Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol

EC Number: 221-665-5
CAS Number: 3179-89-3

CLH-O-0000007056-76-01/F

Adopted

26 November 2021

26 November 2021

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

In accordance with Article 37 (4) of 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: **2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol**

EC Number: **221-665-5**

CAS Number: **3179-89-3**

The proposal was submitted by **Germany** and received by RAC on **7 January 2021.**

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

PROCESS FOR ADOPTION OF THE OPINION

Germany 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 **8 February 2021**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **9 April 2021**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Miguel A. Sogorb**

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 **26 November 2021** by **consensus**.

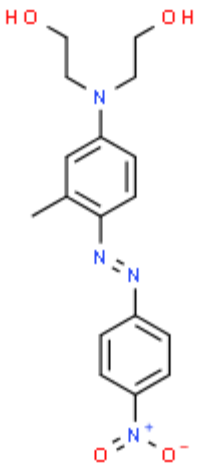
Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	Chemical name	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	No current Annex VI entry										
Dossier submitters proposal	TBD	2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol	221-665-5	3179-89-3	Skin Sens. 1	H317	GHS07Wng	H317			
RAC opinion	TBD	2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol	221-665-5	3179-89-3	Skin Sens. 1	H317	GHS07 Wng	H317			
Resulting Annex VI entry if agreed by COM	TBD	2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol	221-665-5	3179-89-3	Skin Sens. 1	H317	GHS07 Wng	H317			

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Disperse Red 17 (2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol) is listed as a pre-registered substance under REACH. Disperse Red 17 does not have an entry in Annex VI of the CLP regulation. The chemical structure of Disperse Red 17 is shown below:



There is evidence from the literature that Disperse Red 17 elicits skin sensitisation in humans as shown in studies from a high number of dermatological clinics. Disperse Red 17 is listed on the restriction proposal for the placing on the market of textile, leather, hide and fur articles containing skin sensitising substances and on the restriction proposal for substances in tattoo inks and permanent make up.

According to the CLH report, Disperse Red 17 is used to dye fabrics made of synthetic fibres such as polyester. These fibres are used in turn to produce garments that are mostly worn directly on the skin. Disperse Red 17 is also an ingredient in haircare products and is suspected to be used as a colorant in tattoo inks.

The Dossier Submitter (DS) prepared the CLH-report for Disperse Red 17 using data obtained from the public ECHA dissemination site and from a search of the published literature in bibliographic databases. Information found in the Scientific Committee on Consumer Safety (SCCS) Opinion on Disperse Red 17 was also used to prepare the CLH-report.

HUMAN HEALTH HAZARD EVALUATION

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Based on human studies, including diagnostic patch tests and case reports performed in multiple dermatological clinics from different countries, the DS proposed classification

of Disperse Red 17 as a skin sensitiser, Skin Sens. 1 (H317: May cause an allergic skin reaction) with the General Concentration Limit (GCL) of 1 % (w/v).

Comments received during consultation

One Member State Competent Authority supported the DS's classification proposal.

Assessment and comparison with the classification criteria

Animal data

The CLH-report summarised two animal studies, one "sensitive mouse lymph node assay" and one Guinea Pig Maximisation Test (GPMT). The table below summarises both studies.

In a non-guideline compliant "sensitive mouse lymph node assay" Disperse Red 17 of unspecified purity was intradermally injected in a 2 % test chemical-FCA emulsion into two sites on the abdominal skin on both sides of the ventral midline. After five days, topical application on the ears followed with 10 % test substance for three consecutive days (days 6 to 8). The following day, excised auricular lymph nodes were pooled for each experimental group. A single cell suspension consisting of a defined number of local lymph node cells was cultured with [^{3}H] methyl thymidine. After 24 hours, the increase in local lymph node cell number and [^{3}H] methyl thymidine incorporation compared to controls were expressed as a stimulation index, SI. Specifically, SI_n was calculated from the local lymph node cell number after excision; while SI_p was calculated from local lymph node cell proliferation in cell culture. A chemical was regarded as a sensitiser, if SI_{total} ($SI_n \times Si_p$) resulted in a value of 3 or greater. SI values for Disperse Red 17 were SI_n= 0.9 and SI_p= 0.9; this resulted in a SI_{total} of 0.8. SI_{total} for the positive control was 29.6. Thus, the authors and the DS concluded that Disperse Red 17 was not a sensitiser in this test. RAC concurs with this conclusion but notes the limitations of the study; these are: i) this was a non-guideline study performed without observing GLP; ii) there is no information on the systemic toxicity of Disperse Red 17 in treated animals; iii) insufficient characterisation of the test material; and, iv) concentrations higher than 2 % were not tested.

The skin sensitising potential of Disperse Red 17 was investigated in a GPMT according to OECD testing guidelines (OECD TG 406) and in compliance with GLP. A preliminary intradermal study showed that a concentration of 5 % test substance did not induce an irritant response. For induction in the main study, guinea pigs received three intradermal injections of Disperse Red 17 (41.2 % purity) using 5 % test substance in Freund's complete adjuvant (FCA), followed by a single epidermal induction on day 8 using 2.5 % of the test material under occlusive patch for 48 hours. Two weeks after completed induction, animals were challenged by a single application of 2.5% test substance under occlusive conditions for 24 hours. Skin examination followed 24 and 48 hours after removal of the challenge patches. Skin staining due to the test substance was observed in 6/10 animals and precluded accurate assessment of erythema after the challenge application. No adverse reaction was observed in any of the treated guinea pigs. The DS considered this study as not assignable for reliability.

***Table**: Summary of the animal studies on skin sensitisation with Disperse Red 17.*

Study	Dose level	Results	Reference
Sensitive mouse lymph node assay Non-guideline study No information on GLP Study reliability 3: Not reliable 3 BALB/c females/dose	Disperse Red 17 and positive control (p-phenylene-diamine): unknown purity Intradermal injection (day 1): 2 % in saline/Freund's complete adjuvant (FCA) (1:1) Topical application (days 6-8): 10 % in DMF	<u>Day 9:</u> <u>Disperse Red 17</u> SI_n = 0.9 SIp = 0.9 SI_{total} = 0.8 <u>Positive control:</u> SI_n = 4.1 SI_p = 7.3 SI_{total} = 29.6 **Negative**	Ikarashi *et al.*, 1996
GPMT OECD TG 406 GLP-compliant Study reliability 4: Not assignable Dunkin-Hartley female guinea pigs (N=10/ dose, N=5/control)	Disperse Red 17 (purity 41.2 %) dispersed in water Intradermal induction: 0.1 mL 5 % (w/v) test substance/FCA; 0.1 mL 50 % FCA; 0.1 mL 5 % (w/v) test substance Day 6, induction of irritation: 10 % sodium lauryl sulphate Day 8, topical induction: 0.5 mL 2.5 % test substance for 48 h (occluded) Two weeks later, challenge: 2.5 % test substance for 24 h (occluded)	Excessive staining due to the test substance precluded accurate assessment in 6/10 animals No adverse reaction in any of the treated animals **Negative**	Karunaratne, 1995

In conclusion, RAC notes that none of the available animal studies was sufficiently reliable to conclude on the skin sensitising potential of Disperse Red 17.

Human data

The CLH-report compiled published studies corresponding to 6 independent diagnostic patch tests with unselected (consecutive) dermatitis patients together with 32 independent studies performed with selected dermatitis patients plus one case report. For details on all these studies see Table 12 of the CLH-report. The CLH-report only summarised those available studies which were considered reliable (or reliable with restrictions) by the DS, while those studies of low reliability (or not reliable) were not considered by the DS. The table below summarises the main features of these studies relevant for classification. The CLH-report does not contain information about previous exposure levels to Disperse Red 17. Furthermore, human induction studies such as a Human Repeated Insult Patch Test (HRIPT) or Human Maximisation Test (HMT) performed with Disperse Red 17 were not available to the DS.

Table**: Summary table of human patch test data and published cases on skin sensitisation caused by Disperse Red 17.** See Table 12 in CLH-report for detailed information.

Number of studies	Type of study	Positive reactions	Result Frequency
4	Unselected consecutive dermatitis patients	Lower than 1 % (Range: 0.2-0.9 %)	Positive Low/moderate frequency
2	Unselected consecutive dermatitis patients	Higher than 1 % (1.3 %/1.2 %)	Positive High
12	Selected dermatitis patients	Lower than 2 % (Range: 0.1-1.9 %)	Positive Low/moderate frequency
18	Selected dermatitis patients	Higher than 2 % (Range: 3.6-25 %)	Positive High
2	Selected dermatitis patients	0 %	Negative
1	Case report	2/7 women	Positive

There is strong evidence from human data that Disperse Red 17 consistently and repetitively evokes skin sensitisation, as indicated in diagnostic patch tests from individual clinics or collated clinic data (Table above).

Consecutive patients patch-tested with Disperse Red 17 showed frequencies of positive reactions between 0.2 % and 1.3 % (Table above). Four of six studies showed a low to moderate (lower than 2 %) frequency of positive reactions, while the other two studies revealed a high (higher than 2 %) sensitisation frequency (Table above).

Testing Disperse Red 17 in selected dermatitis patients identified between 0 % and 25 % positive patch test reactions (Table above). The majority of the studies identified high frequencies of patients reacting positively to exposure to Disperse Red 17 (18/32 studies, frequency higher than 2 %). A low/moderate frequency of Disperse Red 17 reactions in selected dermatitis patients was seen in 12/32 studies (frequency lower than 2 %) (Table above). Two additional studies on patch testing in selected dermatitis patients revealed negative results for Disperse Red 17 (Table above).

In one published case-report, ten women with suspected textile dye allergy from stockings and other dyed textiles, including a black blouse, blue trousers, or grey pantsuit were investigated. Most subjects reported itching and erythema on the inner thighs, shortly after wearing these fabrics. Positive patch test reactions to Disperse Red 17 were shown in two patients with dermatitis from stockings.

Overall, RAC concludes that, given the occurrence of positive diagnostic patch test reactions from a large number of dermatological clinics, representing numerous different countries, the capability of Disperse Red 17 to elicit skin sensitisation in humans is well demonstrated.

Comparison with the criteria

None of the two animal studies investigating the skin sensitising potential of Disperse Red 17 gave a positive result (summarised above). However, these studies were considered by RAC to be too unreliable to be given any weight for assessing the capability of Disperse Red 17 to elicit sensitisation of human skin.

There was strong evidence (indicated by dermatological patch tests performed in a high number of dermatological clinics from several countries) that Disperse Red 17 evokes skin sensitisation in humans (Table above).

The table below summarises the criteria considered by the Guidance on the Application of the CLP Criteria for setting classification for skin sensitisation based on human data.

***Table**: Criteria for setting classification for skin sensitisation based on dermatitis patients*.

	Skin Sens. 1		Skin Sens. 1A		Skin Sens. 1B	
	Frequency	**Exposure**	**Frequency**	**Exposure**	**Frequency**	**Exposure**
Unselected	≤ 1 %	Low	≥ 1 %	Low	≤ 1 %	High
	≥ 1 %	High	-	-	-	-
Selected	≤ 2 %	Low	≥ 2 %	Low	≤ 2 %	High
	≥ 2 %	High	-	-	-	-

The human data (summarised above) contains 4 studies with unselected consecutive dermatitis patients showing a frequency lower than 1 % (low/moderate frequency) and 2 studies with unselected consecutive dermatitis patients showing a frequency higher than 1 % (high frequency). Thus, all these six studies warrant classification of Disperse Red 17 as Skin Sens. 1.

The human data also contains 12 studies with selected dermatitis patients showing a frequency lower than 2 % (low/moderate frequency) and 18 studies with selected dermatitis patients showing a frequency higher than 2 % (high frequency). Thus, all these 30 studies indicate that Disperse Red 17 warrants classification of as Skin Sens. 1. RAC does not give weight to the 2 negative studies with selected dermatitis patients given the overwhelming number of studies showing positive results.

The distinction between Skin Sens. 1A and Skin Sens. 1B is based on the frequency of positive results and also on the level of exposure. Establishing the level of exposure (low or high) is based on three different criteria (concentration/dose, repeated exposure and number of exposures). RAC notes that the CLH-report shows information only on the third criterion (number of exposures) but not on the other two. Thus, it is not possible to establish the level of exposure and consequently sub-categorisation based on human data is not possible.

In conclusion, RAC agrees with the DS that **Disperse Red 17 should be classified as Skin Sens. 1 (H317: May cause an allergic skin reaction).**

The available information does not enable a conclusion to be drawn regarding a specific concentration limit.

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).