Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of
muscalure; cis-Tricos-9-ene

EC number: 248-505-7

CAS number: 27519-02-4

ECHA/RAC/CLH-O-0000001670-80-02/F

Adopted

30 November 2012

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Substance Name: muscalure; cis-Tricos-9-ene

EC number: 248-505-7

CAS number: 27519-02-4

The proposal was submitted by **Austria**

and received by RAC on **25 January 2012.**

In this opinion, all classifications are given firstly in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS) and secondly, according to the notation of 67/548/EEC, the Dangerous Substances Directive (DSD).

The proposed harmonised classification

	CLP	**DSD**
Current entry in Annex VI to CLP Regulation	Not currently in Annex VI (table 3.1) of CLP Regulation	Not currently in Annex VI (table 3.2) of CLP Regulation
Proposal by dossier submitter for consideration by RAC	Skin Sens. 1B; H317: May cause an allergic skin reaction	R43 – May cause sensitisation by skin contact
Resulting harmonised classification (future entry in Annex VI to CLP Regulation) based on the proposal by the dossier submitter	Skin Sens. 1B; H317: May cause an allergic skin reaction	R43 – May cause sensitisation by skin contact

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/web/guest/harmonised-classification-and-labelling-consultation*** on **25 January 2012**. All parties concerned including Member-State Competent Authorities (MSCA) were invited to submit comments and contributions by **12 March 2012.**

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Paola di Prospero**
Co-rapporteurs, appointed by RAC: **José Luis Tadeo**

The opinion in accordance with Article 37 (4) of the CLP Regulation.

The RAC opinion on the proposed harmonised classification and labelling, taking into account the comments provided by MSCAs and concerned parties in accordance with Article 37 (4) of the CLP Regulation was reached on **30 November, 2012** These comments are compiled in Annex 2.

The opinion of the RAC was adopted by **consensus*.***

OPINION OF THE RAC

The RAC adopted the opinion that **muscalure; cis-Tricos-9-ene** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
	muscalure; cis-tricos-9-ene	248-505-7	27519-02-4	**Skin Sens. 1B**	H317	GHS07 Wng	H317			

Classification and labelling in accordance with the criteria of DSD

Index No	International Chemical Identification	EC No	CAS No	Classification	Labelling	Concentration Limits	Notes
	muscalure; cis-tricos-9-ene	248-505-7	27519-02-4	**R43**	Xi R: 43 S: (2-)24-37		

SCIENTIFIC GROUNDS FOR THE OPINION

The opinion relates only to those hazard classes that have been reviewed in the proposal for harmonised classification and labelling, as submitted by Austria.

Physical hazards

Summary of the Dossier submitter's proposal
No classification is proposed

Comments received during public consultation
No Comments received

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Acute toxicity

Summary of the Dossier submitter's proposal
No classification is proposed.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier submitter's proposal
No classification is proposed.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Skin corrosion/irritation

Summary of the Dossier submitter's proposal
No classification is proposed.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Eye corrosion/irritation

Summary of the Dossier submitter's proposal
No classification is proposed.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Respiratory sensitisation

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as no classification was proposed by the dossier submitter and no comments were submitted during public consultation.

Skin sensitisation

Summary of the Dossier submitter's proposal
The dossier submitter (DS) proposed the harmonised classification of cis-tricos-9-ene to be Skin Sens. 1B, H317 (May cause an allergic skin reaction) in accordance with CLP (DSD; R43 - May cause skin sensitisation by skin contact). In the CLH report, one key study was presented, namely, an OECD 406 Maximisation test (data unpublished, data owner Denka Int., 1991). In that study, the intradermal induction of a 5% mixture of cis-tricos-9-ene in corn oil and Freund Adjuvant resulted in 7/20 animals (35%) which scored positive following epidermal induction (challenge) with undiluted cis-tricos-9-ene (positive animals presented an irritation score ranging from 1 to 4).

Comments received during public consultation
During the public consultation, Germany noted that while the criteria for Cat. 1B are formally fulfilled, all positive readings were observed only at the second day after challenge with animals showing minimal irritation scores ranging from 1 to 4. However, in their experience, reaction to typical sensitizers is most prominent throughout the first 24 hours after challenge, and subsequently, with decreasing intensity. Germany specified that, on the basis of the data provided, there is no plausible explanation for such unusual behaviour.

Assessment and comparison with the classification criteria
RAC agreed with the DS's proposal to classify and label muscalure; cis-tricos-9-ene according the CLP criteria as sensitising, under CLP category 1B, H317.

Classification/labelling for skin sensitization according to CLP Regulation 1272/2008/EC
A guinea pig maximization test indicated that muscalure; cis-tricos-9-ene has moderate skin sensitizing properties: with intradermal induction of a 5% mixture in corn oil and Freund Adjuvant, 7 out of 20 animals (35%) scored positive.
Often reaction to typical sensitizers is indeed most prominent during the first 24 hours after challenge, with subsequent decreasing intensity. However in this study all positive readings were observed only on the second day after challenge (no response in the first

24 hours) with animals showing irritation (red spots, scattered reaction) scores ranging from 1 to 4. There is no plausible explanation for such unusual behaviour because CIS-TRICOS-9-ene is not a skin irritant.
The reaction (35% response at 5% intradermal induction dose) fits with the criterion indicated in the CLP Regulation Table 3.4.4., for category 1B, that represents ≥ 30% response at > 1% intradermal induction dose. The reaction is less strong than that indicated in CLP Regulation table 3.4.4., for category 1A (≥ 60% response at intradermal induction dose of > 0.1% to ≤ 1% or ≥ 30% response at intradermal induction dose of ≤ 0.1%).

The RAC concluded that muscalure; cis-tricos-9-ene should be classified as sensitising, under CLP category 1B, H317 (may cause an allergic skin reaction).

Classification/labeling for skin sensitization according to Directive 67/548/EEC
The DSD criteria are less differentiated (for adjuvant test method, a response of at least 30% of the animals is required). However, according to the DSD criteria classification, R43 is required.

The RAC concluded that muscalure; cis-tricos-9-ene should be classified as sensitising according to the DSD criteria with R43.

Repeated dose toxicity (DSD) and specific target organ toxicity (CLP) – repeated exposure (STOT RE)

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by RAC, as the CLH report did not contain data on this hazard class following the application of the Guidance on Data Requirements for active substances in biocidal products under Directive 98/8/EC (ECB, 2000, 2008). No comments were submitted during public consultation.
The technical note on data requirements is available at
http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/guidance-documents

Germ cell mutagenicity

Summary of the Dossier submitter's proposal
No classification is proposed.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as the CLH report does not contain data about this endpoint and no comments were submitted during public consultation.

Carcinogenicity

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by RAC, as the CLH report did not contain data on this hazard class following the application of the Guidance on Data Requirements for active substances in biocidal products under Directive 98/8/EC (ECB, 2000, 2008). No comments were submitted during public consultation.
The technical note on data requirements is available at
http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/guidance-documents

Reproductive toxicity

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by RAC, as the CLH report did not contain data on this hazard class following the application of the Guidance on Data Requirements for active substances in biocidal products under Directive 98/8/EC (ECB, 2000, 2008). No comments were submitted during public consultation.
The technical note on data requirements is available at
http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/guidance-documents

Aspiration toxicity

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as the CLH report does not contain data about this endpoint and no comments were submitted during public consultation.

Environmental hazards
Summary of the Dossier submitter's proposal

The dossier submitter (DS) proposed no classification for cis-tricos-9-ene (muscalure) regarding its environmental hazard.

1. *Degradation.*

The CLH report did not contain experimental data following the application of the Guidance on Data Requirements for active substances in biocidal products under Directive 98/8/EC (ECB, 2000, 2008). Only QSAR estimations were provided.
The technical note on data requirements is available at
http://ihcp.jrc.ec.europa.eu/our_activities/public-health/risk_assessment_of_Biocides/guidance-documents

a. Biodegradation.

A QSAR estimation on ready biodegradability is provided. The predictions from the models BIOWIN1, 2, 3, 5 and 6 indicate that muscalure; cis-tricos-9-ene is readily biodegradable. Several higher alkanes were used to derive this QSAR estimation. According to Fuchs et al. (2006), the aerobic microbial degradation mechanism for alkanes can also apply to alkenes. In addition, all probability cut-off points as suggested by ECHA (2008)[1] regarding ready biodegradability of the utilised QSAR model were met.

b. Hydrolysis and photolysis in water.

Abiotic degradation due to hydrolysis and photolysis in water was not investigated.
HYDROWIN model v1.67 is not applicable to this kind of chemical and therefore no rate constant could be estimated. The Henry´s law constant (>2.95 x 10^3 Pa x m^3/mol) indicates that if cis-tricos-9-ene reaches the water surface it is partitioned to the atmosphere at a rapid rate.

c. Phototransformation in air.

Muscalure; cis-tricos-9-ene is susceptible to photochemical degradation in the gas phase by OH-radicals and ozone, with half-life of 4.7 h and 2.1 h, respectively. Based on these results, accumulation or long-range transport of muscalure; cis-tricos-9-ene in air is not expected.

2. *Aquatic Bioaccumulation.*

Experimental BCF data was not available and therefore, two BCF values were estimated in the dossier using the log K_{ow} > 8.2 (Competent Authority Report, CAR; Doc. III-A3, Doc. IV-A 3.9/01) (CAR, 2009).
First, the BCF_{fish} was calculated according to the equation provided in the Technical Guidance Document (TGD) on Risk assessment and a value of log BCF = 4.3 was obtained which indicated a high potential for bioaccumulation. However it should be noted that this mathematical relationship has a high degree of uncertainty because of the hydrophobic properties of Muscalure.
Second, based on calculations with the EPI SUITE software BCFBAFWIN v3.00, a log BCF_{fish} of 2.9 was obtained, which is lower than the calculated BCF from the TGD equation.

3. Aquatic toxicity.

Two acute-tests on fish and Daphnia were reported in the CLH report.
The acute toxicity of muscalure; cis-tricos-9-ene was investigated on rainbow trout in a semi-static study for 96 h. The LC_{50} values could not be calculated because no mortality up to the highest tested concentration of 100 mg/L had been observed. The test concentrations were far in excess of the water solubility (7µg/L). This test shows some deficiencies such as the actual exposure concentration could not accurately be established due to the poor solubility of the test substance. In addition, the un-dissolved material present may have disturbed the test system.

The acute toxicity of muscalure; cis-tricos-9-ene to daphnia was investigated in a static study with measured concentrations of muscalure; cis-tricos-9-ene, which were far below nominal values at the end of the study. Test concentrations exceeded the water solubility of muscalure. The LC_{50} was established at 0.25 mg/L (mean measured concentration), effects found at higher values, 0.83 mg/L (mean measured concentration), were attributed to a physical effect (the animals were trapped in a transparent fleece).

[1] ECHA, 2008: Guidance on information requirements and chemical safety Assessment, R.7 b: Endpoint Specific Guidance.

A test on microalgae was not supplied following the application of the Guidance on Data Requirements for active substances in biocidal products under Directive 98/8/EC (ECB, 2000, 2008).

Comments received during public consultation
Two comments on the environmental section were submitted by France. The first comment concerned biodegradation and the fact that the assessment for this endpoint should be based on the intrinsic properties of the substance and not upon the intended use, as has been presented by the dossier submitter. In the revised CLH report, the dossier submitter deleted argumentation about the intended indoor use in the biodegradation section, but this argumentation is still present within the CLH report.
The second comment referred to the aquatic toxicity of this substance that should be considered higher than the threshold value of 1 mg/L, if the result of the daphnia test was expressed as a value of EC_{50}>0.25 mg/L. An argumentation why the aquatic toxicity of daphnia should be considered higher was added to the revised CLH report, as follows: "*…At 0.83 mg/L the observed effects on mobility were attributed to physical burden. Therefore it is considered that an EC_{50} based on toxicological effects would be higher and in any case exceed 1mg/L*".

Assessment and comparison with the classification criteria

According to the dossier submitter, the assessment of cis-tricos-9-ene has been carried out under consideration of the Guidance for waiving data requirements for pheromones for inclusion in Annex I/IA of Directive 98/8/EC. However, this Guidance emphasised that *"…as data required for classification and labelling cannot be generated solely to satisfy this purpose, this evaluation considers only the data that would be required to satisfy biocidal data requirements and does not consider the classification and labelling requirements…"*. Thus, for classification purposes, intrinsic properties of the substance should be taken into consideration, and therefore, the degradation in the environment, bioaccumulation and the aquatic toxicity should be clearly established and described.

Biodegradation:
QSARs estimations have been used to study biodegradation, and according to these results it is reasonable to assume that muscalure; cis-tricos-9-ene will be rapidly degraded to CO2 and water in environmental compartments.

This information is supported by OECD Screening Information Data Set (OECD SIDS, 2004) reported in Doc. IIA of the CAR prepared for Muscalure (CAR, 2009).

In this work C20-C24 branched and linear alkenes (>70% branched) were tested in an OECD 301B test. The internal olefins attained a total of 92% degradation after 28 days and met the 10-day window validity criterion=. The toxicity control attained 100% degradation after 28% days confirming that the test material was not toxic to sewage treatment microorganisms used in the study. All validity criteria required were achieved; therefore C20-24 alkenes, branched and linear can be considered to be readily biodegradable under OCDE 301B.

Cis-tricos-9-ene is structurally quite similar to these internal olefins, it is a C23 alkene, and therefore the results from this test can be used to confirm the QSAR estimations.

It is reasonable to assume that cis-tricos-9-ene is **rapidly/readily degradable.**

Bioaccumulation:
experimental BCF data was not available and therefore, two BCF values were estimated in the dossier using the log K_{ow} > 8.2 (CAR; Doc. III-A3, Doc. IV-A 3.9/01). Both BCF_{fish}

values estimated are above the cut-off values reported in CLP (section 4.1.2.8.1) but are not reliable due to the hydrophobic properties of Muscalure.

Aquatic toxicity:
the CLH report only contains information about short-term toxicity of cis-tricos-9-ene in fish and Daphnia, there is no information regarding toxicity in microalgae.
The LC_{50} value for the acute toxicity to fish could not be calculated because no mortality up to the nominal highest tested concentration of 100 mg/L was observed. This concentration was far above the water solubility of muscalure; cis-tricos-9-ene ($< 7 \times 10^{-6}$ g/L 20°C).
The acute toxicity test in Daphnia shows that the highest tested nominal concentration causing no effects after 48 hours was 10 mg/L (equal to 0.25 mg/L mean measured concentration). However, effects appear at tested concentration of 100 mg/L (n) (equal to 0.82 mg/L), these effects were attributed to a physical effect (the animals were trapped in a transparent fleece, microscopically assessed), therefore it is possible to establish a $LC_{50\ of} > 0.25$ mg/L (mean measured concentrations).

According to the Guidance on the Application of Regulation (EC) No 1272/2008 relating to poorly soluble substances:

a. *Where the acute toxicity is recorded at levels in excess of water solubility, the $L(E)C_{50}$ for classification purposes may be considered to be equal to or below the measured water solubility. In such circumstances it is likely that Chronic Category 1 and/or Acute Category 1 should be applied. In making this decision, due attention should be paid to the possibility that the excess undissolved substances may have given rise to physical effects on the test organism. Where this is considered the likely cause of the effects observed, the test should be considered as invalid for classification purposes.*

b. *Where no Acute toxicity is recorded at levels in excess of water solubility, the $L(E)C_{50}$ for classification purposes may be considered to be greater than the measured water solubility. In such circumstances, consideration should be given to whether the Chronic Category 4 should apply. In making a decision that the substance shows no acute toxicity, due account should be taken of the techniques used to achieve the maximum dissolved concentrations. Where these are not considered as adequate, the test should be considered as invalid for classification purposes;*

The acute toxicity test in fish shows some deficiencies. The actual exposure concentration was not accurately established due to the poor solubility of muscalure and the undissolved material. However, the study was considered reliable (klimish score 2) (CAR,2009). The conclusion of the study is that the **LC_{50} for fish is greater than the water solubility**. From this it appears that cis-tricos-9-ene does not meet the criteria for Aquatic Acute 1 and, considering the fact that cis-tricos-9-ene is considered to be rapidly degradable (from QSAR), the safety net classification criteria (chronic 4) is not met.

With the Daphnia toxicity test, the acute toxicity is also recorded at levels in excess of the water solubility, however, according to the dossier submitter, this effect was attributed to physical effects, and therefore, according to Guidance on the application of Regulation (EC) No. 1272/2008, therefore, the test should be considered invalid for classification purposes.

According to OECD SIDS (2004), the higher molecular weight olefins, those greater than C10, whose water solubility is low, are not expected to cause acute aquatic toxicity. Testing with water accommodated fractions of C20-24 internal branched and linear olefins (similar to muscalure) showed no aquatic toxicity in acute aquatic tests with fish,

invertebrates and algae (see table 3 - additional key elements). The end-points for the three trophic levels are greater than the water solubility, which is in agreement with the available toxicity data to fish for cis-tricos-9-ene.

Taking into account this information, RAC agreed with the DS's proposal **not** to **classify muscalure; cis-triscos-9-ene for environmental hazard.**

CLP classification:

Acute hazard: Not classified.
Chronic hazard: Not classified. No toxic effects were recorded up to the water solubility. Furthermore, muscalure; cis-tricos-9-ene is considered to be rapidly biodegradable

DSD classification:

R50: Not classified.
Not classified as R53 assuming rapid degradation according to QSAR estimations.

Hazards to the ozone layer

Summary of the Dossier submitter's proposal
No information available.

Comments received during public consultation
No comments received.

Assessment and comparison with the classification criteria
This endpoint was not assessed by the RAC, as the CLH report does not contain data about this endpoint and no comments were submitted during public consultation.

ANNEXES:

Annex 1 Background Document (BD), gives detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the dossier submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excl. confidential information).