulsions. If the animals died as a result of these convulsions, this effect is to be regarded as a lethal effect and the classification should be based on this, i.e. acute toxicity. The effect of inducing clonic convulsions does not justify the classification of two hazard classes.<br>The Guidance on the Application of the CLP Criteria states:<br>"There are two hazard classes for single exposure toxicity: 'Acute toxicity' and 'STOT-SE'. These are independent of each other and both may be assigned to a substance or a mixture if the respective criteria are met. Acute toxicity refers to lethality and STOT-SE to non-lethal effects. However, care should be taken not to assign both classes for the same toxic effect, essentially giving a 'double classification', even where the criteria for both classes are fulfilled. In such a case the most appropriate class should be assigned.<br>Acute toxicity classification is generally assigned on the basis of evident lethality (e.g. an LD50/LC50 value) or where the potential to cause lethality can be concluded from evident toxicity (e.g. from fixed dose procedure). STOT-SE should be considered where there is clear evidence of toxicity to a specific organ especially when it is observed in the absence of lethality."<br><br>A double classification for the same effect should be avoided here. |
| Dossier Submitter's Response |
| Thank you for the comment. |
| RAC's response |
| Thank you for your comment. Double classification should indeed be avoided.<br>An overview of mortality and convulsions in the acute neurotoxicity studies is provided below:<br>• 2000 mg/kg bw (drf study): 1 male found dead at approx. 2 h, clonic convulsions noted immediately prior to death; 1 female found dead at approx. 4.5 h, clonic convulsions noted from 1.5 h and also immediately prior to death; 1 female found dead at approx. 2 h, no convulsions; 2 females convulsions and euthanized at approx. 2 h<br>• 1000 mg/kg bw (main study): 1 male found dead at approx. 2 h, clonic convulsions; 1 male found dead at approx. 4.5 h, no significant clinical observations; 2 females found dead at approx. 4 h, clonic convulsions; 1 female clonic convulsions at approx. 3 h, survived<br>• 600 mg/kg bw (drf study): 1 male convulsions at approx. 2 h, survived<br>• 400 mg/kg bw (main study): 1 female euthanized *in extremis* (increased respiration, splayed hindlimbs, immobility)<br>• 200 mg/kg bw (main study): 1 female found dead at approx. 4 h, clonic convulsions<br>In several animals the death may have been a consequence of convulsions, 3 animals died without convulsions being noted. In general, convulsions were observed at doses associated with mortality, therefore they are considered to be covered by the acute toxicity classification. Subtle indications of neurotoxicity at lower doses are not consistent or not sufficiently severe to trigger classification. RAC agreed on no classification for STOT SE. |

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

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 9 |
| Comment received | | | | |
| FMC agrees with the conclusion to retain the classification and labelling of benalaxyl for environmental hazards – aquatic acute and chronic toxicity Category 4 (H400 and H410).<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comments.<br>We have noticed a typing error in *FMC Comments on Proposed Classification*,<br>p. 10**:** "FMC agrees with the conclusion to retain the classification and labelling of benalaxyl for environmental hazards – aquatic acute and chronic toxicity Category 4 (H400 and H410)".<br><br>Please replace **Category 4** by **Category 1.** | | | | |
| RAC's response | | | | |
| Noted. | | | | |

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 29.01.2021 | Germany | | Member State | 10 |
| Comment received | | | | |
| It is not entirely clear why the assessment of acute aquatic risk was based on the study CA 8.2.4.1/01, when the study was originally included in the DAR as supplementary information only. It would be helpful to add some further explanation why this study was identified as key study, despite the lack of chemical analysis. In any case, Table 24 should be amended: the EC50 from this study is not based on measured concentrations, but on nominal concentrations.<br><br>Further, we have noticed a typing error in chapter 11.1, p. 96: "Benalaxyl is stable to hydrolysis at pH 4 and 9;" Typing error: please replace 9 by 7. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comments. We agree with typo mistake.<br>Referring Table 24 data, DS considered the conclusion information regarding calculated value, as follows:<br>" The 48 hour $EC_{50}$ value for benalaxyl and *Daphnia magna* was calculated to be 0.59 mg/L" | | | | |
| RAC's response | | | | |
| Thank you for the comments. After reviewing the study RAC concluded it to be reliable for classification despite the lack of measured concentrations. The study was a screening | | | | |

study for the reproduction study and led to a workable choice of test concentrations in that. There are no physico-chemical properties known that would cause the test concentrations decline during the test. RAC also noted that the test results in the other Daphnia tests were over one order of magnitude higher than in this test. RAC noted that there was a difference in dose preparation technique between the test providing the lowest value and the other ones. Please see the opinion for further details.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United Kingdom | Health and Safety Executive | National Authority | 11 |

Comment received

benalaxyl (ISO); methyl N-phenylacetyl-N-2,6-xylyl-DL-alaninate (EC 275-728-7, CAS 71626-11-4

Aquatic Acute classification:

The key acute Daphnia magna endpoint for benalaxyl of 0.59 mg/L is based on a study (Anonymous, 1993) following OECD 202 Part I (1984) which was part of an OECD 202 Part II (1984) reproduction study. The acute part of the study did not include analytical verification.

A second reliable acute Daphnia magna study (Harris, 2014) including analytical verification reports a 48 hour EC50 value of 15 mg/L for benalaxyl technical.

All other acute toxicity endpoints that are considered reliable and relevant are above 1 mg/L.

We note that the 1993 study (without analytical verification) is likely to be considered less reliable for hazard classification without supporting information (as per CLP guidance (ECHA, 2017) on a case by case basis). Therefore, we think it would be useful for the DS to consider further arguments to support the 1993 study as the key endpoint.

In this instance, it appears acceptable to use the 1993 Daphnia magna study as the key acute study for classification for the following reasons:

- Measured concentrations after 24 to 72 hours in the other ecotoxicity studies with benalaxyl are generally within 80-120% of the initial measured concentrations. This is also the case with the Harris, 2014 study.
- The substance is considered not rapidly degradable, non-volatile and has a relatively low log Koc (<3) which supports that the substance would remain stable in the aquatic phase during the acute Daphnia study.
- Test conditions met the OECD TG 202 Part I (1984) test guideline/criteria for dissolved oxygen and control immobilisation and most of the study parameters were comparable to those recommended in OECD TG 202 (2004). The main deviations were that the frequency of DO, pH and temperature intervals were not reported. Although information on the temperature and pH range throughout the study duration were not available, the single values reported were within the recommended range. Additionally the control data met the OECD TG 202 (2004) validity criteria confirming that test conditions were suitable.
- The study was GLP compliant and the test item is representative based on review of the chronic Daphnia endpoint.
- The OECD TG 202 Part II (1984) endpoint which was issued as the same study report number is considered reliable and is the key endpoint for hazard classification.

We note that the OECD TG 202 Part II (1984) study included analytical verification and wonder if this data is useful to support the application of nominal concentrations for the acute endpoint.

We recognise that the older Daphnia magna study (Anonymous, 1993) was considered supporting information in the PPP RAR (2017) and EFSA conclusion (EFSA, 2020) due to the lack of analytical verification. The PPP risk assessment was driven by chronic toxicity to Daphnia and this difference in acute invertebrate endpoint does not impact the PPP risk assessment.

Aquatic Chronic classification:
We agree with the proposed Aquatic Chronic 1 classification and M-factor of 1 based on the Daphnia magna 21 day NOEC of 0.03 mg/L for reproduction and survival (Anonymous, 1992) given the substance is NRD. We also note that this chronic classification is supported by the Danio rerio 30 d NOEC of 0.079 mg/L based on body weight (Anonymous, 2014) which is in the same concentration range.

We note that EC10 endpoints are preferable chronic endpoints in place of NOEC data for hazard classification (ECHA, 2017). Are EC10 endpoints available for the chronic fish and/or invertebrate endpoints? If not, is it possible to determine them?

References
ECHA, 2017. Guidance on the Application of the CLP Criteria, Version 5.0. Helsinki: ECHA.
EFSA, 2020. Conclusion on the peer review of the peer review of the pesticide risk assessment of the active substance benalaxyl. EFSA Journal 2020; 18 (1):5985, 32 pp. https://doi.org/10.2903/j.efsa.2020.5985
Rapporteur Member State: Romania and Co-Rapporteur Member State: Portugal, 2017. Benalaxyl, active substance data, Volume 3, Annex B.9, Ecotoxicology data. In: Draft Renewal Assessment Report under Regulation (EC) 1107/2009: Benalaxyl. Available [online]: https://www.efsa.europa.eu/en/consultations/call/180116

Dossier Submitter's Response

Thank you for your comments.

RAC's response

Thank you for the comments.
Acute aquatic classification:
Please see the answer to Comment 10.

- RAC considers that Harris 2014 study can not be used to compare measured results against the 1993 study without measured results due to different dosing techniques used which seem to have an effect to the study result.
- RAC agrees with all other reasons presented by the NA and finds the study reliable.

Chronic aquatic classification:

- RAC agrees with the NA comments.
- RAC could not find EC10 values for chronic fish/or invertebrate endpoints.

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | Belgium | | Member State | 12 |
| Comment received | | | | |
| BE CA supports the proposal to classify the substance Benalaxyl with Aquatic acute 1, H400 and Aquatic Chronic 1, H410. Also the proposed M-factor of 1 for acute and chronic aquatic toxicity is supported.<br><br>Typo: In table 24: summary of relevant information on acute toxicity<br>The EC50 for Daphnia magna in the anonymous (1993)-study is reported as being based on measured concentrations instead of nominal concentrations. | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comments.<br>We agree with the typo in table 24. | | | | |
| RAC's response | | | | |
| Thank you for the comments. RAC also support the Dossier Submitter proposal. The error in Table 24 is noted. | | | | |

**OTHER HAZARDS AND ENDPOINTS – Physical Hazards**

| Date | Country | Organisation | Type of Organisation | Comment number |
|---|---|---|---|---|
| 05.02.2021 | United States | FMC Agricultural Sciences | Company-Manufacturer | 13 |
| Comment received | | | | |
| FMC agrees based on the physical and chemical properties of benalaxyl that classification for physiochemical properties and physical hazards it not required.<br><br>ECHA note – An attachment was submitted with the comment above. Refer to public attachment Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf | | | | |
| Dossier Submitter's Response | | | | |
| Thank you for your comments. | | | | |
| RAC's response | | | | |
| Thank you, noted. | | | | |

PUBLIC ATTACHMENTS

1. Benalaxyl_FMC Comments on CLH Dossier, submitted to ECHA, 4 Feb 2021.pdf [Please refer to comment No. 1, 3, 5, 7, 9, 13]