

## Annex XV report

### PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name(s): Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP)

[with  $\geq 0.1\%$  w/w 4-heptylphenol, branched and linear (4-HPbl)<sup>1</sup>]

EC Number(s): -

CAS Number(s): -

Submitted by: Austria

Date: 29 August, 2017

---

<sup>1</sup> The full name of the entry 4-heptylphenol, branched and linear as it is included in the Candidate List is: 4-Heptylphenol, branched and linear [*substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof*]

This document has been prepared according to template: TEM-0049.03

## CONTENTS

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57 .....	5
PART I .....	9
JUSTIFICATION .....	9
1. IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES .....	9
1.1 Name and other identifiers of the substance .....	9
1.2 Composition of the substance .....	10
1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment .....	11
1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach) .....	11
1.5 Physicochemical properties .....	11
2. HARMONISED CLASSIFICATION AND LABELLING .....	13
3. ENVIRONMENTAL FATE PROPERTIES .....	13
4. HUMAN HEALTH HAZARD ASSESSMENT .....	13
5. ENVIRONMENTAL HAZARD ASSESSMENT .....	13
6. CONCLUSIONS ON THE SVHC PROPERTIES .....	15
6.1 CMR assessment .....	15
6.2 PBT and vPvB assessment .....	15
6.3 Assessment under Article 57(f) .....	15
6.3.1 <i>Conclusion on the hazard properties and equivalent level of concern assessment</i> .....	15
PART II .....	19
7. REGISTRATION AND C&L NOTIFICATION STATUS .....	19
7.1 Registration status .....	19
7.2 CLP notification status .....	19
8. TOTAL TONNAGE OF THE SUBSTANCE .....	20
9. INFORMATION ON USES OF THE SUBSTANCE .....	20
10. INFORMATION ON STRUCTURE OF THE SUPPLY CHAIN .....	21
11. ADDITIONAL INFORMATION .....	21
11.1 Substances with similar hazard and use profiles on the Candidate List .....	21
11.2 Alternatives .....	22
11.3 Existing EU legislation .....	22
11.4 Previous assessments by other authorities .....	22
REFERENCES FOR PART I .....	23
REFERENCES FOR PART II .....	23

## TABLES

Table 1: Substance identity.....	9
Table 2: Overview of physicochemical properties.....	12
Table 3: Registration status for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs. ....	19
Table 4: CLP notifications for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs. ....	19
Table 5: Tonnage status for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs. ....	20
Table 6: Uses for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs. ....	20

## ABBREVIATIONS

C&L	Classification & Labelling
dph	Days post hatch
GC/MS	Gas chromatography–mass spectrometry
4-HPbl	4-Heptylphenol, branched and linear
4nHP	4-n-Heptylphenol
IPCS	International Programme on Chemical Safety
LOD	Limit of detection
LOQ	Limit of quantification
OECD	Organisation for Economic Co-operation and Development
RP-HP	Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear
SVHC	Substance of very high concern
UVCB	Substances of Unknown or Variable composition, Complex reaction products or Biological materials
WHO	World Health Organization

## PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

Substance Name(s): Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP)

[with  $\geq 0.1\%$  w/w 4-heptylphenol, branched and linear (4-HPbl)]

EC Number(s): -

CAS number(s): -

- It is proposed to identify the substances as substances of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation.

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear with  $\geq 0.1\%$  w/w of 4-heptylphenol, branched and linear, are identified as substances of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH), because 4-heptylphenol, branched and linear, has been identified as a group of substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH<sup>2</sup>.

The Member State Committee at its 51<sup>st</sup> meeting unanimously agreed that 4-Heptylphenol, branched and linear [*substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof*] meet the criteria set out in Article 57(f) of REACH. The reasoning is laid down in the "Member State Committee support document for identification of 4-heptylphenol, branched and linear (4-HPbl) as a substance of very high concern because of its endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances", adopted on 14 December 2016<sup>3</sup>, as follows:

"Based on the available mechanistic information from *in silico* and *in vitro* studies with 4-heptylphenol isomers it can be unambiguously concluded that 4-HPbl is able to bind to the estrogen receptors of fish, humans and rats and to activate these receptors.

---

<sup>2</sup> Decision of the European Chemicals Agency on the Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV

<https://echa.europa.eu/documents/10162/0f8c5cf3-ccb7-3df6-c351-1c2df00cbc91>

<sup>3</sup> <https://echa.europa.eu/documents/10162/f3dba6ab-8dd8-2457-4213-2f390b0539f1>

In a reliable *in vivo* study with *Sander lucioperca* (Demska-Zakęś, 2005) the ratio of male fish (according to histological determination) was significantly decreased at the lowest used 4-n-heptylphenol (4nHP) concentration (1 µg/L) after 28 days of exposure. The shift in sex ratio was dose-dependent, leading to 98 and 100% female fish at 88 and 144 days post hatch (dph), respectively, indicating that the observed effects on the sex characteristics were irreversible.

The appearance of intersex species comprising sex characteristics from both sexes, e.g. testis-ova / ovotestis and formation of an oviduct (with regressed spermatogenic lobules in the same fish), was significant at 4nHP concentrations of at least 1 µg/L.

4-HPbl belongs to a group of structurally similar alkylphenols monoalkylated predominantly in 4-position with different alkyl chain lengths. To substantiate the findings for 4-HPbl, a read across approach is applied using the following source alkylphenols:

- 4-Nonylphenol, branched and linear: substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof
- 4-*tert*-octylphenol (4-(1,1,3,3-tetramethylbutyl)phenol, EC number: 205-426-2)
- 4-*tert*-pentylphenol (*p*-(1,1-dimethylpropyl)phenol, EC number: 201-280-9)
- 4-*tert*-butylphenol (4-(1,1-dimethylethyl) phenol, EC number: 202-679-0)

Regarding chain length, 4-HPbl is in the middle of 4-nonylphenol, branched and linear and 4-*tert*-octylphenol on the one side and 4-*tert*-pentylphenol and 4-*tert*-butylphenol on the other side. The findings for 4-HPbl were substantiated by the effects seen also in tests performed with the source substances.

- *In vitro* data confirm that all four source substances and the target substance do interact with the estrogen receptors.
- As for 4-HPbl it was demonstrated that exposure to 4-nonylphenol and 4-butylphenol (branched and linear forms) lead to a female biased sex ratio in *Sander lucioperca* at low concentration (effects seen at lowest dose of 1 µg/L).
- Substantial effects were also seen in other fish species (*Pimephales promelas*, *Danio rerio*, *Oryzias latipes*, *Cyprinus carpio*, *Oncorhynchus mykiss*) for the source chemicals. These include effect data like a female biased sex ratio and indicative effects like feminisation of gonadal ducts, testis-ova and effects on secondary sex characteristics.

4-Nonylphenol and 4-*tert*-octylphenol are already identified as substances of very high concern due to their endocrine disrupting properties for the environment, which are considered to give rise to an equivalent level of concern. The effects observed for 4-HPbl are similar to those for 4-*tert*-octylphenol and 4-nonylphenol and occur in similar concentration ranges (ECHA, 2011 and ECHA, 2012).

In summary, it is demonstrated that endocrine disrupting properties for the environment occur for alkylphenols with alkyl chain lengths of 4,5,7,8 and 9 C-atoms.

Taking all the evidence into consideration 4-HPbl are identified as endocrine disruptors for the environment according to the OECD guidance document (OECD,

2012) and the WHO/IPCS definition for endocrine disrupters.

4-HPbl are assessed as substances giving rise to an equivalent level of concern due to their estrogenic mode of action and the type of effects caused by this mode of action (e.g. shift in sex ratio).

- At 1 µg/L the ratio of male fish was significantly decreased and intersex fish appeared. At 10 µg/L the ratio of female fish was significantly increased to approximately 75% while at 200 µg/L approximately 100% fish were female. These effects remained manifest even after the exposure had ceased underlining that exposure during sensitive life stages may change the endocrine feedback system for the entire life.
- On the basis of the available data for 4-HPbl itself and from read across, it appears difficult to derive a safe level although it may exist. A read-across from 4-*tert*-octylphenol and 4-nonylphenol indicates that
  - Effects on non-traditional endpoints may start at much lower concentrations than those considered in the OECD test guidelines.
  - It is not possible to clearly conclude that effects on other organisms such as invertebrates and amphibians are endocrine mediated, although steroids are known to play an important role in both invertebrates (Kendall et al., 1998) and amphibians (Kortenkamp et al., 2012). Owing to the lack of in depth knowledge of their endocrine system and the lack of test systems, it is currently difficult to estimate which species may be more sensitive than fish and which concentration can be regarded as safe for the environment.
- Read across of the effects observed for the similar alkylphenols 4-nonylphenol and 4-*tert*-octylphenol shows that exposure during sensitive life stages may result in effects that remain during the entire life and even in the following generations. Thus local exposure of migratory species might not only locally affect population stability but also in other areas.

Thus in summary, the endocrine mediated effects observed in fish after exposure to 4-HPbl and anticipated on the basis of read-across from other alkylphenols are considered to have the potential to adversely affect population stability and recruitment. These adverse effects not only persist after cease of exposure but also occur after exposure at sensitive live stages. They thus may adversely affect populations in the longer-term and migratory species not only locally but also in regions where no exposure occurred. No reliable information is available for 4-HPbl about whether it can cause ED-related adverse effects on taxa other than fish. 4-*tert*-Octylphenol and 4-nonylphenol cause effects in amphibians and invertebrates that might be endocrine mediated, i.e. caused by an estrogen-like mode of action, although it is not possible to clearly conclude that they are endocrine mediated. Similar effects may be caused by 4-HPbl, but there are no confirmatory data. Based on current data and knowledge, a safe level of exposure is difficult to derive although it may exist.

Consequently, 4-HPbl are considered to give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.”

Therefore, reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP) with  $\geq 0.1\%$ <sup>4</sup> w/w 4-heptylphenol, branched and linear, shall likewise be identified as substances of very high concern due to their endocrine

---

<sup>4</sup> Ref. to REACH, Article 56 (6)a.

disrupting properties in the environment.

Registration dossiers submitted for substances belonging to this group entry?

Yes, for the substance identified by the registrant using the chemical name "reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs." It should be noted that only one starting material consisting of 4-heptylphenol, branched and linear has been registered. This starting material has been identified by the registrant as "phenol, heptyl derivs." (EC No. 276-743-1).

## PART I

### Justification

#### 1. Identity of the substance and physical and chemical properties

##### 1.1 Name and other identifiers of the substance

Table 1: Substance identity

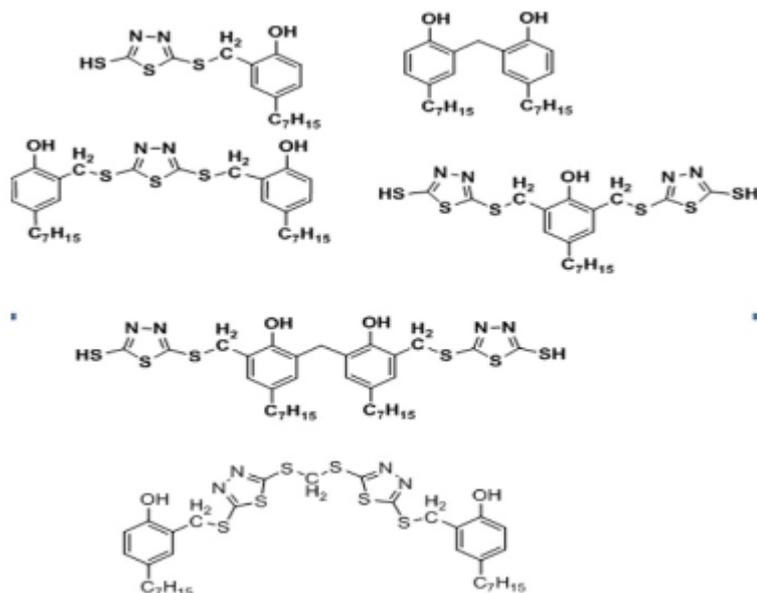
EC number:	-
EC name:	-
CAS number (in the EC inventory):	-
CAS number: Deleted CAS numbers:	-
CAS name:	-
IUPAC name:	Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear [with $\geq 0.1\%$ w/w 4-heptylphenol, branched and linear]
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	-
Molecular weight range:	See confidential Annex II
Synonyms:	-

One of the substances belonging to this group has been registered. It has been identified using the chemical name "Reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.". It is noted that before this registration the following chemical identifiers have been used instead: Formaldehyde, reaction products with branched and linear heptylphenol, carbon disulfide and hydrazine (EC No 300-298-5, CAS 93925-00-9). 1,3,4-thiadiazolidine-2,5-dithione can indeed be manufactured from carbon disulfide and hydrazine.

RP-HP may contain significant amount of process solvent (X) that cannot be removed without affecting the stability of the substance or changing its composition. In this situation, the presence of the solvent (X) may as a result be rightfully quoted in the name of the substance (for example, such substance can be named as "Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear including 'solvent X' "). Such substance will still be covered by this proposed entry as long as it contains  $\geq 0.1\%$  w/w 4-heptylphenol, branched and linear. More generally, any variation in the composition resulting from the use of

different processing agents/solvents and/or additives does not establish a criterion to exclude any substance resulting from the reaction between 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear from the proposal.

Structural formula: idealised structure<sup>5</sup>



## 1.2 Composition of the substance

Name: Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear [with  $\geq 0.1$  % w/w 4-heptylphenol, branched and linear]

Description: group entry

Substance type: UVCB<sup>6</sup>

Information on constituents and additives is given in the confidential Annex II.

<sup>5</sup> Source: ECHA dissemination site: <https://echa.europa.eu/de/registration-dossier/-/registered-dossier/12316>, accessed July 2017

<sup>6</sup> Substances of Unknown or Variable composition, Complex reaction products or Biological materials

### 1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment

Not applicable.

### 1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach)

Not applicable.

### 1.5 Physicochemical properties

For the registered UVCB substance “reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.”, which is covered by the group entry, physicochemical properties are given in Table 2 below.

Table 2: Overview of physicochemical properties

Property	Description of key information	Value [Unit]	Reference/source of information*
Physical state at 20°C and 101.3 kPa	The substance is an amber coloured liquid with no reported odour.	Liquid at 20°C and 1013 hPa	Dissemination site
Melting/freezing point	A melting point or melting range is not available for this UVCB substance. Two pour points are given in the registration dossiers depending probably on different methods and/or compositions of the measured UVCB substance.	Pour point: -3°C  Pour point: 9 ± 3°C	Dissemination site
Boiling point	A boiling point or boiling range is not available, as substance decomposes.	Start of decomposition from 244°C at 1009 hPa	Dissemination site
Vapour pressure	According to EU Method A.4 (Vapour Pressure) Effusion method: vapour pressure balance	0.076 Pa	Dissemination site
Density	Test Guidance: ASTM D4052-09 Standard Test Method for Density and Relative Density of Liquids by Digital Density Meter	1.12 g/mL at 15.6°C	Dissemination site
Water solubility	OECD Guideline 105 for Testing of Chemicals (flask method)	≤ 1.14 x 10 <sup>-4</sup> g/L at 20.0 ± 0.5°C.	Dissemination site
Partition coefficient n-octanol/water (log value)	OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method)	The test substance is a mixture of components with logPow values ranging from 5.31 to 11.41	Dissemination site

\*<https://echa.europa.eu/information-on-chemicals/registered-substances>. Dissemination site was accessed at 19.07.2016

## 2. Harmonised classification and labelling

No harmonised classification and labelling is available for any of the substances in the group of RP-HP. Classification of constituents and additives is given in confidential Annex II.

Furthermore, no harmonised classification and labelling is available for any of the substances in the group of 4-Heptylphenol, branched and linear.

## 3. Environmental fate properties

The identification of RP-HP with  $\geq 0.1\%$  w/w 4-heptylphenol, branched and linear as substances of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) is based on the identification of 4-heptylphenol, branched and linear (4-HPbl) as a group of substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH.

The group of 4-HPbl is already included in the candidate list. A detailed assessment of their environmental fate properties is available in the “Member state committee support document for identification of 4-heptylphenol, branched and linear (4-HPbl) as a substance of very high concern because of its endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances”, adopted on 14 December 2016<sup>7</sup>.

A literature search for new scientific data on 4-HPbl has been performed in July 2017, however, no new data that would add to the assessment of endocrine disrupting properties of 4-HPbl have been identified.

## 4. Human health hazard assessment

See Chapter 3.

A detailed assessment of the human health hazards of 4-HPbl is available in the “Member state committee support document for identification of 4-heptylphenol, branched and linear (4-HPbl) as a substance of very high concern because of its endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances”, adopted on 14 December 2016<sup>7</sup>.

A literature search for new scientific data on 4-HPbl has been performed in July 2017, however, no new data that would add to the assessment of endocrine disrupting properties of 4-HPbl have been identified.

## 5. Environmental hazard assessment

See Chapter 3.

A detailed assessment of the environmental health hazards of 4-HPbl is available in the “Member state committee support document for identification of 4-heptylphenol, branched and linear (4-

---

<sup>7</sup> <https://echa.europa.eu/documents/10162/f3dba6ab-8dd8-2457-4213-2f390b0539f1>

HPbl) as a substance of very high concern because of its endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances”, adopted on 14 December 2016<sup>7</sup>.

A literature search for new scientific data on 4-HPbl has been performed in July 2017, however, no new data that would add to the assessment of endocrine disrupting properties of 4-HPbl have been identified.

## 6. Conclusions on the SVHC Properties

### 6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) REACH.

### 6.2 PBT and vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) REACH.

### 6.3 Assessment under Article 57(f)

Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear [with  $\geq 0.1\%$  w/w 4-heptylphenol, branched and linear] are identified as a substances of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) where they contain any constituent or group of constituents (including impurities) of the group “4-heptylphenol, branched and linear”  $\geq 0.1\%$  in total owing to its endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

#### 6.3.1 Conclusion on the hazard properties and equivalent level of concern assessment

Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear with  $\geq 0.1\%$  w/w of 4-heptylphenol, branched and linear, are identified as substances of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH), because 4-heptylphenol, branched and linear, has been identified as a group of substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 REACH<sup>8</sup>.

The Member State Committee at its 51<sup>st</sup> meeting unanimously agreed that 4-Heptylphenol, branched and linear [*substances with a linear and/or branched alkyl chain with a carbon number of 7 covalently bound predominantly in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof*] meet the criteria set out in Article 57(f) of REACH. The reasoning is laid down in the “Member State Committee support document for identification of 4-heptylphenol, branched and linear (4-HPbl) as a substance of very high concern because of its endocrine disrupting properties which cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMR and PBT/vPvB substances”, adopted on 14 December 2016<sup>9</sup> as follows:

“Based on the available mechanistic information from *in silico* and *in vitro* studies with 4-heptylphenol isomers it can be unambiguously concluded that 4-HPbl is able

---

<sup>8</sup> Decision of the European Chemicals Agency on the Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV

<https://echa.europa.eu/documents/10162/0f8c5cf3-ccb7-3df6-c351-1c2df00cbc91>

<sup>9</sup> <https://echa.europa.eu/documents/10162/f3dba6ab-8dd8-2457-4213-2f390b0539f1>

to bind to the estrogen receptors of fish, humans and rats and to activate these receptors.

In a reliable *in vivo* study with *Sander lucioperca* (Demska-Zakęś, 2005) the ratio of male fish (according to histological determination) was significantly decreased at the lowest used 4-n-heptylphenol (4nHP) concentration (1 µg/L) after 28 days of exposure. The shift in sex ratio was dose-dependent, leading to 98 and 100% female fish at 88 and 144 days post hatch (dph), respectively, indicating that the observed effects on the sex characteristics were irreversible.

The appearance of intersex species comprising sex characteristics from both sexes, e.g. testis-ova / ovotestis and formation of an oviduct (with regressed spermatogenic lobules in the same fish), was significant at 4nHP concentrations of at least 1 µg/L.

4-HPbl belongs to a group of structurally similar alkylphenols monoalkylated predominantly in 4-position with different alkyl chain lengths. To substantiate the findings for 4-HPbl, a read across approach is applied using the following source alkylphenols:

- 4-Nonylphenol, branched and linear: substances with a linear and/or branched alkyl chain with a carbon number of 9 covalently bound in position 4 to phenol, covering also UVCB- and well-defined substances which include any of the individual isomers or a combination thereof
- 4-*tert*-octylphenol (4-(1,1,3,3-tetramethylbutyl)phenol, EC number: 205-426-2)
- 4-*tert*-pentylphenol (*p*-(1,1-dimethylpropyl)phenol, EC number: 201-280-9)
- 4-*tert*-butylphenol (4-(1,1-dimethylethyl) phenol, EC number: 202-679-0)

Regarding chain length, 4-HPbl is in the middle of 4-nonylphenol, branched and linear and 4-*tert*-octylphenol on the one side and 4-*tert*-pentylphenol and 4-*tert*-butylphenol on the other side. The findings for 4-HPbl were substantiated by the effects seen also in tests performed with the source substances.

- *In vitro* data confirm that all four source substances and the target substance do interact with the estrogen receptors.
- As for 4-HPbl it was demonstrated that exposure to 4-nonylphenol and 4-butylphenol (branched and linear forms) lead to a female biased sex ratio in *Sander lucioperca* at low concentration (effects seen at lowest dose of 1 µg/L).
- Substantial effects were also seen in other fish species (*Pimephales promelas*, *Danio rerio*, *Oryzias latipes*, *Cyprinus carpio*, *Oncorhynchus mykiss*) for the source chemicals. These include effect data like a female biased sex ratio and indicative effects like feminisation of gonadal ducts, testis-ova and effects on secondary sex characteristics.

4-Nonylphenol and 4-*tert*-octylphenol are already identified as substances of very high concern due to their endocrine disrupting properties for the environment, which are considered to give rise to an equivalent level of concern. The effects observed for 4-HPbl are similar to those for 4-*tert*-octylphenol and 4-nonylphenol and occur in similar concentration ranges (ECHA, 2011 and ECHA, 2012).

In summary, it is demonstrated that endocrine disrupting properties for the environment occur for alkylphenols with alkyl chain lengths of 4,5,7,8 and 9 C-atoms.

Taking all the evidence into consideration 4-HPbl are identified as endocrine disruptors for the environment according to the OECD guidance document (OECD, 2012) and the WHO/IPCS definition for endocrine disruptors.

4-HPbl are assessed as substances giving rise to an equivalent level of concern due to their estrogenic mode of action and the type of effects caused by this mode of action (e.g. shift in sex ratio).

- At 1 µg/L the ratio of male fish was significantly decreased and intersex fish appeared. At 10 µg/L the ratio of female fish was significantly increased to approximately 75% while at 200 µg/L approximately 100% fish were female. These effects remained manifest even after the exposure had ceased underlining that exposure during sensitive life stages may change the endocrine feedback system for the entire life.
- On the basis of the available data for 4-HPbl itself and from read across, it appears difficult to derive a safe level although it may exist. A read-across from 4-*tert*-octylphenol and 4-nonylphenol indicates that
  - Effects on non-traditional endpoints may start at much lower concentrations than those considered in the OECD test guidelines.
  - It is not possible to clearly conclude that effects on other organisms such as invertebrates and amphibians are endocrine mediated, although steroids are known to play an important role in both invertebrates (Kendall et al., 1998) and amphibians (Kortenkamp et al., 2012). Owing to the lack of in depth knowledge of their endocrine system and the lack of test systems, it is currently difficult to estimate which species may be more sensitive than fish and which concentration can be regarded as safe for the environment.
- Read across of the effects observed for the similar alkylphenols 4-nonylphenol and 4-*tert*-octylphenol shows that exposure during sensitive life stages may result in effects that remain during the entire life and even in the following generations. Thus local exposure of migratory species might not only locally affect population stability but also in other areas.

Thus in summary, the endocrine mediated effects observed in fish after exposure to 4-HPbl and anticipated on the basis of read-across from other alkylphenols are considered to have the potential to adversely affect population stability and recruitment. These adverse effects not only persist after cease of exposure but also occur after exposure at sensitive live stages. They thus may adversely affect populations in the longer-term and migratory species not only locally but also in regions where no exposure occurred. No reliable information is available for 4-HPbl about whether it can cause ED-related adverse effects on taxa other than fish. 4-*tert*-Octylphenol and 4-nonylphenol cause effects in amphibians and invertebrates that might be endocrine mediated, i.e. caused by an estrogen-like mode of action, although it is not possible to clearly conclude that they are endocrine mediated. Similar effects may be caused by 4-HPbl, but there are no confirmatory data. Based on current data and knowledge, a safe level of exposure is difficult to derive although it may exist.

Consequently, 4-HPbl are considered to give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.”

Therefore, reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-

heptylphenol, branched and linear (RP-HP) with  $\geq 0.1\%$ <sup>10</sup> w/w 4-heptylphenol, branched and linear, shall likewise be identified as substances of very high concern due to their endocrine disrupting properties in the environment.

---

<sup>10</sup> Ref. to REACH, Article 56(6)a.

## Part II

### 7. Registration and C&L notification status

The UVCB substance “reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.” is the only representative of the group RP-HP that has been registered under REACH so far.

#### 7.1 Registration status

Table 3: Registration status for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.

From the ECHA dissemination site <sup>11</sup>	
Registrations	<input checked="" type="checkbox"/> Full registration(s) (Art. 10) <input type="checkbox"/> Intermediate registration(s) (Art. 17 and/or 18)

#### 7.2 CLP notification status

Table 4: CLP notifications for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.

	CLP Notifications <sup>12</sup>
Number of aggregated notifications	2
Total number of notifiers	683

<sup>11</sup> <https://echa.europa.eu/substance-information/-/substanceinfo/100.226.747> (accessed 21 06 2017)

<sup>12</sup> C&L Inventory database, <http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database> (accessed 21 06 2017)

## 8. Total tonnage of the substance

Table 5: Tonnage status for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.

Total tonnage band for the registered substance (excluding the volume registered under Art 17 or Art 18) <sup>13</sup>	10-100 t/pa
Tonnage information from public sources other than registration dossiers (if available)	-

## 9. Information on uses of the substance

Table 6: Uses for the reaction product of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and phenol, heptyl derivs.

	Use(s)	Registered use (If not, specify the source of the information)	Use in the scope of Authorisation
Uses as intermediate	-	-	-
Formulation or repacking	Formulation by manufacturer and downstream users: Industrial formulation of lubricant additive, lubricants and greases	Yes	Yes
Uses at industrial sites	Application of lubricant to work pieces or equipment by dipping, brushing or spraying (without exposure to heat), e.g. mould releases, corrosion protection, slide ways  General industrial use of lubricants and greases in vehicles or machinery. Includes filling and draining of containers including enclosed machinery (including engines).	Yes	Yes
Uses by professional workers	Application of lubricant to work pieces or equipment by dipping, brushing or spraying (without exposure to heat), e.g. mould releases, corrosion protection, slide ways  General Professional use of lubricants and	Yes	Yes

<sup>13</sup> <https://echa.europa.eu/registration-dossier/-/registered-dossier/12316> (accessed 21 06 2017)

	greases in vehicles or machinery. Includes filling and draining of containers including enclosed machinery (including engines)		
Consumer uses	General consumer use of lubricants and greases in vehicles or machinery  Consumer use of lubricants and greases in open systems	Yes	Yes
Article service life	-	-	No

Reaction products of 1,3,4-thiadiazolidine-2,5-dithione, formaldehyde and 4-heptylphenol, branched and linear (RP-HP) are used in the formulation of lubricant additives, lubricants and greases. These are used industrially and by professionals in lubricants and greases in vehicles or machinery or by application of lubricant to work pieces or equipment. No more detailed information on the types of industry branches using RP-HP is available. Besides the automotive industry, in principle a wide range of industry branches using machinery may be concerned. Wide dispersive indoor uses and outdoor uses in closed and open systems by industrials, professionals and consumers have been reported via registration.

Main consumer use seems to be as lubricant additives in gear oils available in public supply. Numerous gear oils containing RP-HP in concentrations up to 2,5% have been identified via web search.

The presence of 4-HPbl in consumer products has been verified by chemical analyses by the Environment Agency Austria (unpublished data, see Annex IV for details) in nine out of ten gear oils purchased via Internet. Considering a typical concentration of RP-HP in the formulated gear oils as stated in the safety data sheets (ca. 0,5%) the concentration of 4-HPbl in the RP-HP calculated from the analytical results exceeds the limit of 0,1%.

It is important to note that apart from environmental exposure resulting from the end uses, there is additional concern due to the environmental exposure during the formulation of lubricant additives and lubricants.

## 10. Information on structure of the supply chain

RP-HP are imported into the EU, and the formulation into lubricant additives, lubricants and greases takes place within the EU. The number of formulation steps until the production of the final products is unknown. No information on the number, diversity, and spatial distribution of the actors of the supply chain is available.

## 11. Additional information

### 11.1 Substances with similar hazard and use profiles on the Candidate List

4-heptylphenol, branched and linear (4-HPbl) has already been identified as a group of substances with endocrine disrupting properties for which there is scientific evidence of probable serious effects to the environment which gives rise to an equivalent level of concern to those of other

substances listed in points (a) to (e) of Article 57 REACH<sup>14</sup> and included in the Candidate List.

Furthermore, the similar substances 4-nonylphenol, branched and linear, 4-*tert*-octylphenol and 4-*tert*-pentylphenol are already included in the candidate list due to their endocrine disrupting properties for the environment (Art. 57(f)).

## 11.2 Alternatives

RP-HP are used as corrosion inhibitors in lubricant additives, lubricants and greases. Alternative chemicals for these uses are available and in use. Their suitability to substitute RP-HP depends on the properties needed for specific applications.

## 11.3 Existing EU legislation

4-HPbl is on the Candidate list according to Article 59(1) of REACH.

No existing other relevant EU legislation has been identified.

## 11.4 Previous assessments by other authorities

Phenol, heptyl derivs., as covered by the group entry 4-HPbl, is part of the US EPA HPV Challenge program. Evaluation has started in 2003. Since then several data gaps have been closed by additional tests by industry, and the finalised health and environmental effect data have been made available in 2006.<sup>15</sup>

In another approach by industry alkyl phenols (as a group, including phenol, heptyl derivs.) have been evaluated in the HPV Challenge program. No testing for phenol, heptyl derivs. was proposed as the data gaps had been closed by in silico and read-across methods.

Additionally, EPA's Office of Pollution Prevention and Toxics (OPPT) has collected and evaluated hazard data since 2001 (published in 2009).<sup>16</sup>

No assessments have been identified for RP-HP.

---

<sup>14</sup> Decision of the European Chemicals Agency on the Inclusion of substances of very high concern in the Candidate List for eventual inclusion in Annex XIV  
<https://echa.europa.eu/documents/10162/0f8c5cf3-ccb7-3df6-c351-1c2df00cbc91>

<sup>15</sup> [https://java.epa.gov/oppt\\_chemical\\_search/](https://java.epa.gov/oppt_chemical_search/) (search term 72624-02-3)

<sup>16</sup> [https://java.epa.gov/oppt\\_chemical\\_search/](https://java.epa.gov/oppt_chemical_search/) (search term alkylphenols)

## REFERENCES

### References for Part I

- Demska-Zakęs K. (2005). Effect of select xenobiotics on the development of the fish reproductive system. Dissertations and monographs UWM Olsztyn 103: 1–61 [in Polish].
- ECHA (2011): Member State Committee Support Document for Identification of 4-(1,1,3,3-tetramethylbutyl)phenol as a Substance of Very High Concern because of its endocrine disrupting properties and adverse effects to the environment which gives rise to an equivalent level of concern, December 2011
- ECHA (2012) Member State Committee Support Document for identification of 4-nonylphenol, branched and linear as substances of very high concern because due to their endocrine disrupting properties they cause probable serious effects to the environment which give rise to an equivalent level of concern to those of CMRs and PBTs/vPvBs
- Kendall RJ, Dickerson RL, Suk WA, Giesy JP. (1998). Principles and Processes for Evaluating Endocrine Disruption in Wildlife. Society of Environmental Toxicology & Chemistry.
- Kortenkamp, A., Evans, R., Martin, O., McKinlay, R., Orton, F., and Rosivatz, E. (2012). State of the Art Assessment of Endocrine disruptors, Final Report Annex 1 Summary of the State of the Science Revised Version. pp. 1-486.
- OECD, 2012. Guidance Document on standardised test guidelines for evaluating chemicals for endocrine disruption, Olsen, C.M., Meussen-Elholm, E.T.M., Hongso, J.K., Stenersen, J., Tollefsen, K.E., (2005). Estrogenic effects of environmental chemicals: An interspecies comparison. Comparative Biochemistry and Physiology - C Toxicology and Pharmacology 141, 267-274.

### References for Part II

- EU(2006). Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union, L396: 1-849.
- EU (2007). Corrigendum to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC. Official Journal of the European Union, L136: 3-280.
- EU (2008). Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packing of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. Official Journal of the European Union, L353: 1-1355.