COMPILED COMMENTS ON CLH CONSULTATION

Comments provided during consultation are made available in the table below as submitted through the web form. Please note that the comments displayed below may have been accompanied by attachments which are listed in this table and included in a zip file if non-confidential. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Last data extracted on 15.01.2024

Substance name: cinmethylin (ISO); exo-(±)-1-methyl-4-(1-methylethyl)-2-[(2-methylphenyl)methoxy]-7-oxabicyclo[2.2.1]heptane; exo-(±)-1-methyl-2-(2-methylbenzyloxy)-4-isopropyl-7-oxabicyclo[2.2.1]heptane
CAS number: 87818-31-3
EC number: 402-410-9
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	1
Comment received				
A parallel peer review process for active substance approval according to Reg. (EC) No 1107/2009 is ongoing. Table 51: Labelling with H400 and H410 should be corrected.				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	2
Comment received				
BASF General Comment: According to 2020/1740 Article 11, the Rapporteur Member State ('RMS') is responsible for submitting a proposal or a harmonised classification and labelling to the European Chemicals Agency (ECHA) pursuant to Article 37(1) of Regulation (EC) No 1272/2008 and in accordance with the Agency's requirements to obtain an opinion on a harmonised classification of the active substance. For Cinmethylin, no specific CLH report was prepared, but parts of the Draft Assessment Report ('DAR') written by the RMS according to Regulation (EC) N° 1107/2009 are used, i.e. Volume 1 as a CLH report and Volume 3, CA B2, B6, B8 and B9 as Annexes. Consequently, the same documents are now used for evaluation in different processes, i.e. evaluation of the active substance according to Regulation (EC) No 1107/2009 and the harmonised classification and labelling according to Regulation (EC) No 1272/2008. ECHA published the respective documents on 06th November 2023, and the European Food and Safety Authority ('EFSA') published the DAR, containing the same documents on 06th November 2023. Both publications are currently open for public commenting until 12 January 2024 and 08 January 2024, respectively. In order to fulfil criteria relevant for the assessment of the active substance under Regulation (EC) N° 1107/2009 and Regulation (EC) N° 1272/2008, the used documents contain information related to both Regulations. BASF want to highlight that the comments submitted under Regulation (EC) N° 1107/2009				

are much more comprehensive and consider the complete DAR, whereas the comments submitted here under Regulation (EC) N° 1272/2008 are supposed to consider only information needed for classification and labelling.

BASF General Comment 1 (Toxicology):
CLH Vol 1 – Section 2.6.3.1.1 – Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure (short-term and long-term toxicity), page 74.
The RMS made the following comment:
“Therefore, the applicant is requested to provide a statement on the need of a short-term inhalation toxicity.”

BASF: The applicant considers that a repeated dose inhalation toxicity study with Cinmethylin is not justified for the following reasons:
- Cinmethylin has a borderline moderate volatility (the vapor pressure at 20°C is below the threshold value of volatile substances (8.1x10^-3 vs. 10^-2, respectively));
- The acute inhalation toxicity is low as demonstrated by the absence of mortality in the acute inhalation study at the tested concentration of 5.268 mg/L;
- The test conditions in the inhalation toxicity studies when performed according to the OECD guidelines are irrelevant in comparison to realistic worker exposure scenarios. The formulated product will be diluted with water for application, while the tested substance in the inhalation toxicity studies is used unchanged as liquid aerosol, generated inside the exposure system to maximize inhalation exposure. Under conditions of normal handling and use, human exposure to Cinmethylin via the inhalation route is negligible in view of the vapour pressure and the preferential partitioning of the substance in the liquid phase and low transfer to the gas phase from water-based formulations such as EC-type products. This is thus not comparable to the exposure conditions of the animal inhalation study in which the active substance is administered as particles in aerosol.
In conclusion, no valuable additional information from a short-term inhalation toxicity study is expected, and thus, no need for a further animal study is identified.

BASF General Comment 2 (Toxicology):
CLH Vol 1 – Section 2.6.8.2 – Supplementary studies on the active substance – Mechanistic studies, page 110.
The RMS made the following comment:
“The applicant is requested to provide tabular data together with a statistical analysis for the enzyme induction in the low and the mid dose groups (data gap).”

BASF: Additional statistical evaluation of mRNA expression analyses for the low and mid-dose test groups (200 and 1000 ppm) were performed by the applicant and documented in an amendment (see attached Amendment No. 2, BASF DocID 2023/2052735). Of note, since data of more groups are available, more comparisons were performed. As a consequence, while the unadjusted p-values remain exactly the same as in the original report for the high dose group, the FDR (False Discovery Rate) adjusted p-values are slightly higher (due to multiple testing correction) in comparison to the original report. This resulted in decreased test result significance (from *** to ** to *) for some of the gene/gender/dose combinations. These slight variations have no impact on the outcome of the study.

BASF General Comment 3 (Toxicology):

CLH Vol 1 – Section 2.6.8.2 – Supplementary studies on the active substance – Mechanistic studies, page 111.
The RMS made the following comment:
“The applicant is requested to provide a further explanation for this rather unexpected finding in this in vitro study as it is hypothesized that the thyroid changes are specific only to liver enzyme induction i.e. an increased T4 metabolism as the reason for the T4/T3 decreases and TSH increases. In Volume 1/ED assessment, the applicant hypothesizes that this is likely due to the timing of measurements. This should be further elaborated by the applicant. In addition, the applicant is requested to explain why T4-glucuronidation was induced in rat hepatocytes by the positive control 3-MC but failed to be induced by PB or PCN.”

BASF: Under the study conditions it was indeed not possible to reproduce the increased T4-glucuronidation found in rats in vivo in rat hepatocytes in vitro. It is unclear, why male rat hepatocytes exposed to BAS 684 H did not show increased T4-UGT activity in vitro, although increased T4-UGT activity was shown in vivo after 14 days in male and after 28 days in female rats.
There are two points that might have contributed to this outcome:
1. Disruption of enzyme activity under the respective study conditions in rat hepatocytes:
In Table 1 (presented in the attachment “applicant response to CLH comment page 111”; DocID 2024/2000514), CYP activity and T4-UGT activity after 3 days of incubation are displayed, with the response on the positive control inducers shadowed in grey.
Interestingly, male rat hepatocytes had no CYP2B/3A enzyme activity induction in response to the positive controls Phenobarbital (PB) or Pregnenolone-16α-carbonitril (PCN). Female rat hepatocytes showed likewise a rather weak response with regard to CYP2B induction. Additionally, there is no response on BAS 684 H with regard to CYP2B or CYP3A enzyme activity although expected based on in vivo data and mRNA induction in vitro. The low standard deviation of these measurements indicates a general inability of the test system to produce expected effects of positive controls in rat hepatocytes under the study conditions. Thus, these data indicate that the measurement of enzyme activity in rat hepatocytes was compromised under the conditions of this study after 3 days of incubation. This is consistent with the finding that T4-UGT-activity could only be induced by the positive control inducer of CYP1A2, but not by the respective positive control inducers for CYP2/CYP3 isoforms in rat hepatocytes.
This weakness in the study is not considered to invalidate the complete dataset. In contrast to the rat hepatocytes, human hepatocytes showed full activity of the cell system by the positive control inducers. All positive controls induced the respective CYP enzyme activities as expected and T4-Glucuronidation was induced in both sexes by the positive control inducer for CYP1A enzymes Omeprazole (OME) and CYP2B enzymes Phenobarbital (PB). All standard deviations indicated activity. Therefore, the achieved response to BAS 684 H in human hepatocytes is considered to be reliable. T4-UGT activity in human hepatocytes was slightly increased at 10 and 30 µM compared to the solvent control but the change did not reach the very conservative trigger of 1.5-fold induction. The highest concentration tested (100 µM) showed clearly compromised enzyme activity, most likely due to cytotoxicity, not only for T4-UGT-activity.
Therefore, in absence of a relevant effect of BAS 684 H on T4-glucuronidation in human hepatocytes in vitro, the potential for subsequent changes in circulating levels of thyroid hormones and resulting thyroid toxicity in humans is not expected from these data.
2. Prolonged incubation is needed to see the T4-UGT activity response:
A new publication (Bomann, W., H. Tinwell, P. Jenkinson and F. M. Kluxen (2021). "Metribuzin-induced non-adverse liver changes result in rodent-specific non-adverse thyroid effects via uridine 5′-diphospho-glucuronosyltransferase (UDPGT, UGT) modulation." Regulatory Toxicology and Pharmacology 122: 104884.) shows that a T4-UGT activity in vitro is more apparently induced after 7 days than after 3 days of treatment in rat and

human hepatocytes. In view of the generally mild effects of BAS 684 H on T4-glucuronidation observable in rats after 14 days in males and after 28 days in females, in vitro incubation of rat hepatocytes for longer than 3 days might be required to elicit effects of BAS 684 H on T4-glucuronidation.
In conclusion, the available in vitro comparative enzyme activity study has weaknesses, however the achieved response to BAS 684 H in human hepatocytes is considered to be reliable in view of a lack of significant T4-Glucuronidation response by BAS 684 H while the positive control substances showed the expected increases. Therefore, the outcome of the in vitro study overall supports the conclusion that observed decreased T4 levels as a result of increased T4-glucuronidation in rats are not to be expected in humans.

BASF General Comment 4 (Toxicology):
CLH Vol 1 – Section 2.6.10.1 – Toxicological end point for assessment of risk following long-term dietary exposure – ADI (acceptable daily intake), page 116.

BASF: The applicant disagrees with the RMS's proposal to derive the ADI based on the NOAEL from the 2-year combined chronic toxicity/carcinogenicity study in the rat dated 1985 (leading to an ADI of 0.05 mg/kg bw/day). Indeed, as reported as a deviation by the RMS himself in Vol 3 – B.6 (AS) – Part I, section B.5.2 (page 427), "As compared with the currently valid OECD TG 453 (2009), the spacing for the top dose was greater than 10-fold, not matching the recommended 2.4-fold interval. However, if this study is assessed in combination with a recently and guideline conform GLP-study [see B.6.5.1; KCA 5.5/1 2017/1093414]], an appropriate long-term NOAEL of 200 ppm (9 mg/kg bw/d) for males and 200 ppm (13 mg/kg bw/d) for females can be established". This means that both combined chronic toxicity / carcinogenicity rat studies have to be assessed together to conclude on the long-term NOAEL which is therefore the highest NOAEL determined from the two studies. Therefore, since the long-term NOAEL is set at 9 mg/kg bw/d in the rat, the applicant maintains its proposal to use the NOAEL of 7.9 mg/kg bw/d from the 1-year dog study to derive the ADI as it is considered the lowest long-term NOAEL for BAS 684 H. By applying an uncertainty factor of 100, the applicant concludes to an ADI of 0.08 mg/kg bw/day.

BASF General Comment 5 (Environmental Fate):
CLH Vol 1 – Route and rate of biological degradation in aquatic systems, p. 160.

BASF: If this section is intended as a summary of the route and rate of biological degradation in aquatic systems, the DT50 values obtained in the water/sediment study should be reported. They are currently missing.

BASF General Comment 6 (Environmental Fate):
CLH Vol 1 – 2.8.2.2 Other convincing scientific evidence, p. 163.

BASF: The mention "2.8.2.2 Other convincing scientific evidence: No data provided" is erroneous. Data is available and is reported in the following sub-sections 2.8.2.2.1 to 2.8.2.2.7.

BASF General Comment 7 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.1 Bioaccumulation, Table 48 (p. 169f)

BASF: The applicant kindly asks to include the geomean BCFKLg parent of 100.3 in Vol. 1,

Table 48.
In Table 48, the study with DocID 2017/1208842 is listed as a supportive study and no BCF value is reported. This is conflicting with the RMS's evaluation and conclusions in Vol. 3CA (CA 8.2.2.3/4), Vol. 3CP (Section B.9.3.3 and Table 10.2-1) and in the DAR document "List of Endpoints". The study was considered fully acceptable and information from this study was used for recalculation of the BCF (obtained in study with BASF DocID 2017/1156422) related to the detected amounts of the unchanged parent compound (BAS 684 H) only. The resulting geometric mean BCFKLg parent (whole fish) of 100.3 is listed in the LoEPs in the Ecotox Section of the CP-part (Table 10.2-1) and the DAR document "List of Endpoints". This information is considered essential and therefore, the applicant kindly asks the RMS to include the geomean BCFKLg parent of 100.3 in Vol. 1, Table 48 as well.

BASF General Comment 8 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.1 Bioaccumulation, Table 48 (p. 170)

BASF: The abbreviation "BCFKLg" is used in Table 48 but not explained in the footnotes. The applicant kindly asks the RMS to add "BCFKLg = growth corrected kinetic bioconcentration factor normalized to 5% lipid content" to the abbreviations below Table 48.

BASF General Comment 9 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.1 Assessment of BCF study results by RMS (p. 177) and Section 2.9.2.4.2 Bioaccumulation (p. 201)

BASF: The RMS states that the geometric mean BCFKLg 697 L/kg is the acceptable endpoint. The applicant respectfully disagrees and asks the RMS to consider the proposed more realistic approach based on recalculations of the BCF related to the detected amounts of the unchanged parent compound which results in a geomean BCFKLg parent of 100.3. The RMS states that the geometric mean BCFKLg 697 L/kg is the acceptable endpoint. Consequently, it is concluded that BAS 684 H has a potential to bioaccumulate in the aquatic environment. This is conflicting with information in Vol. 3CP (Section B.9.3.3 and Table 10.2-1) and in the DAR document "List of Endpoints". The applicant respectfully disagrees with this conclusion (also see comment no. above). The BCF of 697 L/kg is based on total radioactive residue (TRR), not discriminating between parent and metabolites. In Vol 3CP, B.9.3.3, a more realistic approach is described which is based on recalculations of the BCF related to the detected amounts of the unchanged parent compound (BAS 684 H) only (i.e., 8.6 - 24.1% of TRR in whole fish). Following this approach, the BCFKLg parent is 59.9 - 168 corresponding to a geometric mean BCFKLg parent of ~100. This endpoint is also reported in the LoEPs in the Ecotox Section of the CP-part (Table 10.2-1) and the DAR document "List of Endpoints". The applicant kindly asks the RMS to consider this information in its assessment and conclusion in Vol. 1 and to provide its opinion on the proposed approach/endpoint (in all relevant documents).

BASF General Comment 10 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.2.3 Acute (short-term) toxicity to algae or aquatic plants (p. 184)

BASF: The applicant kindly asks to report the ErC50 obtained in the Lemna study with three significant digits (i.e., as 0.0885 mg/L).

BASF General Comment 11 (Ecotoxicology):

Vol. 1, Level 2, Section 2.9.2.3 Long-term aquatic hazard (p. 190ff) and Table 52 (p. 200)

BASF: It is noted that for the chronic studies, only the NOEC values are reported under the sections “Concluding” for all groups of organisms and it is stated that these endpoints can be used for the classification purposes. The applicant disagrees and kindly asks to also report the EC10 values.
For the chronic studies, only the NOEC values are reported under the sections “Concluding” for all groups of organisms and it is stated that these endpoints can be used for the classification purposes. In addition, in Table 52, only the NOEC values are reported, except for L. gibba. The applicant kindly disagrees due to the following reasons:
According to the recent CLP Guidance document (EChA July 2017, Version 5.0, page 493 and OECD 54, 2006) the EC10 is the preferred endpoint for chronic classification purposes. Furthermore, with respect to algae and aquatic plants (the most sensitive group for BAS 684 H), ErCx values are the relevant endpoints to be used in aquatic RA (see EFSA AGD 2013). The chronic studies for all groups of organisms provide reliable EC10 values. The lowest NOEC of 0.0023 mg/L was derived from the study on L. gibba and the lowest EC10 of 0.007 mg/L results from the study on M. spicatum (based on the more relevant parameter growth rate). Overall, the endpoints are in a comparable range and both endpoints result in the same classification, i.e., Aquatic Chronic category 1; H410, with an M-factor of 10. Nevertheless, we see no reason to deviate from current guidance documents recommendations and thus, the applicant kindly asks to also report the EC10 values under the sections “Concluding” and in Table 52 for all relevant chronic studies and to preferably consider these endpoints for classification purposes.
Finally, the applicant respectfully wants to highlight that on page 202 reference is made to an old version of the CLP guidance (i.e., V4.1 June 2015 should be replaced by the recent version V5.0 July 2017).

BASF General Comment 12 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.3 Long-term aquatic hazard, Table 50 (p. 190)

BASF: The applicant kindly asks to correct the 14 d EyC10 for G. maxima to 0.027 mg/L (based on total length and dry weight).

BASF General Comment 13 (Ecotoxicology):
Vol. 1, Level 2, Section 2.9.2.3.2 Chronic toxicity to aquatic invertebrates (p. 192f)

BASF: The applicant kindly asks to report the relevant (recalculated) endpoints for the chronic Daphnia study (BAS DocID 2017/1000684) to be consistent in all study summaries (i.e., EC10 = 2.366 mg/L and NOEC = 0.615 mg/L).

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip
ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2024	United Kingdom	Health and Safety Executive	National Authority	3
Comment received				

'The GB CLP Agency would like to highlight that cinmethylin has already been assessed under Article 37A of GB CLP. The conclusions of the Agency are available in the documents linked below. MCL Proposal: https://consultations.hse.gov.uk/crd-clp/clp-001-cinmethylin-gb-mcl-proposal/supporting_documents/gbclpmclproposalcinmethylin.pdf Public Consultation Report: https://www.hse.gov.uk/chemical-classification/classification/harmonised-classification-self-classification/cwbsd-aagt-0360.pdf Technical Report: https://www.hse.gov.uk/chemical-classification/classification/harmonised-classification-self-classification/mcl-aagu-0361.pdf Agency Opinion: https://www.hse.gov.uk/chemical-classification/classification/harmonised-classification-self-classification/cwbsd-aaja-0436.pdf We note that there are two studies assessed by the GB CLP Agency that were not included in The Netherlands' CLH report which RAC may wish to consider in support of the DS' proposal of no classification for eye irritation and STOT RE. The first of these is an in vitro eye irritation: EpiOcular™ OECD 492 study (Remmele M., 2017; described on page 39 of the GB MCL Proposal). The second study is an additional repeated-dose 1-year oral toxicity study in dogs conducted according to US EPA guidelines/similarly to OECD 452 (Anon., 1988; described on page 65 of the GB MCL Proposal). The Agency would also welcome a discussion on the differences in STOT SE classification between the agreed classification in the GB MCL assessment and the proposed classification in the EU CLH report. Finally, the Agency notes that the Registry of Intentions page for cinmethylin lists the proposed skin sensitisation classification as Skin Sens. 1B, whereas in the body of the CLH report (page 63), Skin Sens. 1 is proposed, with the DS stating that sub-categorisation for this endpoint is not possible.'

PHYSICAL HAZARDS

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	4
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	5
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	6
Comment received				
We agree with the proposal that classification for acute oral, dermal and inhalation toxicity is not required for cinmethylin.				

However, acute inhalation toxicity should be discussed in more detail taking into account the old acute inhalation toxicity study in rats. Since 2 out of 6 females died at a dose of 3.5 mg/L (4 h, whole body), classification could have been proposed (Acute Tox.4, H332, congruent with the previous entry in Annex VI). Indeed, it is noted that the study is considered supplementary only due to unspecified purity of the test substance. It is also not comprehensible why the top dose of 3.5 mg/L was the highest attainable concentration, noting that in the new study, the top dose of 5.5 mg/L was attained, and none of the test animals died (4 h, nose-only).

Moreover, it should be noted that classification for aspiration hazard cannot be excluded based on the available data with the formulated product. Thus, further data requirement is supported, and no conclusion on classification for aspiration hazard can be drawn.

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	7
Comment received				
Agree with CLH report 2.6.2.9 - data gap				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	8
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	9
Comment received				
FR: - Skin Irritation – EpiDerm™ SIT there are 2 runs. One run is positive and and one negtative, therefore no final conclusion can be drawn. Averaging runs as Applicant did was never performed in the ring trials that led to development of OECD 439, because these runs are independent runs so there is no reason to deviate from that. A third run should have been undertaken. Can RMS include this in its assessment? The EpiDerm™ SCT allows to identify Cat. 1 items according to OECD 431 and a negative result should be followed up by an OECD 439 (SIT)so based on OECD GD 203. Since the SIT test is not conclusive no final conclusion can be drawn. - Skin Irritation – Rabbits test. Two tests were conducted one in 2016 and one in 1981. Lower weight is attributed to the 1981's one because of deviations (which are not stipulated in the DAR) from OECD 404, but presentation of scores is done according to OECD 404. As such it is unclear why this test cannot be used. These two show discordant results (1981: clear positive and 2016: negative). The test in 2016 should not have been undertaken according to art. 62 because credible in vitro guidelines existed already and OECD Guidance				

203 was already published too. In our opinion this in vivo test should be considered for information only and not used in the overall assessment.
- Overall, the potential for the skin irritation endpoint cannot be finalized in the absence of a 3rd run in OECD 439 SIT

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	10
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	11
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	12
Comment received				
We agree with the proposal that classification for skin corrosion/irritation is not required for cinmethylin.				

HEALTH HAZARDS – Serious eye damage / eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	13
Comment received				
FR: - Eye Irritation – BCOP Test: According to OECD 437, BCOP test can identify either Cat.1 or non-classified eye irritants (respectively OPKIT IVIS score > 55and ≤ 3). Applicant provided custom IVIS thresholds by adjusting to its own in-house historical data. We disagree that this can be performed since there are no provisions in OECD 437 that allow such a change. Changing decision tree and threshold for classification should be supported by ring trial and this is not the case here. There is no reason to adjust OECD 437 thresholds and to deviate from those, especially because this guideline was revised recently. Based on non-corrected values and complying strictly with OECD 437 the IVIS score would be: mean opacity: (3.7 + 0 + 3.0)/3 = 2.23 and mean permeability: (0.003 + 0.004 +0.005) / 3 = 0.004. Hence IVIS = 2.23 + 15 x 0.004 = 2.29. Could RMS include (1) clearly the IVIS based on non-corrected values score obtained in a table 6.2.5.1-1 for transparency & clarity and (2) provide a comparison with OECD 437 thresholds? Please note that we disagree on the methodology that consists in adjusting well-defined thresholds in an OECD guideline for convenience reasons of an applicant and to create a precedent on that. We however agree that based on an IVIS of 2.29 the test item is predicted as 'not classified' based on BCOP decision tree. - Eye Irritation – EpiOcular test. We agree with the outcome of the test. However, the				

methodology for evaluating the test is not compliant with OECD 492. Historical data seemed to be used for evaluation but according to OECD 492 this is done only to demonstrate proficiency of the lab. Moreover, it should be included a comparison of concurrent negative control OD values to ensure acceptability of the test is met (OECD 492 Table 2). - Eye Irritation – Eye irritation in rabbits CA 5.2.5/2. The study has been conducted in 2016 whereas credible in vitro methods already existed. This test should not have been undertaken for animal welfare reasons under Article 62 of Reg. 1107/2009 because results from BCOP (even for instance based on BCOP version of 2013) do show that no classification was warranted. Can DS/RMS include a flag on this for the ECHA rapporteur in the CLH report/DAR to stipulate that this animal test was not needed in 2016?

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	14
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	15
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	16
Comment received				
Based on the weight of evidence assessment taking into account the available studies of skin sensitisation, we agree that the pure active substance cinmethylin can be considered skin sensitising. One positive Buehler test with acceptable reliability, one negative Buehler test with limited reliability (supplementary; test item concentration for induction not adequate), and one Guinea pig maximisation test with negative result, but also strong deviations (no positive controls) were available. Classification for skin sensitising properties is warranted for cinmethylin, and in the absence of complete information on lower concentrations tested, the resulting proposal is supported as Skin Sens 1, H317.				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	17
Comment received				
Agree with CLH report 2.6.2.7 (Aspiration hazard) - classification with H317 kat. 1				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	18

Comment received
BASF agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	19
Comment received				
It is agreed that cinmethylin does not meet the criteria for classification for germ cell mutagenicity based on the available data.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	20
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	21
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	22
Comment received				
FR: Page 415 of Volume 3CAB6 Part I In the carcinogenicity rat study 1 (2018a, study report 2017/1093414) in Volume 3CA B.6.5.1, increased incidence of endometrial adenocarcinoma and of endometrial stromal polyps, as well as increased incidence of hepatocellular carcinoma, were observed (Table 6.5.1-13). Although not reported in the CLH report/Volume 1, these findings should be discussed by ECHA RAC. - Increased incidence of hepatocellular carcinoma was noted in females of the high dose group and was at the upper end of the provided historical control data (HCD). - Statistically significant increase of endometrial adenocarcinoma and endometrial stromal polyps were reported at the high dose. It should also be questioned if the low and mid dose groups should be considered affected by these findings also since 3-fold and 2-fold increases were already observed for adenocarcinoma and polyps respectively. Available HCD were not contemporary to the study (experimental part of the study from				

March 2015 to April 2017; HCD up to 2015). The use of HCD to dismiss the treatment-relationship of a statistically and biologically significant finding is not considered appropriate. More information on the HCD is required (e.g. individual data in order to judge on the distribution, 95th percentiles...) according to minimum requirements of EFSA Administrative Guidance.
Both findings may trigger a classification for carcinogenicity.

Page 453 of Volume 3CAB6 Part I
In the carcinogenicity rat study 2 (1985b, study report CI-427-001) in Volume 3CA B.6.5.2, a discussion on increased incidence of testicular interstitial cell adenomas is proposed (Table 6.5.2-14). Although not reported in the CLH report/Volume 1, these findings should be discussed by ECHA-RAC.

Page 90 of CLH report/Volume 1
In the carcinogenicity mouse study (1986b, study report CI-428-001), statistically significant increased incidences of hepatic tumors (combined adenomas and carcinomas) were observed in both sexes. It is not clear how was demonstrated the infection with MHV in mice included this study. Was specific testing performed to detect the presence of MHV in each mouse? It seems that there was no histopathological non-neoplastic findings and changes in clinical chemistry parameters associated with this disease. Therefore, it should be questioned whether it is appropriate to consider hepatic tumours linked to MHV rather than treatment-related.
Regarding historical control data (HCD) provided for this study, they were not contemporary to the study, covered more than 5-year range around the study date, and were not from the same laboratory. Only range and mean of incidence were provided (no details on individual data, no information on the distribution...). Overall, these HCD should not be considered relevant and should not be used to dismiss the hepatic tumors as treatment-related.
Given the uncertainties linked to the assumed MHV infection in this study and to the non-relevant HCD, a classification for carcinogenicity may be warranted.

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	23
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	24
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	25
Comment received				

The observed findings are not considered sufficient for classification of cinmethylin as carcinogenic.

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	26
Comment received				
FR: Page 101 of Volume 1/CLH report and page 610 of Volume 3CAB6 Part I In the prenatal developmental toxicity in rabbit (2018c, study report 2015/1158053 Vol 3CA B.6.6.2.2 Study 2), increased incidence of developmental findings were observed (please consider that some findings were not discussed in Volume 1/CLH report). Some developmental findings were observed with a higher incidence at the highest dose level of 250 mg/kg bw/d (first part of the study). These findings, although observed with incidences above HCD range, were considered not treatment-related because not reproduced in the group treated at 320 mg/kg bw/d (second part of the study) (e.g. misshapen thoracic vertebra, absent lumbar vertebra, intercostal rib cartilage present, incomplete ossification of thoracic centrum, unilateral ossification of sternebra). It is however noted that the dose spacing between the high dose group in Part I and the high dose group in Part II is slight (x1.28) and this could explain the lack of dose-relationship observed. Furthermore, the second part of the study was conducted 3 years later (first part: sept-oct 2014; second part: nov-dec 2017). However, the same HCD are used for both parts of the study (HCD from 2010-2015). In addition, it is noted that both control groups for each part of the study showed different results. HCD should be updated and each part of the study should be compared with appropriate set of HCD. The final study design should be discussed and uncertainty analysis should be added, particularly regarding the choice of the laboratory to conduct a second part of the study 3 years later, with only a control and a tested group, with a narrow dose-spacing compared to the highest dose of part I; this second part being not OECD compliant (such choices are not permitted by OECD TG). Overall, considering all related uncertainties the findings observed at the dose level of 250 mg/kg bw/d may still be considered treatment-related. It is also noted that at 320 mg/kg bw/d, the findings blood coagulum around urinary bladder and absent lung lobe showed litter incidences above available HCD. Their treatment-relationship should be further discussed. The fact that the findings observed in this study were not reproduced in older studies (CI-432-002 1985b and CI-432-003 1987a) conducted at higher dose levels is not considered adequate. Indeed, high mortality (exceeding OECD TG 414 recommendations) was observed in both studies and the resulting number of dams including in each group was very low (6 to 14 litters), i.e. lower than OECD TG 414 recommendations (at least 16). These studies are therefore not considered reliable to permit an accurate assessment of the teratogenic potential of the active substance and should not be used to dismiss any effects that may be seen in an OECD compliant study.				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	27
Comment received				
BASF agrees to the conclusion for no classification.				

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	28
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	29
Comment received				
Adverse effects on sexual function and fertility: We agree with the DS that based on the available data from a 2-generation study in rats, classification of cinmethylin as toxic for sexual function and fertility is not warranted. Adverse effects on development: We agree with the DS that based on the available data from a developmental study in rats as well as in rabbits, criteria are not met for classification of cinmethylin as suspected of damaging the unborn child.				

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	30
Comment received				
FR agrees that classifications STOT SE3 H335 and Skin Sens 1 H317 are warranted for cinmethylin.				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	31
Comment received				
BASF agrees to the proposed classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	32
Comment received				
Agree with CLH report 2.6.2.10- classification with H335 (STOT-SE 3). Based on symptoms observed in the acute inhalation toxicity study which might be indicative of respiratory tract irritation. And emphasize on that the findings were observed from hour 1				

of exposure until study day 12.

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	33
Comment received				
A classification for STOT SE category 3 (H335) is proposed based on clinical signs observed in the acute inhalation toxicity study. Respiration difficulties (i.e. accelerated, laboured and abdominal respiration) were reported in males as well as females after exposure to 5.3 mg/L cinmethylin (4 h, nose-only). All animals (5/sex) had accelerated respiration from 1 hour after exposure until d1 (males) and d5 (females) of the study. Additionally, some animals showed abdominal respiration (3 males: d0 – d5; 2 females: d0 – d4) and laboured respiration (3 males: d2 – d8; 1 female: d2 – d12). One female showed sounds upon respiration on study days d0 – d1, and d8 – d12. On study day d0, red discharge was observed at the nose (1m/2f), and a red encrusted nose in 1 female on d1. No histopathology was performed. No gross pathological abnormalities were observed during necropsy. Since no human data are available, the observed functional changes observed in the acute inhalation toxicity study in rats should be considered indicative of respiratory tract irritation. Classification with STOT SE 3, H335 is supported.				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
20.12.2023	Germany		MemberState	34
Comment received				
We agree with the conclusion that specific target organ toxicity after repeated exposure relevant for classification of cinmethylin was not observed. However, we noted that findings in the nasal cavity (signs of irritation/inflammation (proteinaceous exudate and granulocytic infiltrates) as well as degeneration of the olfactory epithelium) were observed in studies with dietary administration in rats (90-d, 2-year dietary exposure, 2-gen study), and in mice after 18 months of dietary exposure. No repeated dose inhalation toxicity data is available, although this might be indicated due to volatility of the active substance. After dietary administration, findings in the nasal cavity were observed above concentrations relevant for STOT RE classification. Nevertheless, relevant effects via inhalation cannot be excluded.				

Date	Country	Organisation	Type of Organisation	Comment number
04.12.2023	Denmark		MemberState	35
Comment received				
Agree with CLH report - no classification				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	36
Comment received				
BASF agrees to the conclusion for no classification. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
11.01.2024	France		MemberState	37
Comment received				
FR agrees with the conclusion on classification and labelling for environmental hazards: Cinmethylin is classified in acute aquatic hazard Cat 1 - H400: Very toxic to aquatic life with M-factor = 10 based on L.gibba 7d-ErC50 = 0.0885 mg a.s/Lmm and long-term aquatic hazard Cat 1 - H410 : Very Toxic to aquatic life with long lasting effects with M-factor = 10 based on L. gibba 7d-NOErC = 0.0023 mg a.s/Lmm and considering the substance as non-rapidly degradable.				

Date	Country	Organisation	Type of Organisation	Comment number
09.01.2024	Germany	BASF	Company-Manufacturer	38
Comment received				
BASF agrees to the proposed classifications. ECHA note – An attachment was submitted with the comment above. Refer to public attachment Public attachment.zip ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment 2023-2052735.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
12.01.2024	United Kingdom	Health and Safety Executive	National Authority	39
Comment received				
Bioaccumulation: We note that the BCF endpoints for cinmethylin based on total radioactive residues (TRR) can be recalculated to account for the metabolism of cinmethylin. This is in line with Annex III, Section III.2.1.2 of ECHA's Guidance on the Application of the CLP Criteria (ECHA, 2017) which states that "the BCF from radio-labelled studies should, preferentially be based on the parent compound, so it is appropriate to correct the original values based on TRR when able". The resulting corrected BCF values for cinmethylin are 170 and 59 at exposure concentrations of 0.0005 and 0.005 mg/L, corresponding to a geometric mean of 100.4 and thus the conclusion that cinmethylin is not bioaccumulative according to CLP criteria. Whilst this does not affect this current proposed hazard classification, we feel it is important that the CLH Report does not indicate that cinmethylin itself has the potential to bioaccumulate. Chronic ecotoxicity: The key chronic endpoint used in the CLH proposal is the overall Lemna gibba NOEC of 0.0023 mg/L (mm) based on visual observation of shorter roots. We are unclear whether this NOEC is reliable and relevant to CLP given it does not appear to have a statistical basis - and long-term algal/plant NOEC/ECX endpoints used for Chronic classification purposes would normally be based on growth rate endpoints (where available). The reported statistical growth rate NOErC from the same Lemna study is 0.006 mg/L (mm) based on dry weight, corresponding to a 0.95% effect at this concentration and a 3.66% effect at the LOErC. Such low effect levels below 10% are likely not biologically relevant. For this and other reasons, ErCX endpoints (usually ErC10) are normally preferred over NOECs for classification purposes according to CLP guidance. The following ErC10 values				

are the next most sensitive chronic endpoints from this Lemna study and we consider these would be more reliable to use in preference to the Lemna NOECs.
• 7-day ErC10 frond number = 0.0283 mg/L (mm) (CI 95 % limits: 0.02394 - 0.03276)
• 7-day ErC10 dry weight = 0.03 mg/L (mm) (CI 95% limits: 0.02344 - 0.03656)

If the Lemna NOEC values are not used for the classification, then the Myriophyllum spicatum 14-day ErC10 fresh weight of 0.007 mg/L (mm) (CI 95% limits: 0.001 - 0.04) would appear to be the most sensitive chronic toxicity endpoint, according to the CLH report. In this Myriophyllum study, the statistical NOErC overall of 0.0109 mg/L (mm) based on total shoot length and fresh weight is the lowest tested concentration, so it appears that this ErC10 value has been extrapolated beyond the range of the test concentrations. This extrapolation introduces uncertainty which is reflected in the wide CI with the upper confidence limit being above the LOEC. In contrast to the calculated EC10, the experimental data shows an average growth rate inhibition of 1.3% at the NOErC fresh weight and 12.8% at the LOErC fresh weight. Where EC10 are potentially unreliable, EC20 have previously been used for classification purposes; in this case the ErC20 for Myriophyllum based on fresh weight is 0.027 mg/L (CI: 0.005-0.146). All other ErC10 values from this study are >0.1 mg/L. Given the uncertainties outlined here, either the NOErC of 0.0109 mg/L or the ErC20 fresh weight of 0.027 mg/L would appear to be the lowest, most reliable chronic classification endpoints from this Myriophyllum study.

Overall, however, we consider that the Glyceria maxima study is reliable and relevant for hazard classification purposes - and that this provides the most appropriate chronic classification endpoints for cinmethylin. The following long-term endpoints in the 0.01-0.1 mg/L range are available from this study:
• 14-day NOErC overall = 0.026 mg/L (mm)
• 14-day ErC10 total length = 0.023 mg/L (mm) (CI 95% limits: 0.014 - 0.033)
• 14-day ErC10 wet weight = 0.044 mg/L (mm) (CI 95% limits: 0.035 - 0.052)
• 14-day ErC10 dry weight = 0.035 mg/L (mm) (CI 95% limits: 0.003 - 0.096)
• 14-day ErC20 total length = 0.043 mg/L (mm) (CI 95% limits: 0.029 - 0.056)
• 14-day ErC20 wet weight = 0.068 mg/L (mm) (CI 95% limits: 0.058 - 0.078)
• 14-day ErC20 dry weight = 0.095 mg/L (mm) (CI 95% limits: 0.017 - 0.201)

The most sensitive reliable endpoint overall is the 14-day ErC10 total length of 0.023 mg/L for Glyceria which, for a non-rapidly degradable substance, would give a classification of Aquatic Chronic 1 with a Chronic M-factor of 1 (rather than 10 as proposed in the CLH Report). This value was also used in the GB Mandatory Classification & Labelling (MCL) of cinmethylin. The other reliable Myriophyllum and Lemna NOErC/ErCx values, as described above, are in the same classification range and would also support the same Chronic M-factor of 1.

We note that a number of the aquatic plant studies have been performed in the presence of sediment, which in some case can complicate interpretation, however, in each case above relevant geometric mean measured endpoints for cinmethylin in the water phase are available - and so we consider that these can be used for Aquatic hazard classification purposes.

PUBLIC ATTACHMENTS
1. Public attachment.zip [Please refer to comment No. 2, 5, 8, 10, 14, 18, 21, 23, 27, 31, 36, 38]

CONFIDENTIAL ATTACHMENTS

1. 2023-2052735.pdf [Please refer to comment No. 2, 5, 8, 10, 14, 18, 21, 23, 27, 31, 36, 38]