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 21.02.2024

Substance name: clethodim (ISO); (5*RS*)-2-{(1*EZ*)-1-[(2*E*)-3-chloroallyloxyimino]propyl}-5-[(2*RS*)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one
CAS number: 99129-21-2
EC number: -
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2024	United Kingdom	Arysta LifeScience S.A.S.,	Company-Manufacturer	1
Comment received				
It is noted that the CLH report linked in the consultation appears to be for thermally treated garlic juice and not clethodim. Comments have been made in relation to joint PPP and CLH template for clethodim. ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1602214.UK0 - 4352 STOT RE Cat 2 applicant response 08.02.24.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	2
Comment received				
For the classification of the substance as Acute Tox. 4, H302 see CLH dossier section 2.11.2.1 "Proposed harmonized classification and labelling according to the CLP criteria" Table 80 lists the corresponding ATE of 1133 mg/kg bw. For clarification "oral" should be amended in the future entry in Annex VI: Oral: ATE = 1133 mg/kg bw . A parallel peer review process for active substance approval according to Regulation (EC) No 1107/2009 is ongoing.				

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	3
Comment received				
The DE CA supports the proposal of the DS to maintain the existing classification as acute (oral) toxic, category 4 (H302). The ATE value of 1133 mg/kg body weight is also accepted,				

as it is derived from an acceptable acute oral toxicity study in the most sensitive species (rats). In accordance with Regulation (EG) Nr. 1272/2008, the term 'oral' should be added in the lines „Dossier submitters proposal" and „Resulting Annex VI entry if agreed by RAC and COM" as follows: Oral: ATE = 1133 mg/kg bw. The classification is also supported by the data on mortality in the in vivo chromosomal aberration test in rats, in which clethodim was lethal in females starting at a dose of 1.2 g/kg body weight. No classification is warranted for the dermal or the inhalation route.

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	4
Comment received				
The DE CA agrees with the proposal that skin corrosion/irritation classification is not required for clethodim and supports the use of the labelling phrase EUH066 (Repeated exposure may cause skin dryness or cracking).				

HEALTH HAZARDS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	5
Comment received				
The DE CA agrees with the proposal that classification for serious eye damage/eye irritation is not required for clethodim.				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	6
Comment received				
The DE CA supports the dossier submitter's proposal to maintain the existing classification of clethodim as skin sensitiser, Cat. 1 (H317). The available data show that clethodim exhibits skin sensitising properties, but the information is not sufficient for sub-categorisation.				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	7
Comment received				
It is agreed that clethodim does not meet the criteria for classification for germ cell mutagenicity based on the available data.				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	8
Comment received				

We agree that clethodim does not meet the criteria for classification as carcinogenic. There is no convincing evidence that the increased incidence of lung adenomas and carcinomas in mice is treatment-related.

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	9
Comment received				
Adverse effects on sexual function and fertility: The DE CA agrees with the DS that based on the available data from a two-generation study in rats, including the dose range-finding study, classification of clethodim as toxic to sexual function and fertility is not justified. However, sperm parameters such as morphology, numbers and motility have not been investigated and a firm conclusion regarding male fertility cannot be made/remains associated with some uncertainty. Adverse effects on development: The DE CA agrees with the DS that based on the available data from a reproduction and a teratology study in rats and rabbits the criteria for classifying clethodim as suspected of causing harm to the unborn child are not met. Although external, skeletal and visceral malformations were observed in rats at the highest dose of 700 mg/kg body weight/day, these were associated with high maternal toxicity (mortality rate of 20 %) and are not regarded as relevant for classification.				

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	10
Comment received				
The DE CA agrees with the conclusion that no specific target organ toxicity relevant for the classification of clethodim was observed after single exposure. Toxic effects, such as neurotoxic effects, were observed at doses that resulted in increased mortality and therefore these effects can be considered adequately covered by the classification for acute oral toxicity.				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2024	United Kingdom	Health and Safety Executive	National Authority	11
Comment received				
‘The DS has proposed classification for STOT RE based on mortality seen in the developmental toxicity studies in rats and rabbits. We note that the substance has an existing harmonised classification of Acute Tox 4. (H302). In the dose-range finding rabbit developmental toxicity study (G.E. (1986)), mortality was seen in 2/7 dams at 300 mg/kg bw/d and 2/7 dams at 500 mg/kg bw/d. The first things to note is the lack of a dose response and that mortality did not occur significantly early at the 500 mg/kg bw/d dose, when compared to deaths at 300 mg/kg bw/d. In addition to this, the 2 deaths at 300 mg/kg bw/d had necropsy findings of ‘hairball in the stomach’ and this same finding was seen in 1 dam at the 500 mg/kg bw/d dose. Therefore, it is possible that				

these animals died due to a stomach obstruction. The other death at the top dose occurred 15 minutes after intubation, suggesting an intubating error. We would welcome a discussion on the rabbit mortality and its relevance to STOT RE.

Looking at the full developmental toxicity study in rats (Anon, 1987), 5/25 dams died at the top dose of 700 mg/kg bw/d, which is within the range of Acute Toxicity. 4. No deaths were seen in the dose range finding study which included doses up to 500 mg/kg bw/d. SDA viral infections were also noted in the dose-range finding study (Anon, 1996). Animals infected with these viruses can display symptoms such as sniffling, sneezing, photophobia, chromodacryorrhea, and submandibular swelling. Active infections can also predispose animals to anaesthetic-induced mortality. It is also recommended that animal facilities with the infection should be depopulated, thoroughly cleaned and restocked. Without any information to say otherwise, the full developmental toxicity study in rats may have had incidence of infection, carried over from the preceding dose range finding study. The DS does not mention the presence of the virus but does not mention its absence either. Considering the clinical signs seen in animals of the full study (e.g. excessive lacrimation, chromodacryorrhea), it could be possible that SDA virus was present in these dams. Presence of an infection could possibly make the dams more susceptible to mortality induced by clethodim. Hence, we welcome a discussion over the mortalities in the rats and their relevance to STOT RE.'

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2024	United Kingdom	Arysta LifeScience S.A.S.,	Company-Manufacturer	12
Comment received				
p 63 to p 107 of the combined PPP and CLH report for clethodim. The applicant does not agree with the proposal that STOT-RE 2. H373 be attributed to clethodim. Further details are provided in the attached document (1602214.UK0 - 4352) ECHA note – An attachment was submitted with the comment above. Refer to public attachment 1602214.UK0 - 4352 STOT RE Cat 2 applicant response 08.02.24.pdf				

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	13
Comment received				
In general, the DE CA acknowledges and supports the STOT RE 2 (H373) classification based on maternal mortality observed in the rat teratology toxicity study after 5 – 10 days of treatment at 700 mg/kg body weight/day. It appears that pregnant animals represent a particularly sensitive subpopulation, which is also confirmed by the teratology pilot study in rabbits. However, it should be discussed whether this effect may be sufficiently covered by the classification for acute oral toxicity. In addition, a more detailed justification of the extrapolation for time of exposure would be appreciated.				

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
08.02.2024	France		MemberState	14

Comment received
FR agrees with the general conclusion dealing with the classification for environmental hazard of the substance and with the proposed M factors (acute and chronic): Aquatic acute 1 (M factor = 10) Aquatic chronic 1 (M factor = 10) However, the ECr50 and ECr10 values, respectively, of 0.0886mg/L and 0.00066mg/L, for Glyceria maxima seems to be based on TWA concentrations. Could you, please, justified that the TWA concentrations are more relevant than the geometric mean measured concentrations for semi-static design? These comments will not change the conclusion of the classification proposal.

Date	Country	Organisation	Type of Organisation	Comment number
01.02.2024	Germany		MemberState	15
Comment received				
We do not agree that clethodim is rapidly biodegradable. In our opinion the OECD TG 301D is not plausible because of the given 133-138% ThOD measured after 14-28 days. Even if the as result for the reference substance (sodium benzoate) degradation of more than 130% was given, too; there must be something wrong with the study. The given explanation for the exceedance of the theoretical oxygen demand is not sufficient. If a high oxygen consumption and self-digestion of the inoculum occurred, it cannot be excluded that the amount of this oxygen consumption is very high and clethodim itself is degraded to less than 60%. Mineralisation in the Aerobic Mineralisation in surface water study is very low. We propose to demand a new valid study for Ready biodegradability or a classification as not rapidly degradable.				

Date	Country	Organisation	Type of Organisation	Comment number
29.01.2024	United Kingdom	Health and Safety Executive	National Authority	16
Comment received				
Clethodim: There is some partitioning of clethodim from water to sediment in this Glyceria study (along with degradation), which is also seen in the available water/sediment simulation studies. However, this is limited and all key endpoints are based on twa measured concentrations in the water phase. We therefore agree that the test is relevant for aquatic hazard classification. Based on information presented in the CLH annex B-9, it appears that a clear dose response was not observed in the Glyceria maxima study (see tables 9.2.7-8 and 9.2.7-9). A dose response is only apparent for most parameters at the higher test concentrations, and growth rate effects are only statistically significant at 0.0781 mg/L (measured twa) and above; hence the lowest NOErC is 0.027 mg/L for total leaf length and fresh weight. The confidence intervals around the key ErC10(fresh weight) are wide and unbounded (<0.000064 - 0.00312 mg/L) covering an order of magnitude below the NOErC and multiple hazard classification bands. On this basis, the ErC10(fresh weight) presented in the CLH report (0.00066 mg/L) is unlikely to be a statistically robust endpoint and reliable for Chronic aquatic hazard classification. Therefore, we believe the NOErC of 0.027 mg/L is a				

more robust and reliable endpoint overall. This leads to a classification of Aquatic Chronic 2 for a rapidly degradable substance.

PUBLIC ATTACHMENTS
1. 1602214.UK0 - 4352 STOT RE Cat 2 applicant response 08.02.24.pdf [Please refer to comment No. 1, 12]