Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

Isopropyl (2*E*,4*E*,7*S*)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate; S-methoprene

EC Number: -
CAS Number: 65733-16-6

CLH-O-0000001412-86-114/F

Adopted
3 June 2016

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON ISOPROPYL (2E,4E,7S)-11-METHOXY-3,7,11-TRIMETHYLDODECA-2,4-DIENOATE; S-METHOPRENE

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: **Isopropyl (2*E*,4*E*,7*S*)-11-methoxy-3,7,11-trimethyldodeca-2,4-dienoate; S-methoprene**
EC number: **-**
CAS number: **65733-16-6**
Dossier Submitter: **Ireland**

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
07.09.2015	Ireland	S-Squared Consulting Ltd	BehalfOfAnOrganisation	1

Comment received

Bábolna Bioenvironmental Centre Ltd conducted studies on the active substance S-Methoprene due to the questions regarding the proposed classification Hazard Statements of the active substance most notably the Environmental hazards. S-Squared Consulting Ltd is working with Bábolna Bioenvironmental Centre Ltd on the evaluation of S-Methoprene for its inclusion in Annex I of Directive 98/8/EC.
Please find studies with new eco-toxicology data on S-Methoprene. These studies include:

•S-Methoprene: Degradation and Metabolism in Four Soils of {14C] S-Methoprene Incubated under Aerobic Conditions.
•S-Methoprene: Route and Rate of Degradation of [14C]S-Methoprene in Aerobic Aquatic Sediment Systems.

•Inherent Biodegradability of S-Methoprene In Modified MITI Test (II)

•Effects of S-Methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test (Draft Report)

•Collembolan Reproduction Test in Soil with S-Methoprene technical,

It is believe that using this information, it will help to prove the point that S-Methoprene will not have any unreasonable adverse effects to the environment in relation to persistency and bioaccumulation.
Reference Section 5 Environment Harzard Assessment (page 62)

Full studies will follow.
Dossier Submitter's Response
Thank you for your comment. Regarding the first three studies; • S-Methoprene: Degradation and Metabolism in Four Soils of {14C] S-Methoprene Incubated under Aerobic Conditions. • S-Methoprene: Route and Rate of Degradation of [14C]S-Methoprene in Aerobic Aquatic Sediment Systems. • Inherent Biodegradability of S-Methoprene In Modified MITI Test (II). These studies have been evaluated in-house as part of the Biocide work on the persistency criteria of the substance in the environment, however, these do not contribute to the classification of S-methoprene and therefore we do not propose to include these in the CLH report. However, we will attach our evaluation and study summaries. If required these can be added to the CLH report by the RAC Rapporteur The two remaining ecotoxicology studies (Effects of S-Methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test (Draft Report); **and** Collembolan Reproduction Test in Soil with S-Methoprene technical)were only brought to our attention in September 2015 and were not submitted as part of the Biocide or CLH evaluation process. However, they can be submitted for evaluation by the RAC Rapporteur.
RAC's response
RAC notes that the inherent biodegradability study is part of the CLP report (see Table 49) and was evaluated by the dossier submitter (see page 64). In the opinion, RAC has assessed the study "S-Methoprene: Route and Rate of Degradation of [14C]S-Methoprene in Aerobic Aquatic Sediment Systems" (IIIA 7.1.2.2.2), but found it as not convincing scientific evidence for rapid degradability (see opinion). RAC notes that the study on degradation in four soils is in general not relevant for CLP purposes since biotic or abiotic degradation in the aquatic environment needs to be demonstrated. Also the soil ecotoxicity study is not relevant since there are no relevant classification criteria. Environmental hazard classification is based on aquatic data, namely fish, crustacea and algae or other aquatic plants, see CLP Regulation Annex I 4.1.2.6 and 4.1.2.7.

Date	Country	Organisation	Type of Organisation	Comment number
28.08.2015	Germany		MemberState	2
Comment received				
The German CA agrees upon the proposed environmental classification of S-Methoprene and would like to thank Ireland for the preparation of the CLH-Report. Please include the sentence "Conclusive but not sufficient for classification" in the last column of Table 1.3 Proposed harmonised classification and labelling based on CLP Regulation for CLP Annex I ref. 3.1 Acute toxicity – oral, 3.6 Carcinogenicity, and 3.7 Reproductive toxicity (page 9). Data / Studies are available for the respective endpoints and the results do not trigger classification proposals.				
Dossier Submitter's Response				
Thank you for your comment. We will incorporate the proposed sentence as appropriate.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	Ireland	S-Squared Consulting Ltd	Industry or trade association	3
Comment received				
Bábolna Bioenvironmental Centre Ltd conducted studies on the active substance S-Methoprene due to the questions regarding the proposed classification Hazard Statements of the active substance most notably the Environmental hazards. S-Squared Consulting Ltd is working with Bábolna Bioenvironmental Centre Ltd on the evaluation of S-Methoprene for its inclusion in Annex I of Directive 98/8/EC. •Effects of S-Methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test. It is believe that using this information, it will help to prove the point that S-Methoprene will not have any unreasonable adverse effects to the environment. *ECHA note: The following confidential attachments were submitted with the comment above:* *1) Effects of S-methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test [Final Report]* *2) Reproduction study with other soil non-target macro-organisms: earthworm (Eisenia fetida) reproduction in a chronic toxicity test*				
Dossier Submitter's Response				
Please refer to Comment 1 above.				
RAC's response				
Please refer to Comment 1 above.				

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	4
Comment received				
The CLH regulation criteria are based on hazard only, any considerations about risk should not be taken into account.				
Dossier Submitter's Response				
Agreed.				
RAC's response				
Agreed.				

Date	Country	Organisation	Type of Organisation	Comment number
07.09.2015	Ireland	S-Squared Consulting Ltd	Industry or trade association	5
Comment received				
Bábolna Bioenvironmental Centre Ltd conducted studies on the active substance S-Methoprene due to the questions regarding the proposed classification Hazard Statements of the active substance most notably the Environmental hazards. S-Squared Consulting Ltd is working with Bábolna Bioenvironmental Centre Ltd on the evaluation of S-Methoprene for its inclusion in Annex I of Directive 98/8/EC. Please find studies with new eco-toxicology data on S-Methoprene. These studies include: •S-Methoprene: Degradation and Metabolism in Four Soils of {14C] S-Methoprene				

Incubated under Aerobic Conditions.
•S-Methoprene: Route and Rate of Degradation of [14C]S-Methoprene in Aerobic Aquatic Sediment Systems.

•Inherent Biodegradability of S-Methoprene In Modified MITI Test (II)

•Effects of S-Methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test (Draft Report)

•Collembolan Reproduction Test in Soil with S-Methoprene technical,

It is believe that using this information, it will help to prove the point that S-Methoprene will not have any unreasonable adverse effects to the environment in relation to persistency and bioaccumulation.
Reference Section 5 Environment Harzard Assessment (page 62)

Full studies will follow.

ECHA note: The following confidential attachments were submitted with the comment above:

1) *S-methoprene: Degradation and Metabolism in Four Soils of [^{14}C]S-methoprene Incubated under Aerobic Conditions*
2) *Aerobic degradation in soil – further studies IIIA 7.2.2.1 Route and rate of degradation*
3) *S-Methoprene:Route and Rate of Degradation of [^{14}C]S-Methoprene in Aerobic Aquatic Sediment Systems*
4) *Effects of S-methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test [Draft Report]*
5) *INHERENT BIODEGRADABILITY OF S-METHOPRENE IN MODIFIED MITI TEST (II) [Final Report]*
6) *COLLEMBOLAN REPRODUCTION TEST IN SOIL WITH S-METHOPRENE TECHNICAL [Final Report]*
7) *Section IIIA 7.1.1.2 Inherent Biodegradability*
8) *Section A7.5.2.1 Reproduction study with other soil non-target macro-organisms: Collembolan Reproduction Test in Soil*
9) *Section A7.1.2.2/1 Water/sediment degradation*

Dossier Submitter's Response

Please refer to comment 1 above.

RAC's response

Please refer to Comment 1 above.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	7

Comment received

4.9 Carcinogenicity, p40
Could you please indicate if the studies were performed according to OECD guideline or similar to OECD guideline?

Dossier Submitter's Response

Both studies was carried out prior to the availability of US EPA and OECD guidelines. Both studies were compared to OECD guidelines 453 and 451 for evaluation purposes, respectively. Deviations from the OECD guidelines were documented by both the Applicant and the Competent Authority and were considered during the evaluation of these studies.
RAC's response
Taking into consideration the dossier submitter's response RAC considers that the studies can be used to conclude that no classification of S-methoprene for carcinogenicity is warranted.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	8
Comment received				
4.8 Germ cell mutagenicity, p38 It seems that the gene mutation potential of the substance on mammalian cells is lacking. Indeed, only 2 types of in vitro tests are submitted (bacterial gene mutation and chromosomal aberrations).Moreover, the part is very poorly detailed. Consequently, FR has the opinion that this endpoint is not argued enough and thus, not conclusive.				
Dossier Submitter's Response				
S-Methoprene did not induce gene mutations in bacterial cells *in vitro*. The *in vitro* chromosome aberration test in CHO cells revealed no evidence for clastogenic potential of S-Methoprene. The results of these studies are conclusive and not sufficient for classification. However, we can provide more information in the appropriate section of the CLH report to represent this.				
RAC's response				
RAC agrees with both the commenting MS and the dossier submitter. The set of information is not sufficient to propose classification, although the available information points towards S-methoprene not being mutagenic. Thus, RAC considers that the only option is to not propose classification of this substance.				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	9
Comment received				
4.5.6 Skin sensitisation, p.29 4.5.6.1 Non human information FR considers the negative results of the Buehler test (3 applications) not sufficient to conclude on the sensitising potential of the substance. Please add justifications as required in the biocidal context for the same endpoint.				
Dossier Submitter's Response				
The study was conducted according to U.S. EPA Guideline 81-6 which is equivalent to OECD Guideline 406. The test substance, S-Methoprene, produced no irritation in naive control group animals after the single treatment at challenge. Similarly, the test substance produced no signs of irritation in test group animals after the challenge treatment and therefore did not elicit a sensitising reaction in guinea pigs. In accordance with the criteria defined in CLP				

Regulation (EC) No. 1272/2008, S-Methoprene does not require classification for skin sensitization. The result of the described Buehler test are considered sufficient to conclude on the lack of sensitising potential of the substance and further justification is not considered warranted.
RAC's response
RAC agrees with the dossier submitter that there are no reasons to doubt the validity of the results in the Buehler test because the sensitisation recorded in both the challenged and the naive control groups were 0% and the positive control worked well, inducing sensitisation in at least 80% of the animals. In addition, the US EPA Guideline followed for conducting the assay is consistent with the results. However, RAC also considers that more information would have been desirable. Nevertheless, in the current scenario, the only option is to propose no classification of S-methoprene for skin sensitisation.

OTHER HAZARDS AND ENDPOINTS – Hazardous to the Aquatic Environment

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	10
Comment received				
We support the proposed classification : - H400 with M-factor =1 - H410 with M-factor = 1 Minor comment, p66: the sentence "based on these results, S-Methoprene meets B criterion (CAR IIIA7.4.2.1)." is confusing and should be deleted. As you mention after this sentence, the threshold value for B criteria following the Annex XIII of Reach regulation is 2000 L/kg.				
Dossier Submitter's Response				
Agreed. We will delete the sentence "based on these results, S-Methoprene meets B criterion (CAR IIIA7.4.2.1)."				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
09.09.2015	Sweden		MemberState	11
Comment received				
The Swedish CA support the classification of S-Methoprene in Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) as specified in the proposal. This conclusion is based on the effect of the most sensitive invertebrate Daphnia magna and that the substance is not rapidly degradable and has a high bioaccumulation potential. The SE CA agree with the rationale for the setting of M-factors of 1 for both acute and chronic toxicity for the aquatic organisms.				
Dossier Submitter's Response				
Thank you for your comment.				
RAC's response				
Noted.				

OTHER HAZARDS AND ENDPOINTS – Physical Hazards

Date	Country	Organisation	Type of Organisation	Comment number
11.09.2015	France		MemberState	12
Comment received				
p.8: Oxidizing properties of the substance are missing in the CLH report. However, according to the CAR of the substance, S-Metropene has no oxidizing properties regarding molecular structure. P 15: According to the CAR of the substance, the substance S-Metropene has no explosive properties regarding molecular structure. The term "little explosive" in the table 9 may cause confusion and should not be reported.				
Dossier Submitter's Response				
Agreed. Regarding "Oxidizing properties" a statement will be included indicating S-methoprene has no oxidizing properties. Reference to "little explosive" will be removed.				
RAC's response				
RAC considers the current state of the CLH report as acceptable for assessment of the physical hazards of S-methoprene.				

CONFIDENTIAL ATTACHMENTS RECEIVED:

1) *Effects of S-methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test [Final Report].* Submitted on 11.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 3*]
2) *Reproduction study with other soil non-target macro-organisms: earthworm (Eisenia fetida) reproduction in a chronic toxicity test.* Submitted on 11.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 3*]
3) *S-methoprene: Degradation and Metabolism in Four Soils of [^{14}C]S-methoprene Incubated under Aerobic Conditions.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
4) *Aerobic degradation in soil – further studies IIIA 7.2.2.1 Route and rate of degradation.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
5) *Effects of S-methoprene technical on earthworm (Eisenia fetida) reproduction in a chronic toxicity test [Draft Report].* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
6) *INHERENT BIODEGRADABILITY OF S-METHOPRENE IN MODIFIED MITI TEST (II) [Final Report].* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
7) *COLLEMBOLAN REPRODUCTION TEST IN SOIL WITH S-METHOPRENE TECHNICAL [Final Report].* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
8) *S-Methoprene: Route and Rate of Degradation of [^{14}C]S-Methoprene in Aerobic Aquatic Sediment Systems.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [*Please refer to comment no. 5*]
9) *Inherent Biodegradability.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [Please refer to comment no. 5]

10) *Section A7.5.2.1 Reproduction study with other soil non-target macro-organisms: Collembolan Reproduction Test in Soil.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [Please refer to comment no. 5]
11) *Section A7.1.2.2/1 Water/sediment degradation.* Submitted on 07.09.2015 by S-Squared Consulting Ltd. [Please refer to comment no. 5]