ANNEX 3 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CLH PROPOSAL ON 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

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

The proposal for the harmonised classification and labelling (CLH) of clethodim (ISO); (5RS)-2-{(1EZ)-1-[(2E)-3-chloroallyloxyimino]propyl}-5-[(2RS)-2-(ethylthio)propyl]-3-hydroxycyclohex-2-en-1-one (EC - ; CAS 99129-21-2) was submitted by the Sweden and was subject to a consultation, from 11 December 2023 to 9 February 2024. The comments received by that date are compiled in Annex 2 to the opinion.

During the above consultation of the CLH report for clethodim (ISO), it was replaced by the CLH report for another substance for the last 16 days. Therefore, interested parties were given additional three weeks to submit their comments.

An ad hoc consultation was launched from 27 February 2024 to 19 March 2024 and the comments received are listed below.

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

HEALTH HAZARDS – Acute toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	1
Comment received				
Acute Toxicity – Oral According to the criteria in CLP Annex I, oral LD50 >300 but ≤2000mg/kg bodyweight. Classification Acute toxicity Category 4. H302. is required. BE CA agrees with the RMS. An ATE=1133mg/kg is a justified deduction. Acute Toxicity – dermal According to the criteria in CLP Annex I, dermal LD50 >2000mg/kg bodyweight. Classification is not warranted under Regulation (EC) 1272/2008. BE CA supports the conclusion of the RMS. Acute Toxicity – Inhalation BE CA supports the conclusion of the RMS: Clethodim does not fulfil criteria for classification.				
RAC's response				

HEALTH HAZARDS – Skin corrosion/irritation

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	2
Comment received				
BE CA agrees with the RMS.				

RAC's response

HEALTH HAZARDS – Serious eye damage/eye irritation

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	3
Comment received				
BE CA supports the conclusion of the RMS that Clethodim does not fulfil criteria for classification.				
RAC's response				

HEALTH HAZARDS – Skin sensitisation

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	4
Comment received				
Although a high concentration for the intradermal induction was used (50%), out of the observed contact hypersensitivity BE CA agrees that clethodim needs to be classified as a moderate skin sensitizer category 1, H 317.				
RAC's response				

HEALTH HAZARDS – Germ cell mutagenicity

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	5
Comment received				
Out of the three bacterial reverse mutation assays conducted, only one out of three involved both plate incorporation and pre-incubation test. It is important to note that cytotoxicity was observed in the pre-incubation test, at doses that did not exhibit any cytotoxicity in the plate incorporation test. The other two bacterial reverse mutation assays were conducted exclusively using plate incorporation testing. Additionally, one mutagenicity study aimed at detecting induced forward mutations, two chromosome aberration assays, and one micronucleus test were performed. However, no confirmation of mutagenicity was found. Furthermore, no in vivo testing in somatic cells revealed any toxicity. BE CA supports the conclusion from the RMS.				
RAC's response				

HEALTH HAZARDS – Carcinogenicity

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	6

ANNEX 3 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON CLH PROPOSAL ON 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

Comment received
An increased incidence (exceeding the HCD) of lung tumors was noted in an 1-year oncogenicity study in mice, although a clear dose-response relation was not observed and occurrence was observed at older ages without leading to death. Therefore BE CA agrees with the RMS.
RAC's response

HEALTH HAZARDS – Reproductive toxicity

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	7
Comment received				
No significant decreased fertility indices were observed. Additionally the observed alterations remained within HCD. No significant adverse effect on sexual function or fertility is noted. In a 2-generational study in F1 rats, significantly lower body weights were noted. This study also revealed more kidney abnormalities in F1 from 500ppm and in F2 across all dose levels. However, no further developmental and functional observations in pups were monitored in this study, and dosing before mating period seems to be only 9 weeks instead of 10 weeks. In a developmental study (0-8.3-83.3-292-593mg/kg) in rats, fetal body weights were significantly decreased from 292mg/kg. The incidence of fetuses with external malformations and the occurrence of litters containing fetuses with external malformations were statistically higher than the control group at doses of 583mg/kg. The applicant attributes these findings to maternal toxicity, which is indeed clearly present at this dose level. A NOAEL for maternal toxicity in this study was established at 83.3mg/kg. Some pups exhibited visceral malformations in the cerebellum, aorta, kidneys, bladder and urinary tract were observed from 583mg/kg onwards, however the incidence of visceral malformations per fetus and per litter for the treated groups, did not differ statistically from the control data. From 292mg/kg, statistically significant variations in ossification were detected (incompletely ossified thoracic vertebral centra; incompletely ossified or unossified sacral vertebral transverse processes; incompletely ossified or unossified caudal vertebral transverse processes, and unossified caudal centra; unossified 5th and/or 6th sternebra). From this study, a developmental NOAEL of 83.3mg/kg can be derived. These variations were substance related. BE CA is of the opinion it would be helpful to have more detailed information to thoroughly evaluate these variations (incidence of each variation, HCD). In another developmental study in rabbits (0-20.8-83.3-250mg/kg) fetal ossification was disturbed from 250mg/kg onwards. A developmental NOAEL of 83.3mg/kg is derived. Taken together, it seems reasonable not to classify clethodim for Repro. More detailed data regarding the statistically significant variations in ossification can support this opinion. BE CA concludes that evidence from animal studies is not sufficiently convincing to place the substance in category 1 or 2. No sufficient data about lactation are available.				

RAC's response

HEALTH HAZARDS – Specific target organ toxicity - single exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	8
Comment received				
Out of acute oral toxicity studies, BE CA concludes that no STOT-SE classification is required. The observed clinical signs were all reversed 6days after the administration of the substance. However, it should be noted that newer acute toxicity test protocols with a wide range of observations on signs of toxicity would provide more information relevant for STOT-SE. Neither the acute dermal toxicity study, nor the acute inhalation study, nor the neurotoxicity study establish evidence for qualification. BE CA agrees with the RMS.				
RAC's response				

HEALTH HAZARDS – Specific target organ toxicity - repeated exposure

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	9
Comment received				
Based on findings of mortality at doses lower than the acute oral toxicity levels, it can be concluded that the toxicity is severe enough to warrant classification. Interpolation between the ED and the NOAEL is required to determine whether the effects expected at or below the GV or not. The NOAEL resulting from 28-day, 90-day or lifetime studies on rats and mice is below the guidance value of 100mg/kg. Data from repeat dose studies conducted in dogs and rabbits also indicated a NOAEL <100mg/kg. The severity of toxicity is described as mild to moderate. The increased liver weight and liver hypertrophy observed in the study are significant findings related to liver health. In the 90-day oral study, a LOAEL of 134mg/kg and a NOAEL of 25mg/kg were noted. Additionally, in the 28-day oral study, a LOAEL of 65.5mg/kg and a NOAEL of 12.5mg were observed. No severe histopathological lesions were found, nor were there major disruptions in clinical biochemistry that would indicate more than consequences of liver hypertrophy. In mice, a significant decrease in hemoglobin was observed at 74.4mg/kg, without further changes in hematocrit or RBC count. Liver hypertrophy with histopathologically confirmed discolorations was seen starting at 179mg/kg. An EL of 179mg/kg seems justified based on this. In an 1-year oncogenicity study in mice, significant hematological alterations (significant				

decreased RBC count, hemoglobin and hematocrit) was noted at dose level of 357mg/kg. From 119mg/kg onward centrilobular liver hypertrophy, increased pigmentation and bile duct hyperplasia were observed. Systemic amyloidosis (immunotoxicity) was noted at 357mg/kg onward.

In another developmental pilot rabbit study (gavage), mortality (starting at 300mg/kg) was also observed. However, the presence of paraovarian cysts (a nonneoplastic lesion outside the ovary)– indicated by the applicant to be specific to the strain- and the use of too few animals, made it impossible to determine a NOAEL.

A clear increase in the incidence of bone marrow hyperplasia was observed during a 90-day oral study in dogs starting at 300mg/kg. We also observed significantly disturbed hematological values in the same study, also from 300mg/kg onwards. Such findings were not reported in other studies, and we lack sufficient investigations at the bone marrow level to draw further conclusions. In the same study, an increased weight of (para)thyroid gland was also noted from 300mg/kg onward. Liver hypertrophy with pigmentation was observed from 300mg/kg in this study, with the relative liver weight significantly increased from 75mg/kg onwards. The NOAEL in this study was determined to be 25mg/kg.

In a developmental study on rats with a NOAEL of 83.3mg/kg and a LOAEL of 292mg/kg – based on a clear deterioration in the overall condition of rats- a mortality rate of 20% was observed from 583mg/kg, however, without a clear dose-response relationship.

It seems reasonable to interpolate the effect level somewhere above the NOAEL but below the LOAEL, potentially around the mid-point of slightly higher within this range. As the effect level remains below 100mg, the classification of Clethodim in STOT-RE Category 2 appears appropriate to BE CA.

RAC's response

ENVIRONMENTAL HAZARDS – Hazardous to the aquatic environment

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	United Kingdom	Arysta LifeScience S.A.S.,	Company-Manufacturer	10

Comment received

The manufacturer agrees with the proposed classification.
With respect to ready biodegradability, the relevant study conducted in accordance with OECD TG 301D has previously been concluded to be valid by EFSA (EFSA Journal 2011;9(10):2417) and it was concluded that clethodim is readily biodegradable. In addition, ECHA previously reviewed the OECD TG 301D study and concluded that clethodim meets the criteria for being readily biodegradable (RAC opinion CLH-O-0000001412-86-91/F adopted 4 December 2015).
The manufacturer also notes that Volume 1 concludes that, on the basis of soil, water and sediment degradation data, clethodim does not fulfil the criteria for persistence.

RAC's response

Date	Country	Organisation	Type of Organisation	Comment

				number
19.03.2024	Belgium		MemberState	11
Comment received				
BE CA agrees with the proposed environmental classification. Although the study with Glyceria maxima, performed according to OECD TG 239 is a water-sediment study an thus exposure via sediment can not be excluded, it can be considered relevant in this case: Clothedim is a herbicide, the substance is considered mobile (log Kfoc = 2.20 <3) and shows severe toxicity in this aquatic plant study. Thus based on the results of the aquatic toxicity test on the most sensitive species (Aquatic plants (Glyceria maxima) with 14d ErC50 = 0.0886 mg/L and 14d ErC10= 0.00066 mg/L, the fact that the substance is to be considered as rapidly degradable (readily degradable according to OECD TG 301<d) it is justified to classify, following the classification criteria of the regulation 1272/2008, as Aquatic Acute 1, H400 and Aquatic Chronic 1, H410. The substance shows no potential to bioaccumulate. In view of the proposed classification and toxicity band for acute toxicity between 0.01mg/L and 0.1 mg/l, an M-factor for acute toxicity of 10 could be assigned and an M-factor for chronic toxicity of 10 (rapidly degradable substance and ErC10 between 0.0001 mg/L and 0.001 mg/L)				
RAC’s response				

ADDITIONAL HAZARDS – Hazardous for the ozone layer

Date	Country	Organisation	Type of Organisation	Comment number
19.03.2024	Belgium		MemberState	12
Comment received				
We agree that classification for the ozone layer is not warranted.				
RAC’s response				