

Committee for Risk Assessment
RAC

Opinion
proposing harmonised classification and labelling
at EU level of

2-phenylhexanenitrile

EC Number: 423-460-8
CAS Number: 3508-98-3

CLH-O-0000001412-86-181/F

Adopted
5 December 2017

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

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

Chemical name: 2-phenylhexanenitrile

EC Number: 423-460-8

CAS Number: 3508-98-3

The proposal was submitted by **Spain** and received by RAC on **25 October 2016**.

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Spain has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at <http://echa.europa.eu/harmonised-classification-and-labelling-consultation/> on **7 December 2016**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **1 February 2017**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bogusław Barański**

Co-Rapporteur, appointed by RAC: **Steven Dungey**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **5 December 2017** by **consensus**.

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATE	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	608-039-00-0	2-phenylhexanenitrile	423-460-8	3508-98-3	Acute Tox. 4* Aquatic Acute 1 Aquatic Chronic 1	H302 H400 H410	GHS07 GHS09 Wng	H302 H410			
Dossier submitters proposal	608-039-00-0	2-phenylhexanenitrile	423-460-8	3508-98-3	Modify Acute Tox. 4 Aquatic Chronic 2 Remove Aquatic Acute 1	Retain H302 Modify H411 Remove H400	Retain GHS07 GHS09 Wng	Retain H302 Modify H411			
RAC opinion	608-039-00-0	2-phenylhexanenitrile	423-460-8	3508-98-3	Modify Acute Tox. 4 Aquatic Chronic 2 Remove Aquatic Acute 1	Retain H302 Modify H411 Remove H400	Retain GHS07 GHS09 Wng	Retain H302 Modify H411		Add oral: ATE ¹ = 500 mg/kg	
Resulting Annex VI entry if agreed by COM	608-039-00-0	2-phenylhexanenitrile	423-460-8	3508-98-3	Acute Tox. 4 Aquatic Chronic 2	H302 H411	GHS07 GHS09 Wng	H302 H411		oral: ATE ¹ = 500 mg/kg	

¹ Converted acute toxicity point estimate according to Table 3.1.2 of Annex I.

FOUNDATIONS FOR ADOPTION OF THE OPINION

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The substance 2-phenylhexanenitrile is included in Annex VI and classified as Acute Tox. 4*, H302 (minimum classification). The Dossier Submitter proposed to update the existing harmonised classification for acute oral toxicity in accordance with the CLP criteria based on the available animal data.

Acute toxicity: oral route

2-phenylhexanenitrile was tested for acute oral toxicity in Sprague-Dawley rats (5 males and 5 females per dose) according to a fixed dose method procedure (EU B.1 bis) in a GLP-compliant study (1996). 2-phenylhexanenitrile was administered orally at 2000, 500 and 50 mg/kg bw.

Deaths were observed at mid and high dose groups:

2000 mg/kg/bw:	M 2/5, F 2/5 (mortality of 40%)
500 mg/kg/bw:	M 1/5, F 0/5
50 mg/kg/bw:	M 0/5, F 0/5.

Clinical signs among rats at 500 and 2000 mg/kg bw included piloerection, abnormal body carriage, abnormal gait, decreased respiratory rate, pallor of the extremities, increased salivation, walking on toes and unsteadiness. In addition, the animals of the highest dose group showed lethargy, increased urine production and hair loss. In rats at 50 mg/kg bw only piloerection was recorded. In general, recovery was complete with the exception of hair loss that persisted to the end of the observation period (Day 15) in one surviving rat of the high-dose group.

The body weight gain was decreased in several animals at 2000 mg/kg bw, but no differences were observed at the end of the study. No abnormalities were recorded in the macroscopic examination on Day 15.

Taking into account that the substance 2-phenylhexanenitrile caused death in 1/10 animals at 500 mg/kg bw and in 4/10 animals at 2000 mg/kg bw, DS has proposed classification in category 4 for acute oral toxicity according to CLP Regulation.

Comments received during public consultation

Two MSCAs supported the DS's proposal to classify of 2-phenylhexanenitrile for acute oral toxicity category 4. One MSCA recommended the setting of a harmonized ATE value when a substance is classified for acute toxicity in order to facilitate the consistent classification of mixtures.

Assessment and comparison with the classification criteria

Classification

The substance 2-phenylhexanenitrile caused deaths in 2/5 males and 2/5 females at 2000 mg/kg bw. According to the guidelines of fixed dose method EU B.1 bis (Appendix 2, Flow chart for the main study) the tested item should be classified in category 4 of GHS, if ≥ 2 deaths caused in 5 animals at dose of 2000 mg/kg bw. This classification is further supported by one death in 5 animals given by gavage 500 mg/kg. Therefore, classification of 2-phenylhexanenitrile as **Acute Tox. 4 with the hazard statement H302 (Harmful if swallowed)** is supported by RAC.

Acute toxicity estimate (ATE)

To facilitate the consistent classification of mixtures containing 2-phenylhexanenitrile a harmonized ATE is proposed. According to the CLP Regulation the = ATE for the classification of a substance in a mixture via the oral route is derived using the LD₅₀ where available. Since the exact value of LD₅₀ is not available, the appropriate conversion value from Table 3.1.2 that relates to a classification in category Acute Tox. 4 should be taken. The converted acute toxicity point estimate for 2-phenylhexanenitrile based on its classification would therefore be **500 mg/kg bw**.

ENVIRONMENTAL HAZARD EVALUATION

RAC evaluation of aquatic hazards (acute and chronic)

Summary of the Dossier Submitter's proposal

2-Phenylhexanenitrile is currently listed in Annex VI of the CLP Regulation (EC) 1272/2008 with the classification Aquatic Acute 1 – H400 and Aquatic Chronic 1 – H410 (M-factors not specified, although a notification in the CLP Inventory (self classification) indicates M-factors of 1 for both), based on an algal 72-h E_bC₅₀ of 0.81 mg/L and lack of rapid degradation. The Dossier Submitter proposes that it does no longer requires classification as Aquatic Acute 1, based on the growth rate effect endpoint from the same algal study (72-h E_rC₅₀ = 2.58 mg/L), and that the Aquatic Chronic 1 classification should be modified to Aquatic Chronic 2 based on the same endpoint, as well as the surrogate method for fish and *Daphnia*.

Degradation

The substance hydrolyses with a half-lives of 25.9, 15.4 and 4.7 days at pH 4, 7 and 9 respectively.

A ready biodegradation test following OECD TG 301D (closed bottle test) resulted in no degradation after 28 days (based on oxygen consumption). The substance was not inhibitory to micro-organisms at the test concentration, so it is not readily biodegradable.

Further data are available from an aerobic sewage treatment simulation test (OECD TG 303A, with some modifications in line with a draft US protocol) but the CLP Guidance indicates that data from such tests cannot be used for assessing degradation in the aquatic environment.

In summary, 2-phenylhexanenitrile does not undergo rapid abiotic degradation (the hydrolysis half-life is > 16 days at pH 4 at 25 °C) and is not readily biodegradable. It is therefore not considered to be rapidly degradable.

Bioaccumulation

The octanol-water partition coefficient (log K_{ow}) is 3.14 at 21 °C (OECD TG 107 - shake flask method). No further information is available. This is below the CLP criterion for a bioaccumulative substance (log K_{ow} >4), so the Dossier Submitter considers that 2-phenylhexanenitrile does not have potential to bioaccumulate in aquatic organisms.

Aquatic toxicity

Short-term aquatic toxicity data are available for all three trophic levels, with long-term toxicity data only available for aquatic plants (algae). A summary of the relevant information is provided in the following table (the key endpoints used in hazard classification are highlighted in bold). All studies were performed under static conditions with results expressed in terms of mean measured concentrations, unless stated otherwise.

Table 1: Summary of relevant information on aquatic toxicity

Method	Test organism	Endpoint	Toxicity values in mg a.s./L	Reference
Short-term toxicity to fish				
OECD TG 203 (semi-static)	<i>Oncorhynchus mykiss</i> (Rainbow Trout)	96-h LC ₅₀	2.2 (95 % CI: 1.5 – 3.2)	Bell <i>et al.</i> , 1996a
Long-term toxicity to fish				
N.a.				
Short-term toxicity to aquatic invertebrates				
OECD TG 202	<i>Daphnia magna</i>	48-h EC ₅₀	1.6 (95 % CI: 1.3 – 1.9)	Bell <i>et al.</i> , 1996b
Long-term toxicity to aquatic invertebrates				
N.a.				
Toxicity to algae and aquatic macrophytes				
OECD TG 201	<i>Pseudokirchneriella subcapitata</i>	72-h E _r C ₅₀ 72-h NOE _r C	2.58 (95 % CI: 2.44 – 2.74) 0.26	Bell <i>et al.</i> , 1996c
N.a. – data not available CI – confidence interval				

The substance is moderately volatile, so there is a possibility that it could evaporate from test solutions if suitable precautions are not taken. Declines in test concentrations were observed in the studies (e.g. concentrations were 30 – 60 % of nominal values after 72 h in the algal study) but this is not important in this case because the data are presented in terms of mean measured concentrations. 95 % confidence intervals have been included in the table where relevant to give an indication of the variability of the data as they are close to the classification cut-off values.

Comments received during public consultation

Three Member State Competent Authorities (MSCA) provided public comments, and all agreed with the proposed declassification for acute aquatic hazards. One MSCA asked for clarification that control growth in the algal study was exponential (greater than factor 16) and this was confirmed by the Dossier Submitter.

Assessment and comparison with the classification criteria

Degradation

2-Phenylhexanenitrile does not undergo rapid abiotic degradation under all relevant environmental conditions (the hydrolysis half-life is > 16 days at pH 4 at 25 °C) and is not readily biodegradable. It is therefore not considered to be rapidly degradable.

Bioaccumulation

The substance is not potentially bioaccumulative because it has a log K_{ow} value (3.14) below the CLP Regulation threshold of 4. The substance is weakly surface active (59.5 mN/m at 20 °C and 33 mg/L), which means that results from the shake flask method might not be fully reliable. However, since the criterion for surface activity is 60 mN/m, this is a borderline case which probably makes little difference to the result.

Aquatic toxicity

Short-term aquatic toxicity data are available for three trophic levels. The lowest acute toxicity value is a 48-h EC_{50} of 1.6 mg/L in *Daphnia*. As this is above 1 mg/L, the substance **does not meet the criteria for classification with Aquatic Acute 1**.

Reliable long-term aquatic toxicity data are only available for aquatic plants (algae), with a 72-h NOE_rC of 0.26 mg/L. As this is in the range 0.1 – 1 mg/L and the substance is not rapidly degradable, it meets the criteria for classification with Aquatic Chronic 2 (H411). No long-term data are available for fish or *Daphnia*, but based on the acute L(E) C_{50} data in the range of 1 – 10 mg/L and the lack of rapid degradation, the surrogate approach leads to the same result. No M-factor is required. RAC supports the Dossier Submitter's proposal to classify as **Aquatic Chronic 2 (H411)**.

ANNEXES:

- Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in 'RAC boxes'.
- Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and RAC (excluding confidential information).