Committee for Risk Assessment

RAC

Annex 1

Background document

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

Reaction mass of *N*,*N*'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and *N*,*N*'-ethane-1,2-diylbis(12-hydroxyoctadecanamide); [1]

Reaction mass of *N*,*N*'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]

EC Number: 430-050-2 [1] - [2]
CAS Number: - [1] - [2]

CLH-O-0000007073-80-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

18 March 2022

CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

Chemical name:

Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and N,N'-ethane-1,2-diylbis(12-hydroxyoctadecanamide);[1]

Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]

EC Number: **430-050-2**
CAS Number: **-**
Index Number: **616-127-00-5**

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Version number: 2 **Date: 30 November, 2020**

CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	**Reaction mass of *N,N'*-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and *N,N'*-ethane-1,2-diylbis(12-hydroxyoctadecanamide);[1]** **Reaction mass of *N,N'*-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]**
Other names (usual name, trade name, abbreviation)	Thixatrol Plus
ISO common name (if available and appropriate)	*N/A*
EC number (if available and appropriate)	430-050-2
EC name (if available and appropriate)	**Reaction mass of *N,N'*-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and *N,N'*-ethane-1,2-diylbis(12-hydroxyoctadecanamide);[1]** **Reaction mass of *N,N'*-ethane-1,2-diylbis(decanamide) and 12-hydroxy-*N*-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]**
CAS number (if available)	-
Other identity code (if available)	-
Molecular formula	Not applicable as the substance is a multi-constituent substance
Structural formula	Not applicable as the substance is a multi-constituent substance
SMILES notation (if available)	Not applicable as the substance is a multi-constituent substance
Molecular weight or molecular weight range	368-625 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*N/A*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*N/A*
Degree of purity (%) (if relevant for the entry in Annex VI)	

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
1-[2-(decanoylamino)ethylamino]-1-decanone (EC: -, CAS 51139-08-3)	See confidential annex	-	-
1-[2-(decanoylamino)ethylamino]-12-hydroxy-1-octadecanone (EC: -, CAS 146781-64-8)	See confidential annex	-	-
12-hydroxy-1-[2-(12-hydroxyoctadecanoylamino)ethylamino]1-octadecanone (EC 204-613-6, CAS 123-26-2)	See confidential annex	-	Skin Sens. 1B Skin Irrit. 2 Eye Irrit. 2 STOT SE 3 Aq. Chronic 3 Aq. Chronic 4

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No relevant impurities				

Some of the registrants of the substance have reported impurities. These have been taken into consideration and are not considered to affect the classification proposed in this dossier. Further information on the impurities is considered to be confidential. See confidential annex.

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No additives					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: For substance with an existing entry in Annex VI of CLP

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	616-127-00-5	reaction mass of: *N,N'*-Ethane-1,2-diylbis(decanamide); 12-Hydroxy-*N*-[2-[1-oxydecyl)amino]ethyl]octadecanamide; *N,N'*-Ethane-1,2-diylbis(12-hydroxyoctadecanamide)	430-050-2	-	Skin Sens. 1 Aquatic Chronic 2	H317 H411	GHS09 GHS07 Wng	H317 H411			
Dossier submitters proposal	616-127-00-5	Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and N,N'-ethane-1,2-diylbis(12-hydroxyoctadecanamide);[1] Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]	430-050-2 [1] - [2]	- [1] - [2]	**Add** Aquatic Acute 1 **Modify** Aquatic Chronic 1	**Add** H400 **Modify** H410	**Retain** GHS09 Wng	**Modify** H410		**Add** M-factor acute=100 M-factor chronic=10	
Resulting Annex VI entry if agreed by	616-127-00-5	Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and N,N'-ethane-	430-050-2 [1]	- [1]	**Skin Sens. 1** **Aquatic Acute 1** **Aquatic Chronic 1**	**H317** **H400** **H410**	**GHS07** **GHS09** **Wng**	**H317** **H410**		**M=100** **M=10**	

RAC and COM		1,2-diylbis(12-hydroxyoctadecanamide);[1] Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]	- [2]	-[2]							

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	*hazard class not assessed in this dossier*	No
Flammable gases (including chemically unstable gases)	*hazard class not assessed in this dossier*	No
Oxidising gases	*hazard class not assessed in this dossier*	No
Gases under pressure	*hazard class not assessed in this dossier*	No
Flammable liquids	*hazard class not assessed in this dossier*	No
Flammable solids	*hazard class not assessed in this dossier*	No
Self-reactive substances	*hazard class not assessed in this dossier*	No
Pyrophoric liquids	*hazard class not assessed in this dossier*	No
Pyrophoric solids	*hazard class not assessed in this dossier*	No
Self-heating substances	*hazard class not assessed in this dossier*	No
Substances which in contact with water emit flammable gases	*hazard class not assessed in this dossier*	No
Oxidising liquids	*hazard class not assessed in this dossier*	No
Oxidising solids	*hazard class not assessed in this dossier*	No
Organic peroxides	*hazard class not assessed in this dossier*	No
Corrosive to metals	*hazard class not assessed in this dossier*	No
Acute toxicity via oral route	*hazard class not assessed in this dossier*	No
Acute toxicity via dermal route	*hazard class not assessed in this dossier*	No
Acute toxicity via inhalation route	*hazard class not assessed in this dossier*	No
Skin corrosion/irritation	*hazard class not assessed in this dossier*	No
Serious eye damage/eye irritation	*hazard class not assessed in this dossier*	No
Respiratory sensitisation	*hazard class not assessed in this dossier*	No
Skin sensitisation	*hazard class not assessed in this dossier*	No
Germ cell mutagenicity	*hazard class not assessed in this dossier*	No
Carcinogenicity	*hazard class not assessed in this dossier*	No
Reproductive toxicity	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-single exposure	*hazard class not assessed in this dossier*	No
Specific target organ toxicity-repeated exposure	*hazard class not assessed in this dossier*	No
Aspiration hazard	*hazard class not assessed in this dossier*	No
Hazardous to the aquatic environment	Hazard classification proposed	Yes
Hazardous to the ozone layer	*hazard class not assessed in this dossier*	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The harmonised classification of Thixatrol Plus as R43 and N;R51-53 was agreed under the Dangerous Substances Directive 67/548/EEC (DSD) and was included in the Annex I of DSD. The harmonised classification was translated to the CLP Classification as Skin Sensitisation 1: H317, and Aquatic Chronic 2: H411, and included in the Annex VI of CLP.

This proposal aims to update the current environmental classification by including Aquatic Acute 1 (M-factor 100) and changing Aquatic Chronic 2 to Aquatic Chronic 1 (M-factor 10).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Change in existing entry due to new data
Change in existing entry due to changes in the criteria

5 IDENTIFIED USES

Thixatrol Plus is used as a rheological additive in coating products, fillers, putties, plasters, modelling clay, finger paints and adhesives and sealants. Uses at industrial sites, by professional workers and by consumers as well as article service-life are registered under the REACH Regulation ((EC) No 1907/2006).

6 DATA SOURCES

Registration dossiers submitted for the substance under the REACH Regulation ((EC) No 1907/2006).

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid (powder), off-white		
Melting/freezing point	>= 122.6 - <= 126.1 °C	Zeneca Specialties, 1997	EU Method A.1 (Capillary method)
Boiling point	ca. 352 °C at 101.3 kPa	Zeneca Specialties, 1997	EU Method A.2 (Differential Scanning Calorimetry.)
Relative density	1.04 at 20 °C	Zeneca Specialties, 1997	EU Method A.3 (Pycnometer method)
Vapour pressure	< 0 Pa at 25 °C < 3.5 x 10^{-9} Pa at 25 °C	Zeneca Specialties, 1997	EU Method A.4, effusion method by loss of weight,estimated value EPISuite MPBPVP (v1.43) QSAR model (using smiles of the three main constituents)
Surface tension	51.9 mN/m at 23 °C	Zeneca Specialties, 1997	EU Method A.5 (Plate method)

Property	Value	Reference	Comment (e.g. measured or estimated)
Water solubility	< 0.034 mg/L at 22 °C	Zeneca Specialties, 1997	EU Method A.6 (flask method)
Partition coefficient n-octanol/water	5.4 - 6.6 at 25 °C 6.12-11.31	Zeneca Specialties, 1997	EU Method A.8 (HPLC method) EPISuite KOWWIN (v1.68) QSAR model (using smiles of the three main constituents)
Flash point	Not applicable		
Flammability	Not flammable	Zeneca Specialties, 1997	EU Method A.10
Explosive properties	Based on the chemical structures of the components of the substance, the result for the explosive properties has been predicted negative.		
Self-ignition temperature	The substance did not ignite below its melting point range of 122.6 - 126.1°C.	Zeneca Specialties, 1997	EU Method A.16
Oxidising properties	Based on the chemical structures of the components of the substance, the result for the oxidising properties has been predicted negative.		
Granulometry	D50 4.13 - 596 µm	Zeneca, 1998	Air elutriation method/ Laser diffraction method
Stability in organic solvents and identity of relevant degradation products	Solubility in n-octanol 3290 mg/L at 25 °C		EU Method A.8 (estimation method)
Dissociation constant	No data		
Viscosity	Not applicable		

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not relevant for the classification proposal in this dossier.

10 EVALUATION OF HEALTH HAZARDS

Not assessed in this dossier. No public consultation proposed.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

11.1 Rapid degradability of organic substances

Table 8: Summary of relevant information on rapid degradability

Method	Results	Remarks	Reference
Test type: ready biodegradability OECD Guideline 301 B (Ready Biodegradability: CO_2 Evolution Test) GLP	Readily biodegradable (not meeting 10d window) % Degradation of test substance: 69.3 after 28 d (CO_2 evolution)	1 (reliable without restriction) experimental result **Test material (EC name): Thixatrol Plus (purity 96.9 %)**	Chemex International plc, 1998 (Study summary included in the REACH registration dossier)

11.1.1 Ready biodegradability

A ready biodegradation screening test according to OECD 301B is available for Thixatrol Plus. The test substance and inorganic nutrient medium were inoculated with activated sewage sludge (concentration of suspended solids 30 mg/L) and incubated for up to 28 days at 23 °C. 55 mg of substance was used as sole source of organic carbon. It is indicated a Total Organic Carbon (TOC) of 40 mg in 2 L of mineral medium, which results in 20 mg C/L, and hence, is within the range of 10-20 mg C/L indicated in the OECD guideline. The degradation of the substance was determined to be 69.3 % after 28 days based on CO_2 evolution. The degradation did not meet the criteria for the 10-days window although it was very close to meeting them. After 10 days the degradation was 9.62 % and after 21 days it had reached a level of 59.27 %. The validity criteria of the test were met. The reference substance, sodium acetate, reached 66.9 % degradation after 14 days and the mean blank CO_2 evolution was 19.9 mg/L.

It is noted that Thixatrol Plus is a multiconstituent substance consisting of three main constituents and the degradation of different constituents may differ. Ready biodegradability tests are intended for pure substances and are generally not applicable for complex compositions containing different types of constituents. However, the OECD "Guidelines for the Testing of Chemicals, Revised Introduction to the OECD Guidelines for Testing of Chemicals, Section 3 Part I: Principles and Strategies Related to the Testing of Degradation of Organic Chemicals" (OECD, 2006) indicates that "*it is sometimes relevant to examine the ready biodegradability of mixtures of structurally similar chemicals".* Still "*a case by case evaluation should however take place on whether a biodegradability test on such a complex mixture would give valuable information regarding the biodegradability of the mixture as such (i.e. regarding the degradability of all the constituents) or whether instead an investigation of the degradability of carefully selected individual components of the mixture is required*". The OECD document and the ECHA Guidance on the Application of CLP criteria (Annex II, Version 5.0, July 2017) also state that the 10-day window need not be applied if the test is carried out on a mixture of structurally similar constituents and if it is anticipated that a sequential biodegradation of the individual constituents is taking place. This applies to multi-constituent and certain UVCB substances (such as oils and surfactants) consisting of structural similar constituents with different chain-lengths, degree and/or

site of branching or stereo-isomers, even in their most purified commercial forms.

The main constituents of Thixatrol Plus are structurally similar; they all have two amide groups connected by an ethyl group and two linear alkyl sidechains. The alkyl sidechains are either C10 or C18, the latter having an hydroxyl group. The constituent with two short sidechains (referred to as constituent A in the this dossier) is more watersoluble and hence more bioavailable to the microorganisms than the other two constituents that have either one short and one long sidechain (constituent B in this dossier) or two long sidechains (constituent C in this dossier). Therefore, a sequential degradation of the constituents can be expected, and as a consequence, the 10 day window criteria do not need to be applied.

It is also noted that according to ECHA Guidance R.7b (ECHA, 2017b), the pass levels for ready biodegradability tests relate to measured sum parameters for DOC depletion, oxygen use or CO2 production and imply total degradation (assume that 30-40 % of the organic carbon of the test substance is either assimilated by the microbial biomass for growth or present as products of biosynthesis). Therefore, as the substance reached 69 % degradation, it can be assumed that not much of the substance remained after 28 days. There is no information on the proportions of the three constituents in the test material, but according to the registration information on typical concentrations, all the constituents are present at a significant concentration (above 10 %) and the most abundant constituent is the constituent B followed by the constituent C. Consequently, since almost complete degradation of the entire substance was observed in the ready biodegradation test, and considering that the constituents are structurally relatively similar (they differ in the length of the linear alkyl chains), it can be assumed that all three main constituents have degraded either almost completely or at least to a significant extent.

EPISuite BIOWIN v4.10 models were performed for the main constituents of the substance as supporting information (see Table 9). In the BIOWIN 1, 2, 5 and 6 models, a biodegradability probability score above 0.5 predicts fast or ready biodegradability of the substance. In BIOWIN 3 model, a score in the range of $\geq$ 2.25 - <2.75 predicts ultimate biodegradation in “weeks to months” and a score $\geq$ 2.75 ultimate biodegradation in “weeks” (or faster). According to the REACH Guidance R.11: PBT/vPvB Assessment (ECHA, 2017), the output of the models BIOWIN 2, BIOWIN 3 and BIOWIN 6 of the EPISuite BIOWIN QSAR models can be used to make a screening assessment of persistence. The following outcome indicate that a substance may potentially be persistent: BIOWIN 2 <0.5 and BIOWIN 3 <2.2 or BIOWIN 6 <0.5 and BIOWIN 3 <2.2. However, borderline cases should be carefully examined, e.g. when the estimate of the BIOWIN 3 gives a result in the range 2.25 to 2.75.

The results of the BIOWIN models for the main constituents are shown in the below table. The BIOWIN 1, 2, 5 and 6 models predict that all three constituents are readily biodegradable as the results are well above 0.5. For the constituent A and B, the results of the BIOWIN 3 model also indicate fast ultimate biodegradation as they are 2.75 or above. However, it is noted that the result of BIOWIN 3 model for the constituent C is a borderline case (in the range 2.25 to 2.75) as it is close to the screening criterion specified in the ECHA Guidance R.11 for potential persistence.

Table 9 Episuite Biowin V4.10 Models For The Main Constituents

Constituent	BIOWIN model				
	1	2	3	5	6
1-[2-(decanoylamino)ethylamino]-1-decanone (constituent A)	1.2092	0.9989	2.8729	0.7591	0.8063

Constituent	BIOWIN model				
	1	2	3	5	6
1-[2-(decanoylamino)ethylamino]-12-hydroxy-1-octadecanone (constituent B)	1.3069	0.9979	2.7495	0.8340	0.8369
12-hydroxy-1-[2-(12-hydroxyoctadecanoylamino)ethylamino]1-octadecanone (constituent C)	1.4046	0.9957	2.6261	0.9090	0.8635

11.1.2 BOD_5/COD

No relevant data available.

11.1.3 Hydrolysis

No relevant data available.

11.1.4 Other convincing scientific evidence

No relevant data available.

11.1.4.1 Field investigations and monitoring data (if relevant for C&L)

No relevant data available.

11.1.4.2 Inherent and enhanced ready biodegradability tests

No relevant data available.

11.1.4.3 Water, water-sediment and soil degradation data (including simulation studies)

No relevant data available.

11.1.4.4 Photochemical degradation

No relevant data available.

11.2 Environmental transformation of metals or inorganic metals compounds

Not relevant.

11.3 Environmental fate and other relevant information

Not relevant.

11.4 Bioaccumulation

11.4.1 Estimated bioaccumulation

EPISuite KOWWIN (v1.68) QSAR model predicts log Kow values of 6.12, 8.51 and 11.31 for the three main constituents of Thixatrol Plus.

11.4.2 Measured partition coefficient and bioaccumulation test data

There is no experimental information on the bioaccumulation of the Thixatrol Plus or of the similar substances.

The log Kow values of the constituents measured using the HPLC method are in the range of 5.4-6.6. There is uncertainty in the measured values because the HPLC method is applicable only for log Kow values up to 6 and the log Kow values of the constituents predicted by the KOWWIN QSAR model are in the range of 6.12-11.31.

In conclusion, since there is no experimental data on bioaccumulation and the measured and predicted log Kow values of all main constituents are above 4, Thixatrol Plus is considered to have a high bioaccumulation potential for classification purposes.

11.5 Acute aquatic hazard

Table 10: Summary of relevant information on acute aquatic toxicity. As the name of the substance is quite long, 'Thixatrol Plus' has been used instead in the document. Information on substance purity was not available.

Method	Species	Test material	Results	Remarks	Reference
OECD Guideline 203 (Fish, Acute Toxicity Test) EU Method C.1 (Acute Toxicity for Fish) GLP freshwater static	*Rainbow trout (Oncorhynchus mykiss)*	**Thixatrol Plus** Exposure to a water accommodated fraction (WAF)	LL50 (96 h): > 1000 mg/l loading rate test mat. (nominal) based on: mortality NOELR (96 h): 1000 mg/l loading rate test mat. (nominal) based on: mortality	1 (reliable without restriction)	Chemex International Plc (1998b) (Study summary included in the REACH registration dossier)
OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) EU Method C.2 (Acute Toxicity for Daphnia) GLP freshwater static	*Daphnia magna*	**Thixatrol Plus**	EL50 (48 h): 15.63 — 250 mg/L test mat. (nominal) based on: immobilisation	1 (reliable without restriction)	Chemex International Plc (1998c) (Study summary included in the REACH registration dossier)

OECD Guideline 201 (algal growth inhibition) EU Method C.3 (Algal Inhibition test) GLP freshwater static	*Chlorella vulgaris*	**Thixatrol Plus**	NOEC (72 h): 25.6 mg/L based on: growth rate (Freshwater study on Chlorella vulgaris. No ErC50 could not be calculated as the dissolved concentration of test substance was not determined.)	1 (reliable without restriction)	Chemex International Plc (1998d) (Study summary included in the REACH registration dossier)
OECD 201 (1984*)* (algal growth inhibition) EU Method C.3 (Algal Inhibition test) GLP freshwater static	*Chlorella vulgaris*	**Thixatrol Plus**	EL50 (72 h): > 1000 loading rate WAF test mat. (nominal) based on: growth rate and biomass	1 (reliable without restriction)	Chemex International Plc (1998e) (Study summary included in the REACH registration dossier)
ISO 10253 (Water quality - Marine Algal Growth Inhibition Test with Skeletonema costatum and Phaeodactylum tricornutum) GLP saltwater static	*Skeletonema costatum*	**Thixatrol Plus**	ErC50 (48 h): 0.0012 mg/L (95% CL of 0.0011-0.0013 mg/L) (meas.) based on: growth rate ErC10 (48 h): 0.00087 mg/L (95% CL of 0.00068-0.0010 mg/L) (meas.) based on: growth rate NOErC (48 h): 0.000359 mg/L (meas.) based on: growth rate	1 (reliable without restriction) **Key study**	Harlan Laboratories Ltd (2011) (Study summary and full study report included in the REACH registration dossier)
ISO 10253 (Water quality - Marine Algal Growth Inhibition Test with Skeletonema costatum and Phaeodactylum tricornutum) saltwater static	*Skeletonema costatum*	**Thixatrol Plus**	EC50 (72 h): 4.08 mg/L loading rate, water accomodated fraction (nominal) based on: growth rate		Hyder Environmental Laboratories (1998a) (Study summary included in the REACH registration dossier)
short-term toxicity PARCOM 190.5	*Corophium volutator*	**Thixatrol Plus**	NOEC (10 d): 1000 mg/kg sediment dw test mat. (nominal) based on: mortality	1 (reliable without restriction)	Hyder Environmental Laboratories (1998b) (Study summary included in the REACH

GLP saltwater static			LC50 (10 d): > 10000 mg/kg sediment dw test mat. (nominal) based on: mortality		registration dossier)

11.5.1 Acute (short-term) toxicity to fish

One acute study following OECD 203 is available for Thixatrol Plus. Rainbow trout were exposed to a water accommodated fraction (WAF) at a loading rate of 1000 mg/L during 96 hours. No mortality or other adverse effects were observed. Therefore the reported 96h LL50 is >1000 mg/L. It is noted that the loading rate is well above the water solubility limit of the constituents of the substance, there is no information on the measured concentrations or on the method used for the preparation of the WAFs. Therefore, it is not possible to confirm that the fish were actually exposed to the test substance, and hence, the study is considered not reliable.

Due to the low solubility of the substance, long-term testing is considered more relevant for the substance. However, no long-term tests with fish are available for the substance.

11.5.2 Acute (short-term) toxicity to aquatic invertebrates

In an acute study performed according to OECD 202, *Daphnia magna* were exposed to the registered substance for a period of 48 hours. In the study summary, immobilisation is reported for all the concentrations tested but it is not stated what the test concentrations were. It is stated that the immobilisation did not follow a clear concentration response and that it may have been caused by physical effects due to undissolved substance particles. 50% immobilisation was observed at 31.25 mg/l and 40% immobilisation at 62.5 mg/l. According to the registrants, the 48-hr EC50 value could not be calculated with any degree of confidence but is thought to lie between 15.63 and 250 mg/l based on nominal concentrations. As the nominal test concentrations were well above the water solubility of the substance, there is no further information on the measured test concentrations and test conditions, and some of the effects may have been caused by undissolved test material, the study is not considered reliable.

11.5.3 Acute (short-term) toxicity to algae or other aquatic plants

Four studies on algae are available for the substance; two marine algal growth inhibition tests with *Skeletonema costatum* performed according to ISO 10253 and two freshwater algae tests following OECD TG 201. In the key study, *Skeletonema costatum* was exposed to five concentrations of the test substance in aqueous solution and to a dilution water control at 20°C under static conditions for 72 hours. The saturated solution method was used to prepare the test solution by stirring 50 mg/L of the test material in culture medium during 24 hours after which any undissolved test substance was removed by filtration (0.2 µm Gelman Acrocap, discarding the first 1 litre in order to pre-condition the filter). The nominal test substance concentrations were 0.00029, 0.00093, 0.0029, 0.0093 and 0.29 mg/L. The test concentrations were measured at 0 and 72 h by high performance liquid chromatography – mass spectrometry (HPLC-MS). The test included three replicate vessels for each treatment group and six vessels for the control group. Potassium dichromate was used as reference substance (positive control). Samples of the algal population were taken at 0, 24, 48 and 72 hours from each treatment and control group and the cell densities determined using a haemocytometer and light microscope.

The measured test concentrations ranged from 15 to 124 % of the nominals at 0 hours and from 18 to 227 % after 72 hours. There was significant and variable interference seen around the test samples´ peaks in the chromatogram analyses. All control samples, both of the definitive test as well as of the paralel procedural recovery trial, gave positive responses at the same retention times as the samples with the test substance. Therefore, the registrant considered that the analytical method used was not applicable for the test substance,

and they reported the results based on nominal concentrations.

However, based on the initial method validation trials and procedural recovery trial, it seems that the analytical method can be considered applicable for most of the test substance concentrations used in the definitive test but less aplicable for the lowest test susbtance concentration (0.00029 mg/L). Furthermore, it is not clear why the controls gave a positive response in the definitive test and procedural recovery trial because in the initial trial comparing different test solution preparation methods, the measured concentrations in the controls were below the limit of quantification (LOQ 0.0068 µg/L). Therefore, it cannot be excluded that the samples of the controls that gave positive response were contaminated with the test substance.

In conclusion, since the test substance has low water solubility and high adsorption potential, the real exposure concentrations were likely lower than the nominal concentrations used in the test, especially in the case of the higher test concentrations. Therefore, it is considered justified to determine the results based on the geometric mean of the measured concentrations at 0 and 72 hours in case of the nominal test concentrations of 0.00093, 0.0029, 0.0093 and 0.29 mg/L. In case of the lowest test concentration (0.00029 mg/L) only the measured concentration at 0 hours is used for calculating the results because the measured concentration at 72 hours was well above the nominal concentration (227 %), and thus, there could have been some error in the measurement. Hence, the mean measured concentrations used for the recalculation of the results were 0.000359, 0.000383, 0.00107, 0.00153 and 0.0235 mg/L.

In the control cultures the number of cells increased by a factor in the range of 177-230 and the average growth rates were in the range of 1.73-1.81 day^{-1} during the 72 hour study period . The coefficient of variation of the growth rates was below 7 % in the controls. Hence, the validity criteria of the ISO 10253 guideline regarding the growth in the control cultures were met for the 72 hour study period. These criteria were also met after 48 hours of exposure. However, it is noted that constant exponential growth occurred only up to 48 hours exposure in the controls and at 72h exposure the growth had slowed down. Hence, the validity criterion of the OECD TG 201 regarding the mean coefficient of variation for section-by-section specific growth rates not exceeding 35% is fulfilled until 48 hours of exposure but not for the whole 72 hours study duration. Although the ISO 10253 guideline does not include this validation criterion, constant exponential growth in the control cultures is considered important for the reliability of the results.

Therefore, the dossier submitter considered only the data up to 48 hours exposure valid and recalculated the results. As indicated above, the test concentrations were measured only at 0 and 72 hours. However, since the substance has low water solubility and high adsorption potential, it can be assumed that any lost of the test substance due to adsorption occurred relatively fast, and hence, the real exposure concentrations at 48 hours is expected to be similar to the measured concentrations at 72 hours. Therefore, the mean measured concentrations as explained above were used by the dossier submitter to calculate the results at 48 hours of exposure. This resulted in a 48h-ErC50 of 0.0012 mg/L (95% CI of 0.0011-0.0013 mg/L) for inhibition of growth rate (based on the mean measured concentrations).

In another marine algal study with *Skekeletonema costatum*, water accomodated fractions over the range of 1 to 10 mg/l loading rate were used. The 72-h EC50 for growth rate was determined to be 4.08 mg/L loading rate. It was not possible to determine a NOEC value. There is very little information on the study available, the loading rates were above the water solubility limit of the substance and there is no information on whether the test concentrations were analytically verified. Therefore, the study is not considered reliable for classification purposes.

The two freshwater algae studies are not considered reliable as they used nominal concentrations/ loading rates well above the water solubility limit of the substance, the results are based on nominal concentrations/loading rates and no analytical measurement of the test concentrations were made.

11.5.4 Acute (short-term) toxicity to other aquatic organisms

A *Corophium volutator* sediment reworker test was performed on the test substance following the PARCOM Guidence 190.5. Adult Corophium were exposed to sediment spiked with the test substance for 10 days. Test concentrations up to 10,000 mg/kg dry weight sediment were used. The 10-day LC50 value was determined to be >10000 mg/kg dry weight of sediment, with a slight indication of a concentration response at the tested range. The 10-d NOEC was determined to be 1000 mg/kg dry weight of sediment. None of the concentrations tested induced 100% mortality.

11.6 Long-term aquatic hazard

Table 11: Summary of relevant information on chronic aquatic toxicity

Method	Species	Test material	Results	Remarks	Reference
OECD Guideline 211 (Daphnia magna Reproduction Test) EU Method C.20 (Daphnia magna Reproduction Test) GLP freshwater semi-static	*Daphnia magna*	**Reaction mass of N, N'-ethane1,2-diylbis(hexanamide) and 12-hydroxy-N-[2-[(1-oxyhexyl)amino]ethyl]octadecanamide and N, N'-ethane-1,2-diylbis(12-hydroxyoctadecan amide) (EC 432-430-3)**	mat. (meas. (TWA)) based on: immobilisation NOEC (21 d): 0.9 mg/L test mat. (meas. (TWA)) based on: reproduction LOEC (21 d): 2.5 mg/L test mat. (meas. (TWA)) based on: immobilisation LOEC (21 d): 2.5 mg/L test mat. (meas. (TWA)) based on: reproduction	2 (reliable with restrictions) Read-across from supporting substance (structural analogue or surrogate)	Harlan Laboratories Ltd, 2009 (Study summary included in the REACH registration dossier)

11.6.1 Chronic toxicity to fish

No relevant data available.

11.6.2 Chronic toxicity to aquatic invertebrates

No long-term studies are available for Thixatrol Plus but a semi-static Daphnia Reproduction study according to OECD 211 is available for the structurally similar substance Thixatrol Max (EC No. 432-430-3). Daphnids (10 individuals per treatment, held individually) were exposed during 21 days to five test concentrations of Thixatrol Max and to a dilution water control under semi-static conditions. The saturated solution method was used to prepare the test solution by stirring 50 mg/L of the test material in culture medium during 24 hours after which any undissolved test substance was removed by filtration (0.2 µm Gelman Acrocap, discarding the first 100 ml in order to pre-condition the filter). The time weighted mean measured test substance concentrations were 0.025, 0.071, 0.24, 0.90 and 2.5 mg/L. The number of live and dead adult Daphnia, young daphnids (live and dead) and unhatched eggs were determined daily. Also observations on the general

condition and size of the adults were made daily. At the end of the test the lengths of the surviving adults were measured. A 21d-NOEC of 0.90 mg/L is reported for reproduction (mean number of live offspring produced per adult), immobilisation and length based on time-weighted mean measured concentration.

The validity criteria of the OECD TG 211 regarding parent mortality (≤ 20%) and the mean number of living offspring produced per parent animal surviving at the end of the test (> 60) were met. It is noted that according to the guideline, the same validity criterion for mortality (20%) can be used for accidental and inadvertent parental mortality for each of the test concentrations. In the second highest test concentration (0.90 mg/L) 30% mortality occurred but according to the study information, this was not statistically significantly different from the control. However, even if the mortalities in this groups are considered accidental and inadvertent, they are above the validity criterion of 20%.

On the other hand, as 30% mortality occurred in the test concentration 0.90 mg/L (which was the second highest concentration) and 70% mortality in the highest concentration, it could be considered that the mortality follows a dose-response at the two highest concentrations. In this case the NOEC for mortality could be the next lowest concentration (0.24 mg/L). If the mortalities in the 0.90 mg/L treatment are considered to be caused by the test substance, the NOEC for reproduction could also result in a lower value than the one reported in the study. This is because the NOEC for reproduction reported in the study is calculated by omitting from the analysis the adults that died during the study (and their offspring) in the 0.90 mg/L treatment. However, if the mortalities in this concentration are not considered accidental or inadvertent, the individuals that died and their offspring should be included in the analysis when calculating the mean number of offspring per adult. However, since raw data on the number of offspring per adult is not available, it is not possible to re-calculate the results.

Thixatrol Plus is similar with the substance Thixatrol Max. Both substances have three main constituents out of which one (EC 204-613-6) is common for both substances and the other main constituents differ only in the length of the shorter alkyl sidechain attached to the amide group(s). In Thixatrol Plus the shorter chain is C10 and in Thixatrol Max it is C6. The constituents of Thixatrol Plus with longer alkyl chains are expected to be less water soluble and to have higher log Kow values than the constituents of Thixatrol Max with shorter sidechains. This could lead to some differences in the toxicity of the two substances to daphnia. However, since the available chronic toxicity value of Thixatrol Plus for algae (ErC10 of 0.00087 mg/L, see next section) is three orders of magnitude lower than the reported NOEC of Thixatrol Max for daphnia (0.9 mg/L, or potentially 0.24 mg/L, see the paragraph above), it is expected that daphnia are not more sensitive to Thixatrol Plus than the algae.

11.6.3 Chronic toxicity to algae or other aquatic plants

In the key study following ISO 10253, a 48h- ErC10 of 0.00087 mg/L (95% CL of 0.00068-0.0010 mg/L) and 48h-NOErC of 0.000359 mg/L (based on mean measured concentrations) are determined for the marine alga *Skeletonema costatum*. See section 11.5.3 for more information on the study.

According to the current ECHA Guidance on the application of the CLP criteria (Version 5.0, July 2017), when EC10 values are available these are preferred over NOEC values in chronic toxicity studies. This applies in cases where EC10 and NOEC values are available for the same endpoint. EC10 values are considered more appropriate for aquatic chronic classification because NOEC values strongly depend on the experimental design (number of doses, width of the inter-dose interval, etc.), whereas EC10 values are derived from the whole concentration-response curve. Therefore, the 48h- ErC10 of 0.00087 mg/L is used for the classification.

11.6.4 Chronic toxicity to other aquatic organisms

No relevant data available.

11.7 Comparison with the CLP criteria

11.7.1 Acute aquatic hazard

No reliable acute studies with Thixatrol plus are available for fish and aquatic invertebrates. One valid acute study with the marine alga *Skeletonema costatum* is available and it resulted in a 48-h ErC50 of 0.0012 mg/L (mean measured concentration). In an acute study with the sediment dwelling organism *Corophium volutator* a 10-day LC50 value of >10000 mg/kg dry weight of sediment was determined.

In conclusion, the lowest available acute value is the 48-h ErC50 of 0.0012 mg/L for *Skeletonema costatum* which is below the classification threshold of 1 mg/L for Aquatic Acute 1 and in the range of $0.001 < L(E)C50 \leq 0.01$ mg/L leading to an acute M-factor of 100.

11.7.2 Long-term aquatic hazard (including bioaccumulation potential and degradation)

The degradation of Thixatrol Plus was 69.3 % after 28 days (based on CO_2 evolution) in an OECD TG 301B study. The degradation did not meet the 10 day window criteria. However, since Thixatrol Plus is a multiconstituent substance consisting of structurally similar constituents and it can be anticipated that a sequential biodegradation of the individual constituents takes place, the 10 day windows criteria does not need to be applied. BIOWIN QSAR models performed for the main constituents support the conclusion of rapid degradability of the substance. In conclusion, Thixatrol Plus is considered to be rapidly degradable for classification purposes.

No experimental information on the bioaccumulation of Thixatrol Plus is available. The measured and estimated log Kow values of the three main constituents are above the cut-off value of 4 indicated in the CLP. Therefore, the substance is considered to have bioaccumulation potential for classification purposes.

No chronic toxicity data for Thixatrol plus is available for fish and aquatic invertebrates. For the marine alga *Skeletonema costatum* a 48h- ErC10 of 0.00087 mg/L (based on mean measured concentration) is available. This is below the classification threshold of 0.01 mg/L for Aquatic Chronic 1 for rapidly degradable substances and in the range of $0.0001 < NOEC \leq 0.001$ mg/L justifying a chronic M-factor of 10.

A *Daphnia magna* Reproduction study with the similar substance Thixatrol Max is available. Two of the main constituents of Thixatrol Plus are expected to be less water soluble and to have higher log Kow values than two of the main constituents of Thixatrol Max with shorter sidechains. This could lead to some differences in the toxicity of the two substances to daphnia, and therefore, the study is not fully adequate for classification of Thixatrol Plus. However, it can be used as supporting information. As the available chronic toxicity value of Thixatrol Plus for algae (ErC10 of 0.00087 mg/L) is three orders of magnitude lower than the reported NOEC of Thixatrol Max for daphnia (0.9 mg/L, or potentially 0.24 mg/L, see the section 11.6.2) it is expected that daphnia are not more sensitive to Thixatrol Plus than the algae.

Since (fully) adequate chronic data is not available for fish and aquatic invertebrates, the surrogate approach (Figure 4.1.1 and Table 4.1.0 in Annex I of CLP) should also be applied in the chronic classification, and the most stringent outcome should be selected. However, valid acute data is not available for fish and aquatic invertebrates either, and hence, it is not possible to apply the surrogate approach for these trophic levels.

As no reliable information on fish is available, some uncertainty remains. However, this only affects the M-factor as the substance already receives the most stringent category for aquatic chronic classification based on the available algae data.

11.8 CONCLUSION ON CLASSIFICATION AND LABELLING FOR ENVIRONMENTAL HAZARDS

Aquatic Acute 1, H400, M-factor 100

Aquatic Chronic 1, H410, M-factor 10

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

Thixatrol Plus (Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide and N,N'-ethane-1,2-diylbis(12-hydroxyoctadecanamide);[1]; Reaction mass of N,N'-ethane-1,2-diylbis(decanamide) and 12-hydroxy-N-[2-[(1-oxodecyl)amino]ethyl]octadecanamide; [2]) is a multi-constituent substance that is used as a rheological additive in coating products, fillers, putties, plasters, modelling clay, finger paints and adhesives and sealants. Uses at industrial sites, by professional workers and by consumers as well as article service-life are registered under the REACH Regulation (EC) No 1907/2006.

The substance is currently listed in Annex VI of the CLP Regulation (EC) No 1272/2008 with a classification for environmental hazards as Aquatic Chronic 2 (H411). The Dossier Submitter (DS) proposed to update the current environmental classification by including Aquatic Acute 1 with an M-factor of 100 based on *Skeletonema costatum* 48h E_rC_{50} value of 0.0012 mg/L and changing Aquatic Chronic 2 to Aquatic Chronic 1 with M-factor of 10 based on *S. costatum* 48-h E_rC_{10} value of 0.00087 mg/L, rapid degradability and high bioaccumulation potential.

Degradation

There is one ready biodegradation test available for Thixatrol Plus. The biodegradation of the Thixatrol Plus was determined following OECD TG 301B using activated sewage sludge over 28 days at 20 mg TOC/L and 23°C. The degradation of the substance was determined to be 69.3% after 28 days based on CO_2 evolution. The degradation did not meet the criteria for the 10-day window although it was very close to meeting them. After 10 days the degradation was 9.62% and after 21 days it had reached a level of 59.27%. The validity criteria of the test were met. The reference substance, sodium acetate, reached 66.9% degradation after 14 days and the mean blank CO_2 evolution was 19.9 mg/L.

In the CLH report, the DS noted that Thixatrol Plus is a multi-constituent substance consisting of three main constituents and the degradation of different constituents may differ.

Ready biodegradability tests are intended for pure substances and are generally not applicable for complex compositions containing different types of constituents.

However, the OECD "Guidelines for the Testing of Chemicals, Revised Introduction to the OECD Guidelines for Testing of Chemicals, Section 3 Part I: Principles and Strategies Related to the Testing of Degradation of Organic Chemicals" (OECD, 2006) indicates that "it is sometimes relevant to examine the ready biodegradability of mixtures of structurally similar chemicals". Still "a case-by-case evaluation should however take place on whether a biodegradability test on such a complex mixture would give valuable information regarding the biodegradability of the mixture as such (i.e., regarding the degradability of all the constituents) or whether

instead an investigation of the degradability of carefully selected individual components of the mixture is required".

The OECD document and the ECHA Guidance on the Application of CLP criteria (Annex II, Version 5.0, July 2017) also state that "the 10-day window need not be applied if the test is carried out on a mixture of structurally similar constituents and if it is anticipated that a sequential biodegradation of the individual constituents is taking place. This applies to well-defined multi-constituent and certain UVCB substances (such as oils and surfactants) consisting of structurally similar constituents with different chain-lengths, degree and/or site of branching or stereo-isomers, even in their most purified commercial forms."

The main constituents of Thixatrol Plus are structurally similar. Constituents have two amide groups connected by an ethyl group and two linear alkyl sidechains. The alkyl sidechains are either C10 or C18, the latter having a hydroxyl group (see table below for the constituent identities). The constituent with two short sidechains (constituent A) is more water-soluble and hence more bioavailable to the microorganisms than the other two constituents that have either one short and one long sidechain (constituent B) or two long sidechains (constituent C). Therefore, a sequential degradation of the constituents can be expected, and consequently, the 10-day window criteria need not be applied.

The DS also noted that according to ECHA Guidance R.7b (ECHA, 2017b), the pass levels for ready biodegradability tests relate to measured sum parameters for DOC depletion, oxygen use or CO_2 production and imply total degradation (assume that 30-40 % of the organic carbon of the test substance is either assimilated by the microbial biomass for growth or present as products of biosynthesis). Therefore, as the substance reached 69% degradation, it can be assumed that not much of the substance remained after 28 days.

There is no information on the proportions of the three constituents in the test material, but according to the registration information on typical concentrations, all the constituents are present at a significant concentration (above 10%) and the most abundant constituent is the constituent B followed by the constituent C.

Consequently, since almost complete degradation of the entire substance was observed in the ready biodegradation test, and considering that the constituents are structurally relatively similar, it can be assumed that all three main constituents have degraded either almost completely or at least to a significant extent.

Estimation of ready biodegradability of the main constituents of Thixatrol Plus is also available in the CLH report. EPISuite BIOWIN v4.10 models were performed for the main constituents of the substance as supporting information. The results are shown in table below. The BIOWIN 1, 2, 5 and 6 models predict that all three constituents are readily biodegradable as the results are well above 0.5. For the constituent A and B, the results of the BIOWIN 3 model also indicate fast ultimate biodegradation as they are 2.75 or above. However, it is noted that the result of BIOWIN 3 model for the constituent C is a borderline case (in the range 2.25 to 2.75) as it is close to the screening criterion specified in the ECHA Guidance R.11: PBT/vPvB Assessment (ECHA, 2017) for potential persistence.

***Table**: Results of QSAR calculations done with the EPISuite Biowin V4.10 models for the main constituents of Thixatrol Plus*

Constituent	**BIOWIN model**				
	1	**2**	**3**	**5**	**6**
1-[2-(decanoylamino)ethylamino]-1-decanone (**constituent A**)	1.2092	0.9989	2.8729	0.7591	0.8063
1-[2-(decanoylamino)ethylamino]-12-hydroxy-1-octadecanone (**constituent B**)	1.3069	0.9979	2.7495	0.8340	0.8369
12-hydroxy-1-[2-(12-hydroxyoctadecanoylamino)ethylamino]1-octadecanone (**constituent C**)	1.4046	0.9957	2.6261	0.9090	0.8635

Based on available data, the DS concluded that Thixatrol Plus can be considered as rapidly degradable.

Bioaccumulation

QSAR calculations with EPISuite KOWWIN (v1.68) resulted in log K_{ow} values of 6.12, 8.51 and 11.31 for the three main constituents of Thixatrol Plus.

There is no experimental information on the bioaccumulation of Thixatrol Plus or of similar substances.

The log K_{ow} values of the constituents measured using the HPLC method are in the range of 5.4 - 6.6. There is uncertainty in the measured values because the HPLC method is applicable only for log K_{ow} values up to 6 and the log K_{ow} values of the constituents predicted by the KOWWIN QSAR model are in the range of 6.12 - 11.31.

Based on available data, the DS concluded that, since there are no experimental data on bioaccumulation and the measured and predicted log K_{ow} values of all main constituents are above the cut-off value of 4 in the CLP Regulation, Thixatrol Plus is considered to have a high bioaccumulation potential.

Aquatic Toxicity

For Thixatrol Plus, aquatic acute toxicity data are available for all three trophic levels, while for aquatic chronic toxicity only algae data are available. In addition to aquatic chronic toxicity, a study on marine algae using Thixatrol Plus and one aquatic chronic toxicity study with invertebrate (*Daphnia magna*) using Thixatrol Max is presented in the CLP report. All the studies presented in the CLH report are considered not reliable by DS with exception of one study with marine algae *S. costatum* using Thixatrol Plus and a study with *D. magna* using Thixatrol Max. A summary of the information on aquatic toxicity is provided in the following table (the key endpoints used in hazard classification are highlighted in bold). Thixatrol Plus has a low water solubility (< 0.034 mg/L at 22°C) and high adsorption potential.

***Table**: Summary of information on aquatic toxicity of Thixatrol Plus and Thixatrol Max considered in the CLH report.*

Method/Substance	**Species**	**Endpoint**	**Toxicity value (mg/L)**	**Reference/Reliability**
Short-term toxicity				

OECD TG 203, EU Method C.1 Thixatrol Plus	*Oncorhynchus mykiss*	96h LL_{50} mortality 96h NOELR mortality	> 1000 n 1000 n	Chemex International Plc (1998b) Not reliable
OECD TG 202, EU Method C.2 Thixatrol Plus	*Daphnia magna*	48h EL_{50} immobilisation	15.63 — 250 n	Chemex International Plc (1998c) Not reliable
OECD TG 201, EU Method C.3 Thixatrol Plus	*Chlorella vulgaris*	72h E_rC_{50} 72h NOEC growth rate	/ 25.6	Chemex International Plc (1998d) Not reliable
OECD TG 201 (1984), EU Method C.3 Thixatrol Plus	*Chlorella vulgaris*	72h EL_{50} growth rate, biomass	> 1000 n	Chemex International Plc (1998e) Not reliable
ISO 10253 Thixatrol Plus	*Skeletonema costatum*	48h E_rC_{50} growth rate	**0.0012** mm	Harlan Laboratories Ltd (2011) Reliable
ISO 10253 Thixatrol Plus	*Skeletonema costatum*	72h EC_{50} growth rate	4.08 n	Hyder Environmental Laboratories (1998a) Not reliable
Long-term toxicity				
OECD TG 201, EU Method C.3 Thixatrol Plus	*Chlorella vulgaris*	72h NOEC growth rate	25.6	Chemex International Plc (1998d) Not reliable
OECD TG 211 Thixatrol Max	*Daphnia magna*	21d NOEC reproduction 21d LOEC Immobilisation 21d LOEC reproduction	0.9 mg/L meas. (TWA) 2.5 mg/L meas. (TWA) 2.5 mg/L meas. (TWA)	Harlan Laboratories Ltd, 2009 Reliable
ISO 10253 Thixatrol Plus	*Skeletonema costatum*	48h ErC_{10} growth rate 48h NOE_rC growth rate	**0.00087** mm 0.000359 mm	Harlan Laboratories Ltd (2011) Reliable

Note: n – nominal concentrations; mm – mean measured; / - could not be calculated as the dissolved concentration of test substance was not determined; TWA – time weighted mean measured

Acute aquatic toxicity

In an acute toxicity test following OECD TG 203, rainbow trout (*Oncorhynchus mykiss*) were exposed to a water accommodated fraction (WAF) at a loading rate of 1000 mg/L for 96 hours. No mortality or other adverse effects were observed. The reported 96-h LL_{50} is >1000 mg/L. The DS noted that the loading rate is well above the water solubility limit of the constituents of the substance and there is no information on the measured concentrations or on the method used for the preparation of the WAFs. Therefore, it is not possible to confirm that the fish were exposed to the test substance, and hence, the study is considered not reliable by the DS.

The acute toxicity of Thixatrol Plus to *D. magna* was determined in a 48h a static test system, according to OECD TG 202. Immobilisation is reported for all tested concentrations, but the test concentrations are not stated. It is stated that the immobilisation did not follow a clear concentration response and that it may have been caused by physical effects due to undissolved substance particles. 50% immobilisation was observed at 31.25 mg/L and 40% immobilisation at 62.5 mg/L. According to the registrants, the 48h EC_{50} value could not be calculated with any degree of confidence but is thought to lie between 15.63 and 250 mg/L based on nominal concentrations. As the nominal test concentrations were well above the water solubility of the substance, there is no further information on the measured test concentrations and test conditions, and some of the effects may have been caused by undissolved test material, the study is considered not reliable by the DS.

Four aquatic toxicity studies with algae are available for Thixatrol Plus, two with marine algae and two with freshwater algae. The only study considered reliable by the DS is algae growth inhibition tests with *S. costatum* carried out in accordance with ISO 10253 guideline. Marin algae *S. costatum* was exposed to Thixatrol Plus for 72 hours under static exposure conditions to the nominal concentrations of 0.00029, 0.00093, 0.0029, 0.0093 and 0.29 mg/L. The measured test concentrations ranged from 15 to 124 % of the nominals at 0 hours and from 18 to 227 % after 72 hours. The mean measured concentrations were 0.000359, 0.000383, 0.00107, 0.00153 and 0.0235 mg/L. The validity criteria of the ISO 10253 guideline were met for 48- and 72-hour study periods. DS indicated that validity criterion of the OECD TG 201 regarding the mean coefficient of variation for section-by-section specific growth rates not exceeding 35% is fulfilled until 48 hours (section CV = 12.5%) but not for the whole 72 hours (section CV = 55.5%) exposure. Although the ISO 10253 guideline does not include this validation criterion, constant exponential growth in the control cultures is considered important for the reliability of the results by the DS. Therefore, the DS considered only the data up to 48 hours exposure valid and recalculated the results. As indicated above, the test concentrations were measured only at 0 and 72 hours. However, since the substance has low water solubility and high adsorption potential, the DS has assumed that any loss of the test substance due to adsorption occurred relatively fast, and hence, the real exposure concentrations at 48 hours is expected to be similar to the measured concentrations at 72 hours. Therefore, the mean measured concentrations as explained above were used by the DS to calculate the results at 48 hours of exposure. The 48h E_rC_{50} of 0.0012 mg/L, 48h E_rC_{10} of 0.00087 mg/L and 48h NOE_rC of 0.000359 mg/L based on mean measured concentrations were calculated.

One toxicity study with the marine algae *S. costatum* following ISO 10253 guideline and two studies for freshwater algae *Chlorella vulgaris* following OECD TG 201 were considered not reliable by the DS. The toxicity study with marine algae *S. costatum* was considered not reliable as the loading rates were above the water solubility limit of the substance and there is no information weather the test concentrations were analytically verified, while the toxicity study with freshwater algae studies were considered not reliable due to the following: use of nominal concentrations/loading rates well above the water solubility limit of the substance, results are based on loading rates and no analytical measurement of the test concentrations were made. In the toxicity study with marine algae *S. costatum* the 72h E_rC_{50} value of 4.08 mg/L loading rate was determined while the determination of the NOEC value in this study was not possible.

Data for the sediment-dwelling organism *Corophium volutator* was reported in CLH report. The study performed according to PARCOM Guidance 190.5 resulted in 10d EC_{50} value of > 1000 mg/kg dry weight of sediment and 10-d NOEC value of 1000 mg/kg dry weight of sediment for sediment dwelling organism (*C. volutator*).

Reliable acute aquatic toxicity data on Thixatrol Plus are available for algae and sediment dwelling organism, while reliable data for fish and invertebrates are lacking. The lowest acute toxicity value for algae is mean measured 48h E_rC_{50} value of 0.0012 mg/L for marine algae *S. costatum* and for sediment dwelling organism 10-day LC_{50} value of >10000 mg/kg dry weight for *C. volutator*. The lowest acute toxicity value of 0.0012 mg/L is lower than the classification threshold value of 1 mg/L, therefore the substance should be classified as Aquatic Acute 1, H400 with an M-factor of 100 ($00.1 < L(E)C_{50} \leq 0.01$).

Chronic aquatic toxicity

No chronic toxicity tests with fish are available for Thixatrol Plus.

No chronic toxicity tests with invertebrates are available for Thixatrol Plus but there is one study available for *D. magna* with a structurally similar substance Thixatrol Max (EC No. 432-430-3). In a chronic toxicity test using Thixatrol Max, according to OECD TG 211, *D. magna* were exposed to the substance for 21 days under semi-static conditions to the time weighted mean measured concentrations of 0.025, 0.071, 0.24, 0.90 and 2.5 mg/L. A 21-d NOEC of 0.90 mg/L is reported for reproduction (mean number of live offspring produced per adult), immobilisation and length based on time-weighted mean measured concentration. The validity criteria of the OECD TG 211 (parent mortality ≤ 20% and number of living offspring > 60) were met. The DS noted that according to OECD TG 211 validity criterion for mortality (20%) can be used for accidental and inadvertent parental mortality for each test concentrations. At 0.90 mg/L 30% mortality occurred but was not statistically significantly different from the control. However, even if the mortalities in this groups are considered accidental and inadvertent, they are above the validity criterion of 20%. On the other hand, 30% mortality occurred at 0.90 mg/L (second highest concentration) and 70% mortality at 2.5 mg/L (highest concentration), it could be considered that mortality follows a dose-response at the two highest test concentrations. Therefore, the NOEC for mortality could be the next lowest concentration (0.24 mg/L). If the mortalities at 0.90 mg/L are considered to be caused by the test substance, the NOEC for reproduction could also result in a lower value than the one

reported in the study. However, since raw data on the number of offspring per adult is not available, it is not possible to re-calculate the results.

Read-across to Thixatrol Max

Thixatrol Plus and Thixatrol Max have three main constituents out of which one (EC 204-613-6) is common for both substances and the other main constituents differ only in the length of the shorter alkyl sidechain attached to the amide group(s). In Thixatrol Plus, the shorter chain is C10 and in Thixatrol Max it is C6. The constituents of Thixatrol Plus with longer alkyl chains are expected to be less water soluble and to have higher log Kow values than the constituents of Thixatrol Max with shorter sidechains. This could lead to some differences in the toxicity of the two substances to daphnia. Taking in to account the latter and lack of information (e.g., purity, composition) on Thixatrol Max the DS considered the *D. magna* reproduction study not fully adequate for classification of Thixatrol Plus and should be used as supporting information. However, since the available chronic toxicity value of Thixatrol Plus for algae (48-h E_rC_{10} = 0.00087 mg/L) is three orders of magnitude lower than the reported NOEC of Thixatrol Max for daphnia (21-d NOEC = 0.9 mg/L, or potentially 0.24 mg/L), it is expected that daphnia are not more sensitive to Thixatrol Plus than the algae.

The information about toxicity studies with algae is available under acute toxicity.

Reliable chronic toxicity data on Thixatrol plus are available for algae, while reliable data for fish and invertebrates are lacking. The lowest chronic toxicity value for algae is a mean measured 48h E_rC_{10} value of 0.00087 mg/L for marine algae *S. costatum* which is below the classification threshold of 0.01 mg/L for Aquatic Chronic 1 for rapidly degradable substances and in the range of 0.0001 < NOEC ≤ 0.001 mg/L justifying a chronic M-factor of 10.

Due to the lack of reliable acute toxicity data for fish and invertebrates, the surrogate approach for these trophic levels could not be applied.

Comments received during public consultation

Three Member State (MS) and one National Authority provided comments on proposed classification for environmental hazards by the DS. One MS agreed with proposed classification of the substance, while the second MS agreed with some reservations explained below. Two MS asked for clarifications regarding the labelling of the reliability of the studies in the CLH report.

The first MS asked for additional detailed descriptions of algae tests and questioned the reliability of the key study on marine algae *S. costatum* with regard to the problem in the chemical analysis: a EC_{50} was expressed for 48 hours because the validity criterion of OECD TG 201 (CV section growth rate <35%) were not met for 72 hours; chemical analysis was based on the measurement at 0 and 72 hours; whereas the toxicity values were expressed for 48 hours, which were different from the 72 or 96 hours for algae required by the CLP guidance. The MS also questioned the use of 48 hours exposure period for classification of the substance. MS asked the DS to provide the 72 hours toxicity values.

The DS explained that in line with the ISO 10253 and OECD TG 201 guidelines and ECHA Guidance (R.7b) a shorter test duration than the typical 72 hours can be used to calculate the results (including EC_{10} and NOEC) in algal toxicity tests if all validity criteria are met at the shorter duration. Therefore, the DS considered that the results at 48 hours could be used for acute and chronic classification of the substance. The following values at 72 hours were provided by the DS: E_rC_{50} of 0.00138 mg/L (mean measured), E_rC_{50} of 0.0054 mg/L (nominal), E_rC_{10} of 0.00123 mg/L (mean measured), NOE_rC of 0.0029 mg/L (nominal) and NOE_rC of 0.00107 mg/L (mean measured). The DS indicated that values at 72 hours also justify the classification of the substance as Aquatic Acute 1with M-factor of 100 and Aquatic Chronic 1 but with lower M-factor (M-factor of 1).

In regards of the problems with the analytical methods, the DS explained that based on the initial method validation trials and procedural recovery trial, the analytical method can be considered applicable for most of the test substance concentrations used in the definitive test but less applicable for the lowest test substance concentration (0.00029 mg/L). Since the test substance has low water solubility and high adsorption potential, the real exposure concentrations were likely lower than the nominal concentrations used in the test, especially in the case of the higher test concentrations. Therefore, and considering a precautionary approach, it is considered justified to determine the results based on the geometric mean of the measured concentrations instead of the nominal concentrations.

The DS also pointed out that test concentrations were measured only at 0 and 72 hours. However, since the substance has low water solubility and high adsorption potential, it can be assumed that any loss of the test substance due to adsorption occurred relatively fast, and hence, the real exposure concentrations at 48 hours is expected to be similar to the measured concentrations at 72 hours.

The MS agreed with the DS that surrogate approach could not be applied for fish and invertebrates due to lack of valid data. The MS also agreed that Thixatrol Plus is rapidly degradable and has bioaccumulation potential.

The MS pointed out that it cannot be determined whether read across to Thixatrol Max is valid due to lack of data on Thixatrol Plus (e.g., composition, structure, etc.) and in addition, the results, and details of the chronic toxicity test on daphnia with Thixatrol Max (e.g., nominal concentrations, chemical analysis, etc.) are not described. The DS stated where the information regarding main constituents, concentration ranges and minor constituents/impurity are reported for Thixatrol Plus and indicated that no detailed information (e.g., purity, concentrations of different constituents) is available for Thixatrol Max. The DS pointed out that there can be some differences in the toxicities of the two substances and hence the Thixatrol Max study is not considered fully adequate for the classification of Thixatrol Plus and hence is only used as supporting information. Additional data for long term daphnia study with Thixatrol Max are provided by the DS.

The second MS asked for verification of the experimental conditions (e.g., test medium, initial cell concentration, light) in the key study with algae as this could affect the exponential growth during exposition. The DS confirmed that experimental conditions were in line with ISO 10253 Guideline.

The MS made a comment regarding the stability of the substance and questioned the use of 48 hours exposure period for classification of the substance. The DS response is the same as to the first commenting MS.

Based on the Figure 2 in Annex I (p.11) the MS hypothesized that the EC_{50} at 72 hours could be < 1 mg/L but in order to strengthen the assumption the information about historical controls for algae species used in this study would be needed.

The third MS was of the opinion that there are constituents reported in the confidential annex that are impurities. The DS clarified that information included in confidential annex is reported as in the registration dossier.

The National Authority also made a comment regarding the key algae toxicity study. They requested the raw cell data for controls and calculated coefficient of variance (CoV) section-by-section values for each time point as this is necessary to consider the OECD TG 201 validity criteria and its relevance to *S. costatum* as this algae species is not included as OECD TG 201 test species. It was noted that *S. costatum* is composed of chains (OECD TG 201 recommends test species that are single cells or rods) and as a result more clumping of *S. costatum* may be expected which could contribute to 'relatively high-count variability'. The DS provided required data (see RCOM) and indicated that algal cells were counted using haemocytometer and light microscope to obtain accurate count.

The National Authority questioned the use of 48 hours endpoints for chronic classification and suggested the surrogate approach as was previously used in the case for etridiazole. The DS explained that in case of etridiazole, a 48-h E_rC_{50} from the OECD TG 201 study with *Pseudokirchneriella subcapitata* was chosen as the most relevant value as the CoV of the growth rate in the control was > 35% due to reduced growth rate at 72-h and 120-h. The 48-h E_rC_{50} was used to conclude on the acute toxicity of the substance. However, for the chronic toxicity RAC considered that the 48h NOEC/EC_{10} from this study could not be directly compared with the CLP criteria and used the surrogate approach instead, i.e., the chronic classification was based on the 48h E_rC_{50} for *P. subcapitata*. The DS noted that using the surrogate approach for the algal chronic toxicity (48h E_rC_{50} = 0.0012 mg/L) would also justify classification as Aquatic Chronic 1, but the M-factor would be 100 instead of 10 as proposed by DS based on the 48h E_rC_{10} of 0.00087 mg/L.

Assessment and comparison with the classification criteria

Degradation

The available ready biodegradability test (OECD TG 301B) indicated 69.3% degradation over 28 days. The 10-days window criterion was not fulfilled.

However, it is indicated in ECHA´s guidance Chapter R.7b ver. 4.0 and the guidance on the application of the CLP criteria ver. 5.0 that "the ten-day window may be waived for certain complex substances like multi-constituent substances consisting of structural similar constituents and if it is anticipated that a sequential biodegradation of the individual constituents is taking place".

Thixatrol Plus is a multi-constituent substance and sequential biodegradation of the individual constituents can be expected, so the 10-day window could be waived for Thixatrol Plus.

Furthermore, according to ECHA´s guidance Chapter R.7b ver. 4.0, the pass levels for ready biodegradability tests relate to measured sum parameters for DOC depletion, oxygen use or CO2 production and imply total degradation (assume that 30-40 % of the organic carbon of the test substance is either assimilated by the microbial biomass for growth or present as products of biosynthesis). Therefore, as the substance reached 69% degradation, it can be assumed that not much of the substance remained after 28 days.

In addition, the overall results of EPISuite BIOWIN QSAR estimations (six models) further support that Thixatrol Plus can be considered readily biodegradable.

RAC therefore agrees with the DS that Thixatrol Plus should be considered as rapidly degradable for the purpose of hazard classification.

Bioaccumulation

RAC agrees with the DS that Thixatrol Plus has a high potential to bioaccumulate in aquatic organisms. The basis for this is that measured and estimated log K_{ow} values were above the CLP Regulation threshold of 4.

Aquatic toxicity

The only reliable data on the aquatic toxicity on Thixatrol Plus are from an ISO 10253 marine algae growth inhibition test with *S. costatum,* giving a 48-h E_rC_{50} of 0.0012 mg/L, a 48-h E_rC_{10} of 0.00087 mg/L, and a 48-h NOE_rC of 0.000359 mg/L based on mean measured concentrations.

RAC agrees with the DS that exponential growth is important for the reliability of the results therefore the data up to 48 hours exposure should be taken in to account for the classification of the substance. As indicated by the DS the exponential growth was demonstrated for 48 hours and all validity criteria according to ISO 10253 and OECD TG 201 were met for exposure period of 48 hours. Not all validity criteria specified in OECD TG 201 were met for the 72 hours exposure. The second criterion, i.e., mean CV sectional growth rate < 35% was met only for the 0-48 hours period (12.5 %) but not over the period 0-72 h (55.5 %) which means that exponential growth was not observed over the entire exposure duration (72 hours) and thus not compliant with exponential growth, as defined by OECD TG 201. The use of shorter exposure periods (48 h test results) is acceptable according to ISO 10253, OECD TG 201 and ECHA Guidance document R.7b. providing that the exponential growth is observed and all validity criteria are met at shorter exposure duration (48h). Therefore, RAC agrees with the DS that growth rate reduction endpoints ErC_{50} and NOE_rC/E_rC_{10} after 48 hours of exposure are valid (validity criteria fulfilled) and reliable and thus should be taken in to account for classification of the substance.

In the CLP guidance (version 5.0, July 2017) it is indicated "The algal growth inhibition test is a short-term test that provides both acute and chronic endpoints." Algae also cover diatoms and therefore, endpoints on *S. costatum* should have been considered for the chronic classification. RAC supports the use of the acute algae study with *S. costatum* as a source for a chronic $NOEC/EC_{10}$ hence the NOE_rC/E_rC_{10} after 48 hours could be considered as a chronic endpoint. In addition, RAC considers that the E_rC_{10} should take precedence over N_rOEC.

Following the CLP guidance, E_rC_{10} values are preferred as these are statistically derived from the entire dataset, and less dependent on test design considerations as the NOEC.

RAC acknowledges that OECD TG 201 is a guideline for freshwater algae and not for saltwater diatoms, i.e., *S. costatum*. However, RAC is of the opinion that guideline validity criteria could be applied for *S. costatum* as:

- Given that the algae *S. costatum* form long chains the number of algal cells was counted using haemocytometer and light microscope as is also recommended for the OECD TG 201 test species *Anabaena flos-aquae* (Cyanobacteria) which also develops aggregates of nested chains of cells/clumps to compensate the count variability.
- OECD TG 201 allows modification of test conditions so long as sufficient growth is achieved. The experimental conditions used in the test were in line with the ISO 10253 guideline and sufficient growth is achieved.

RAC is of the opinion that there are some uncertainties with respect to analytics, i.e., Thixatrol Plus was detected in the control of the definitive test and procedural recovery test. However, no Thixatrol Plus was detected in the control in pre-study media preparation trials, the detection system had acceptable linearity and the procedural recoveries were acceptable for most of the test substance concentrations except for lowest test concentration. Therefore, RAC is of the opinion that the analytical method could be considered applicable. Taking into account that the substance has low water solubility and high adsorption potential, the real exposure concentrations were likely lower that the nominal concentrations used in the test so the effect value should be related to geometric mean measured concentrations. This is also in line with ECHA guidance (Chapter R.7b, p.26) where it is indicated that if measured concentrations are < 80% of nominal concentrations, for static tests the geometric mean measured concentrations should be calculated.

RAC agrees with the DS that since the substance has low water solubility and high adsorption potential, it can be assumed that any loss of the test substance due to the high adsorption potential occurred relatively quickly, so the real exposure concentrations at 48 hours are expected to be similar to the measured concentrations at 72 hours. This assumption in also in line with the CLP guidance I.4.3 (version 5.0, July 2017, p. 561) where it is stated that when the adsorption is one of the factors contributing to concentration loss - in the case of adsorption: "*this can occur for substances of high adsorption characteristics such as high log Kow substances. Where this occurs, the loss of concentration is usually rapid, and exposure may best be characterised by the end of test concentrations*;"

Data for estuarine invertebrate *C. volutator* was reported in the CLH report but was not used for classification by RAC because the endpoint values were presented in relation to sediment concentrations of Thixatrol Plus (mg/kg dry weight of sediment). No mg/L endpoints were available.

RAC agrees with the DS to read-across of aquatic chronic toxicity data from Thixatrol Max. The main assumption to justify the read-across approach is structural similarity of the constituents of the Thixatrol Plus and Thixatrol Max. Both substances have three main constituents, one common constituent and the other two constituents differ only in the length of the shorter alkyl sidechain. RAC supports the DS's view that two constituents of Thixatrol

Plus with longer alkyl chains are expected to be less water soluble and to have higher log Kow values than the two constituents of Thixatrol Max with the shorter sidechains. Consequently, this could lead to some differences in the toxicity of the two substances to *D. magna*.

RAC agrees with the DS that the chronic toxicity study with *D. magna* using Thixatrol Max should be considered as supporting information despite deficiencies pointed out by the DS (lack of information and difference in toxicity).

Acute toxicity

In the case of Thixatrol Plus, reliable acute toxicity data are available only for algae. RAC considers the 48h EC_{50} of 0.0012 mg/L (mean measured) for the marine algae *S. costatum* as a reliable result and therefore as appropriate for setting the acute classification. Based on this value, Thixatrol Plus meets the classification criteria as Aquatic Acute 1. As 0.001 $< L(E)C_{50} \leq$ 0.01, the M-factor is 100. RAC noted that also calculated 72h ErC_{50} of 0.00138 mg/L (mean measured) and 72h ErC_{50} of 0.0054 mg/L (nominal) would lead to same classification.

Chronic toxicity

In the case of Thixatrol Plus, reliable chronic toxicity data are available only for algae. RAC considers the 48h E_rC_{10} of 0.00087 mg/L (mean measured) and 48h NOE_rC of 0.000359 mg/L (mean measured) for the marine algae *S. costatum* as reliable results and relevant for chronic classification. As the 48h E_rC_{10} value of 0.00087 mg/L is below threshold value of 0.01 mg/L and the substance considered as rapidly degradable, RAC concludes that a classification as Aquatic Chronic 1 (H400) is justified. As 0.0001 < NOEC ≤ 0.001 mg/L, the chronic M-factor is 10.

In conclusion, RAC agrees with the DS that Thixatrol Plus warrants **classification as:**

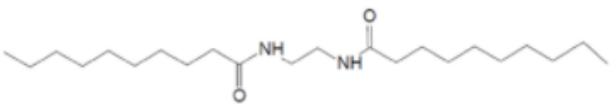
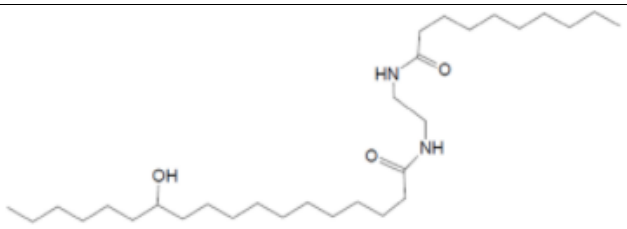
Aquatic Acute 1 (H400), M = 100

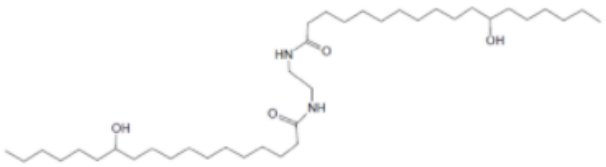
Aquatic Chronic 1 (H410), M = 10

Supplemental information - In depth analyses by RAC

The structural formulas of the main constituents of Thixatrol Plus as reported in the registration dossier on the disseminated side of ECHA are presented in Table below.

***Table**: Structural formulas of the main constituents of Thixatrol Plus as reported in the registration dossier on the disseminated side of ECHA*

Constituent	Structural formula
Constituent A 1-[2-(decanoylamino)ethylamino]-1-decanone	
Constituent B 1-[2-(decanoylamino)ethylamino]-12-hydroxy-1-octadecanone	

Constituent C 12-hydroxy-1-[2-(12-hydroxyoctadecanoylamino)ethylamino]1-octadecanone	

12 EVALUATION OF ADDITIONAL HAZARDS

12.1 Hazardous to the ozone layer

Not assessed in this dossier. No public consultation proposed.

13 ADDITIONAL LABELLING

Not relevant for this dossier.

14 REFERENCES

15 ANNEXES

Confidential Annex