

## **ANNEXES TO RAC's OPINION ON SKIN SENSITISING SUBSTANCES**

### **ANNEX I. SUBSTANCES OF CONCERN OUTSIDE THE SCOPE OF THIS RESTRICTION PROPOSAL**

#### **Benzyl benzoate**

Benzyl benzoate (CAS 120-51-4, EC 204-402-9) has no harmonised or self-classification as a skin sensitiser. The REACH registration dossier only describes one negative OECD TG 429 LLNA study. Nevertheless, the SCCS established benzyl benzoate as a contact allergen in humans in their opinion on Fragrance allergens in cosmetic products (SCCS/1459/11) which therefore listed as one of the 26 allergenic fragrances according to the Cosmetic Products Regulation (CPR, Regulation EU 1223/2009).

Benzyl benzoate was quantified in the ANSES study in 21% of footwear articles at concentrations ranging from 13 to 45 mg/kg in 6 footwear articles and was also detected in textiles using thermal desorption. Allergic contact dermatitis was observed in association with the quantification. Nevertheless, no firm causality with benzyl benzoate was established. The substance seems to be used as dye accelerator or as a plasticizer for certain polymers. Benzyl benzoate also presents biocidal properties although its use as an active substance is not approved in the EU.

Based on the SCCS analysis, RAC acknowledges that benzyl benzoate is a contact allergen in humans. The ANSES study also demonstrated that benzyl benzoate can be present in clothes and footwear articles. RAC therefore considers that skin sensitisation caused by an exposure to benzyl benzoate in clothes and footwear might be a concern although no clear risk was established in the ANSES study.

#### **Butyl hydroxyl toluene (CAS 128-37-0, EC 204-881-4)**

Butyl hydroxyl toluene (BHT) has a harmonised classification as Acute Tox. 4\* H302 according to the previous EU Directive 67/548/EEC on classification, labelling and packaging of substances. In the REACH registration dossier, many studies were described showing conflicting results regarding skin sensitisation of BHT. A self-classification as Skin Sens. 1 was retained by 44 notifiers.

In the ANSES study, BHT was quantified in all the footwear articles at concentrations between 11 and 71 mg/kg]. BHT was also thermally extracted from 15 textile articles with a maximum concentration of 165 mg/kg. Allergic contact dermatitis was observed after exposure to some of the footwear articles without firm link with BHT.

RAC agrees that there is a concern regarding the skin sensitisation hazard of butyl hydroxyl toluene. The ANSES study also confirms that BHT is present in textile and footwear finished articles.

#### **2-phenoxyethanol (CAS 122-99-6, EC 204-589-7)**

2-phenoxyethanol has a harmonised classification as Acute Tox. 4\* H302 and Eye Irrit. 2 H319 according to the previous EU Directive 67/548/EEC on classification, labelling and packaging of substances. No self-classification as skin sensitiser was retained for this substance by the notifiers. Phenoxyethanol was recently the object of a RAC opinion on harmonised classification. However, skin sensitisation was not

open for discussion in the CLH proposal. No conclusion was therefore provided by RAC on the skin sensitisation potential of 2-phenoxyethanol. In addition, the SCCS did not highlight a skin sensitisation hazard of phenoxyethanol in their related opinion in 2016 (SCCS/1575/16).

Phenoxyethanol was quantified in all the footwear articles at concentrations between 11.30 and 68 mg/kg in leather. This chemical was also detected in 7 textiles using thermo-desorption at a maximum concentration of 11.30 mg/kg.

Overall, although 2-phenoxyethanol has a concern of skin irritation, no clear dataset demonstrating skin sensitisation is available for this substance. RAC however agrees that 2-phenoxyethanol can be present in textile and leather finished articles.

#### ***Para tertbutyl phenol (4-tert-butylphenol CAS 98-54-4, EC 202-679-0)***

Para-tert-butylphenol (ptBP) has a harmonised classification as Skin Irrit. 2 H315, Eye Dam. 1 H318, STOT SE 3 H335 and Repr. 2 H361f. Although in their opinion (Nov 2010), RAC concluded that ptBP did not fulfill the classification criteria for skin sensitisation based on the available information, several human data in the report showed very variable picture of human sensitisation to ptBP. This chemical is restricted according to the Cosmetics Products Regulation (Annex II/340) as well as in the Toys Safety Directive (No 2009/48/EC) where it is defined as an allergenic fragrance.

The ANSES study indicated that p-tert-butylphenol was present in 12 textile and leather articles at concentrations up to 152 mg/kg. The study concluded that the presence of formaldehyde in the analyses, at concentration up to 425 mg/kg, in conjunction with ptBP, was a potential indicator of ptBP formaldehyde resin in footwear.

Overall, scientific evidences suggest that para-tert-butylphenol has a low sensitisation capacity by itself. Nevertheless, exposure to p-tert-butylcatechol might lead to cross-reactions with p-tert-butylphenol. Formaldehyde has a harmonised classification as Skin Sens. 1 and is therefore in the scope of the restriction proposal. The concern related to ptBP formaldehyde resin is therefore expected to be covered by the present restriction.

#### **Chromium (III)**

Chromium (VI) has a harmonised classification within Annex VI of CLP regulation and therefore is included within the scope of the restriction but Cr (III) does not have such harmonised classification and therefore is outside the scope of the restrictions. Some concerns have been raised by the DS and in the public consultation (comments 2368 and 2379) regarding the skin sensitisation potential of Cr (III) in leather and leather articles. It is also known that Cr (III) is poorer protein binder than Cr (VI) and can leak out the leather gaining contact with skin, especially whether tanning inappropriate washing of leather has not removed the unbound Cr (III).

Hedberg and co-workers (2018) exposed 10 Cr-allergic subjects and 22 controls exposed to patches of serial dilutions of Cr(VI) for 2 days, patches of serial dilutions of Cr(III) for 2 days, Cr-tanned leather bracelets (containing no other metal than Cr) and Cr-free tanned leather bracelets (containing no other metal than Cr). These authors found: no positive reactions in the Cr-negative controls, either in patch or bracelet tests; no positive reactions to Cr-free leather bracelets; 10 individuals reacting to Cr (VI) patches; 7 individuals reacting to Cr(III) patches and 4 individuals reacting to bracelets. Although the chromium-allergic participants reacted positively to 10-100 fold lower concentration of Cr (III) as compared to Cr

(VI) in the Hedberg study, the releases of Cr (III) at normal skin conditions or in contact with rain are expected to be 1000-1000 000 fold greater as compared to chromium (VI) (Mathiason et al, 2015).

RAC has also addressed this question with publications in the scientific open literature and has found several of them demonstrating the capability of Cr (III) to elicit skin sensitisation. Hasen and co-workers (2003) tested in 18 chromium-allergic patients the capability of Cr (III) and Cr (VI) dissolved in synthetic sweat to induce allergy after 48-hours of exposure. They found dose-response positive reactions for both forms of chromium and estimated MET10 of 6 and 1 ppm for Cr(III) and Cr (VI); respectively. In a follow up study Hansen and co-workers (2006) tested 2211 consecutive eczema patients finding 31 positive reaction to Cr (III) among the Cr (VI) reacting patients.

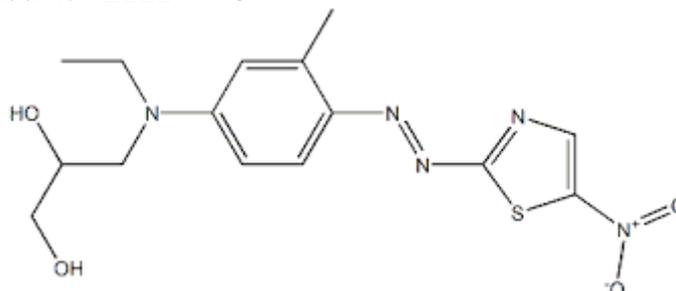
In conclusion, RAC noted several studies showing that Cr (III) is able to induce allergic contact dermatitis in Cr (VI)-sensitised individuals, although the elicitation threshold of Cr (III) seems to be clearly higher than the elicitation threshold of Cr(VI). Therefore, **based on the scientific evidences, RAC concludes that there is a concern for the sensitising properties of chromium III and it should be looked into further in the future**

## **ANNEX II. IN SUPPORT OF HAZARD IDENTIFICATION**

### **1.1 Azo dyes**

#### **CI Disperse Blue 102**

The chemical name of this substance is 1,2-propanediol, 3-[ethyl[3-methyl-4-[2-(5-nitro-2-thiazolyl)diazenyl]phenyl]amino]-. The chemical structure is shown below and its CAS number is 12222-97-8.

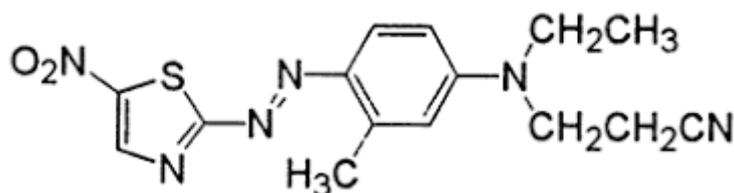


Chemical structure of CI Disperse Blue 102 (CAS number 12222-97-8)

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding lack of data on patch testing with Disperse Blue 102. No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Blue 103.

#### **CI Disperse Blue 106**

The chemical name of this substance is ethanol, 2-[ethyl[3-methyl-4-[2-(5-nitro-2-thiazolyl)diazenyl]phenyl]amino]-. The chemical structure is shown below and its CAS number is 12223-01-7.



Chemical structure of CI Disperse Blue 106 (CAS number 12223-01-7)

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 30 positive reactions (4.7%) against Disperse Blue 106.

The case of a 35-year-old man with a 2-year history of severe facial dermatitis was presented by Hansson and co-workers (1997). The patient had operated at the work an automatic colour film-developing machine for the past 5 years. After 3 years of this work, he developed strongly pruritic erythematous dermatitis on his forehead. The patient was patch tested with several allergens and gave positive against Disperse blue 106.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 44 non-occupational (28.6%) positive reaction against Disperse Blue 106.

Seidinari and co-workers (2005) patch tested with Disperse Blue 106 a total of 1094 children (509 boys and 585 girls) from 1995 to 2001 finding a positive response in 5.7% of them.

Malinauskiene and co-workers (2013) reviewed studies, reports on contact allergy to disperse dyes during the period 1990–2012 finding 16 aimed and 13 screening studies with positive results against Disperse Blue 106. The prevalence was 16.7% (342/2051) and 1.9% (639/35334) in the aimed and screening studies; respectively.

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and 5 of them showed positive answer to Disperse Blue 106. In another study only 2/60 patched patients showed positive reaction against Disperse Blue 106 (Ryberg et al., 2009).

Contact allergy to Disperse Blue 106 was tested in two different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 16/159 patients (9.8%) were positive; while in the second study 2% (10/500) was positive (Morgardt-Ryberg 2009).

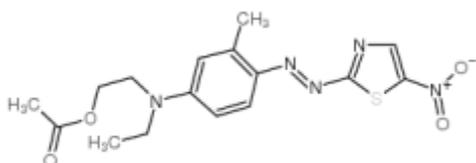
The positive reactions to Disperse Blue 106 were tested in 32 German and Austrian patch test clinics between 1995 and 1999 with 1847 patients finding erythematous reaction in 34, erythema, infiltration and possibly papules in 44, erythema, infiltration and papulovesicles in 12 and erythema, infiltration and confluent papulovesicles in 8 (Uter et al., 2001).

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 0.003, 0.03 and 0.3% solution of Disperse Blue 106 on a surface of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by 37, 79 and 82%; respectively. It allowed to the authors to postulate Disperse Blue 106 as a strong sensitiser.

Sonnenburg and co-workers (2012) used the so-called called loose-fit co-culture based sensitisation assay (LCSA) based on co-culture of primary human keratinocytes and allogenic dendritic cell-related cells for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Blue 106 was considered an extreme sensitiser with an EC<sub>50</sub> of 2 µM.

### **CI Disperse Blue 124**

The chemical name of this substance is ethanol, 2-[ethyl[3-methyl-4-[2-(5-nitro-2-thiazolyl)diazenyl]phenyl]amino]-, 1-acetate. The chemical structure is shown below and its CAS number is 61951-51-7.



Chemical structure of CI Disperse Blue 124 (CAS number 61951-51-7)

Disperse Blue 124 is self-classified by 23 notifiers as skin sensitiser category 1.

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 34 positive reactions (5.3%) against Disperse Blue 124.

The case of a 35-year-old man with a 2-year history of severe facial dermatitis was presented by Hansson and co-workers (1997). The patient had operated at the work an automatic colour film-developing machine for the past 5 years. After 3 years of this work, he developed strongly pruritic erythematous dermatitis on his forehead. The patient was patch tested with several allergens and gave positive against Disperse blue 124.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 84 (79 non-occupational and 5 occupational) (54.5%) positive reaction against Disperse Blue 124.

Seidinari and co-workers (2005) patch tested with Disperse Blue 124 a total of 1094 children (509 boys and 585 girls) from 1995 to 2001 finding a positive response in 1.9% of them.

Malinauskiene and co-workers (2013) reviewed studies, reports on contact allergy to disperse dyes during the period 1990–2012 finding 15 aimed, and 14 screening studies with positive results against Disperse Blue 124. The prevalence was 15.5% (376/2363) and 1.7% (517/19964) in the aimed and screening studies; respectively.

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and 6 of them showed positive answer to Disperse Blue 124. In another study only 2/60 patched patients showed positive reaction against Disperse Blue 124 (Ryberg et al., 2009).

The positive reactions to Disperse Blue 106 were tested in 32 German and Austrian patch test clinics between 1995 and 1999 with 1829 patients finding erythematous reaction in 39, erythema, infiltration and possibly papules in 33, erythema, infiltration and papulovesicles in 14 and erythema, infiltration and confluent papulovesicles in 8 (Uter et al., 2001).

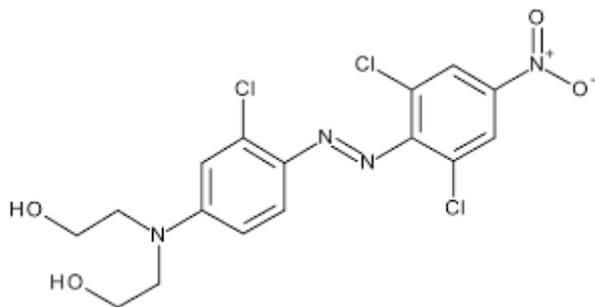
Contact allergy to Disperse Blue 124 was tested in 2 different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 6/159 patients (3.8%) were positive; while in the second study 1.8% (9/500) was positive (Morgardt-Ryberg 2009).

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 0.003 and 0.03 solution of Disperse Blue 124 on a surface of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by 21 and 79%; respectively. It allowed to the authors to postulate Disperse Blue 124 as a strong sensitiser.

Sonnenburg and co-workers (2012) used the LCSA for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Blue 124 was considered an extreme sensitiser with an EC<sub>50</sub> of 0.25 µM.

### **CI Disperse Brown 1**

The chemical name of this substance is 2,2'-[[3-chloro-4-[(2,6-dichloro-4-nitrophenyl)azo]phenyl]imino]bisethanol. The chemical structure is shown below and its CAS number is 23355-64-8.



Chemical structure of CI Disperse Brown 1  
(CAS number 23355-64-8)

Disperse Brown 1 is self-classified by 13 notifiers as skin sensitiser category 1; although another 33 notifiers did not self-classify the substance.

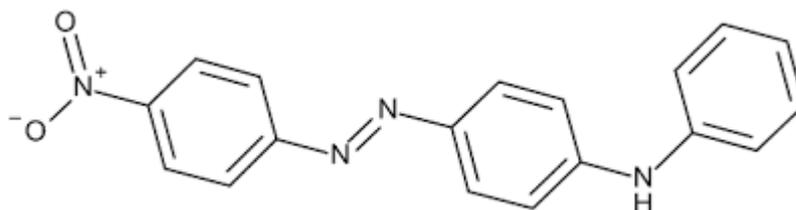
Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 1 positive reactions (0.2%) against Disperse Brown 1.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding three non-occupational (1.9%) positive reaction against Disperse Brown 1.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 10 aimed and 2 screening studies with positive results against Disperse Brown 1. The prevalence was 1.5% (22/1498) and 0.1% (2/2355) in the aimed and screening studies; respectively.

### **CI Disperse Orange 1**

The chemical name of this substance is 4-[(4-nitrophenyl)azo]-N-phenylaniline. The chemical structure is shown below and its CAS number is 2581-69-3.



Chemical structure of CI Disperse Orange 1 (CAS number 2581-69-3)

Disperse Orange 1 is self-classified by 2 notifiers as skin sensitiser category 1.

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 3 positive reactions (0.5%) against Disperse Orange 1.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 10 (8 non-occupational and 2 occupational) (6.5%) positive reaction against Disperse Orange 1.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 9 aimed and 4 screening studies with positive results against Disperse Orange 1. The prevalence was 2.3% (34/498) and 0.9% (52/6184) in the aimed and screening studies; respectively.

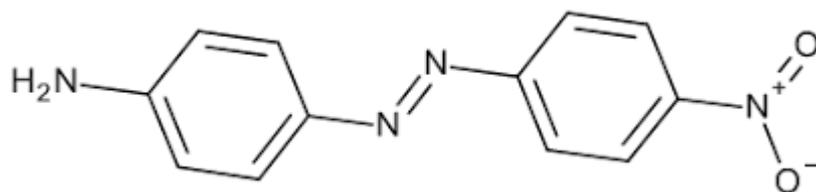
Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and 17 of them showed positive answer to Disperse Orange 1. In another study only 2/60 patched patients showed positive reaction against Disperse Orange 1 (Ryberg et al., 2009).

Contact allergy to Disperse Orange 1 was tested in 2 different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 2/159 patients (1.3%) were positive; while in the second study 1.2% (6/500) was positive (Morgardt-Ryberg 2009).

A case report was found in the literature where is described as a 66-year-old male with a 2-year history of severe hand eczema (Figure 1A) progressively worsening course was positively reacted to Disperse Orange 1 patch test.

### **CI Disperse Orange 3**

The chemical name of this substance is 4-[(4-nitrophenyl)azo]aniline . The chemical structure is shown below and its CAS number is 730-40-5.



Chemical structure of CI Disperse Orange 3 (CAS number 730-40-5)

Disperse Orange 3 is self-classified by a total of 34 notifiers as skin sensitiser category 1; while 2 other notifiers did not self-classified Disperse Orange 3.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 9 (7 non-occupational and 2 occupational) (5.8%) positive reaction against Disperse Orange 3.

Malinauskiene and co-workers (2013) reviewed studies, reports on contact allergy to disperse dyes during the period 1990–2012 finding 17 aimed, and 12 screening studies with positive results against Disperse Orange 3. The prevalence was 10.6% (244/2256) and 1.2% (334/27899) in the aimed and screening studies; respectively.

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and 1 of them showed positive answer to Disperse Orange 1. In another study 5/60 patched patients showed positive reaction against Disperse Orange 1 (Ryberg et al., 2009).

Contact allergy to Disperse Orange 3 was tested in 2 different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 5/159 patients (3%) were positive; while in the second study 3.6% (18/500) was positive (Morgardt-Ryberg 2009).

A case report was found in the literature where is described as a 66-year-old male with a 2-year history of severe hand eczema (Figure 1A) progressively worsening course was positively reacted to Disperse Orange 1 patch test.

Seidinari and co-workers (2005) patch tested with Disperse Orange 3 a total of 1094 children (509 boys and 585 girls) from 1995 to 2001 finding a positive response in 1.8% of them.

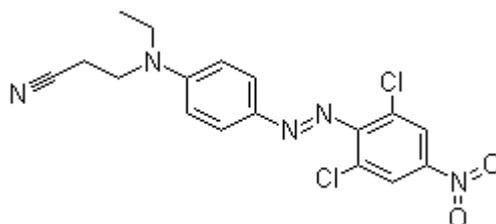
On the opposite to the above stated results, Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding no positive reactions against Disperse Orange 3.

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 30% solution of Disperse Orange 3 on a surface of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by a non-statistically significant 30%. It allowed to the authors to postulate Disperse Orange 3 as a very weak sensitiser.

Sonnenburg and co-workers (2012) used the LCSA for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Orange 3 was considered a strong sensitiser with an EC<sub>50</sub> of 18 µM.

### **CI Disperse Orange 37/59/76**

The chemical names of Disperse Orange 37 and 59 are 3-[[4-[(2,6-dichloro-4-nitrophenyl)azo]phenyl]ethylamino]propiononitrile and propanenitrile, 3-[[4-[2-(2,6-dichloro-4-nitrophenyl)diazenyl]phenyl]ethylamino]-; respectively. The chemical structure of Disperse Orange 37 is shown below and its CAS number is 13301-61-6. The CAS numbers for Disperse Orange 59 and 76 are 12223-33-5 and 51811-42-8; respectively.



Chemical structure of CI Disperse Orange 37 (CAS number 13301-61-6)

Disperse Orange 3 (CAS number 13301-61-6) is self-classified by a total of 26 notifiers as skin sensitiser category 1; while 4 other notifiers did not self-classified Disperse Orange 37.

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 10 and 30% solutions of Disperse Orange 37 on a surface of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by 16 and 53%, respectively. It allowed to the authors to postulate Disperse Orange 37 as a very weak.

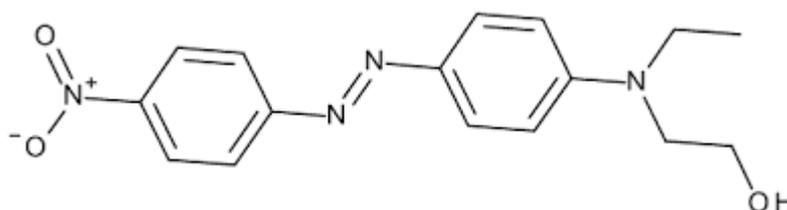
Sonnenburg and co-workers (2012) used the LCSA for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Orange 37/76 (CAS number 13301-61-6) was considered an extreme sensitiser with an EC<sub>50</sub> of 1 µM.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 noting lack of studies with positive results against Disperse Orange 37.

Finally, Disperse Orange 37/59/76 was identified in the ANSES study (2018) as responsible for cases of skin sensitisation reported by patients to physicians after wearing clothing articles or footwear.

#### **CI Disperse Red 1**

The chemical name of this substance is 2-[ethyl[4-[(4-nitrophenyl)azo]phenyl]amino]ethanol. The chemical structure is shown below and its CAS number is 2872-52-8.



Chemical structure of CI Disperse Red 1 (CAS number 2872-52-8)

Disperse Red 1 is self-classified by a total of 57 notifiers as skin sensitiser category 1; while 2 other notifiers did not self-classified Disperse Red 1.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 9 (7 non-occupational and 2 occupational) (5.8%) positive reaction against Disperse Red 1.

Malinauskiene and co-workers (2013) reviewed studies, reports on contact allergy to disperse dyes during the period 1990–2012 finding 17 aimed, and 13 screening studies with positive results against Disperse Red 1. The prevalence was 7.5% (17/2266) and 0.8% (236/30120) in the aimed and screening studies; respectively.

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and

22 women) were patch tested and 6 of them showed positive answer to Disperse Red 1. In another study 4/60 patched patients showed positive reaction against Disperse Red 1 (Ryberg et al., 2009).

Contact allergy to Disperse Red 1 was tested in 2 different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 2/159 patients (1.3%) were positive; while in the second study 1.6% (3/500) was positive (Morgardt-Ryberg 2009).

Seidinari and co-workers (2005) patch tested with Disperse Red 1 a total of 1094 children (509 boys and 585 girls) from 1995 to 2001 finding a positive response in 2.3% of them.

On the opposite to the above stated results, Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding no positive reactions against Disperse Red 1.

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 3, 10 and 30% solution of Disperse Red 1 on a surface of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by 26, 50 and 61%; respectively. It allowed to the authors to postulate Disperse Red 1 as a moderate sensitiser.

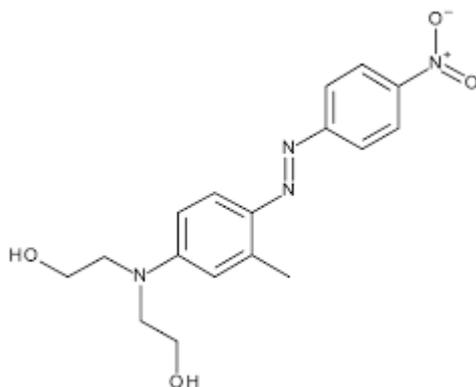
Sonnenburg and co-workers (2012) used the LCSA for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Red 1 was considered an extreme sensitiser with an EC<sub>50</sub> of 3 µM.

### ***CI Disperse Red 17***

The chemical name of this substance is 2,2'-[[3-methyl-4-[(4-nitrophenyl)azo]phenyl]imino]bisethanol. The chemical structure is shown below and its CAS number is 3179-89-3. Disperse Red 17 is self-classified by a total of 3 notifiers as skin sensitizer category 1; while 84 other notifiers did not self-classified Disperse Red 17.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 6 non-occupational (3.9%) positive reactions against Disperse Red 17.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 16 aimed and 5 screening studies with positive results against Disperse Red 17. The prevalence was 3.4% (64/1883) and 0.3% (17/6511) in the aimed and screening studies; respectively.



Chemical structure of CI Disperse  
Red 17 (CAS number 3179-89-3).

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and five of them showed positive answer to Disperse Red 17. In another study 3/60 patched patients showed positive reaction against Disperse Red 17 (Ryberg et al., 2009).

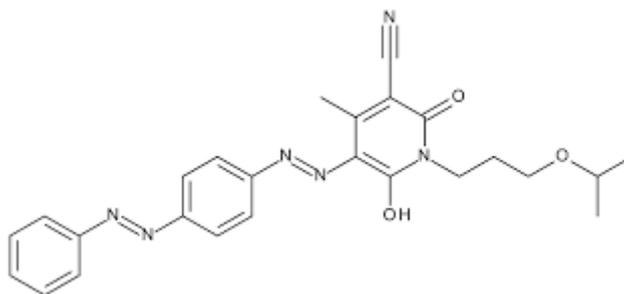
Contact allergy to Disperse Red 17 was tested in 2 different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 6/159 patients (3.8%) were positive; while in the second study 1.2% (6/500) was positive (Morgardt-Ryberg 2009).

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 4 positive reactions (0.6%) against Disperse Red 17.

The case of a 35-year-old man with a 2-year history of severe facial dermatitis was presented by Hansson and co-workers (1997). The patient had operated at the work an automatic colour film-developing machine for the past 5 years. After 3 years of this work, he developed strongly pruritic erythematous dermatitis on his forehead. The patient was patch tested with several allergens and gave positive against Disperse Red 17.

**CI Disperse Orange 149**

The chemical name of this substance is 6-hydroxy-1-(3-isopropoxypropyl)-4-methyl-2-oxo-5-[4-(phenylazo)phenylazo]-1,2-dihydro-3-pyridinecarbonitrile. The chemical structure is shown below and its CAS number is 85136-74-9.



Chemical structure of CI Disperse Orange 149  
(CAS number 85136-74-9).

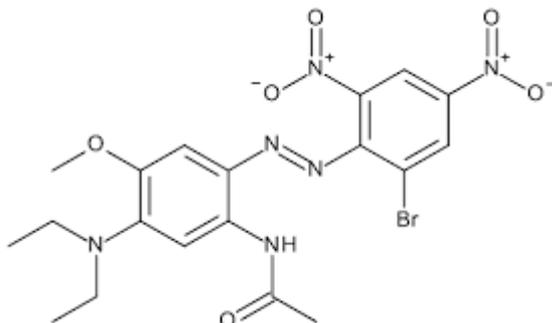
Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding lack of data on patch testing with Disperse Orange 149. Moreover, the REACH registration dossier of this substance does not contain information about skin sensitisation. No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Orange 149.

**CI Disperse Blue 291**

According to DS CAS and EC numbers are not specified for CI Disperse Blue 291 because there are numerous CAS and EC numbers associated with this chemical. According to DS 1 CAS and EC numbers are not specified for CI Disperse Blue 291 because there are numerous CAS and EC numbers associated with this chemical. However, RAC found that this disperse dye corresponds to the substance with name chemical name N-[2-[(2-bromo-4,6-dinitrophenyl)azo]-5-(diethylamino)-4-methoxyphenyl]acetamide which chemical structure is shown below. Two different

CAS numbers (56548-64-2 and 83929-84-4) were found associated to CI Disperse Blue 291.

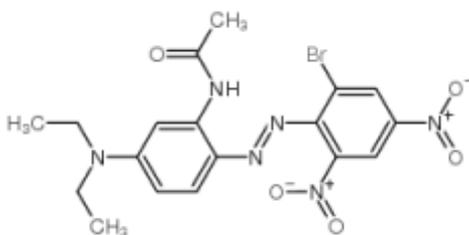
Disperse Blue 291 (CAS number 56548-64-2) is self-classified by a total of 21 notifiers as skin sensitiser category 1; while 19 other notifiers did not self-classified Disperse Blue 291.



Chemical structure of CI Disperse Blue 291 (CAS number 56548-64-2).

### ***CI Disperse Violet 93***

The chemical name of this substance is C.I. Disperse Violet 93:1. The chemical structure is shown below and its CAS number is 122463-28-9.

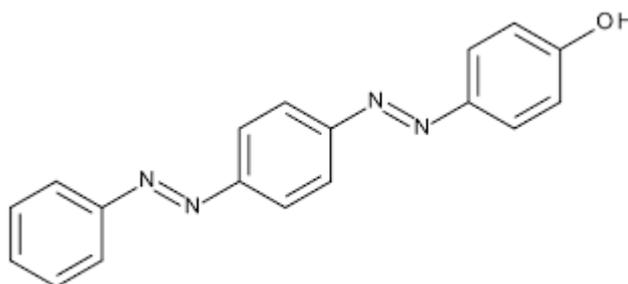


Chemical structure of CI Disperse Violet 93 (CAS number 122463-28-9).

No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Violet 93.

### ***CI Disperse Yellow 23***

The chemical name of this substance is p-[[p-(phenylazo)phenyl]azo]phenol. The chemical structure is shown below and its CAS number is 6250-23-3.



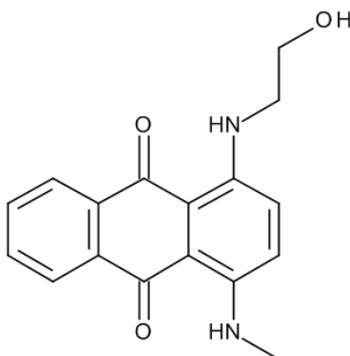
Chemical structure of CI Disperse Yellow 23 (CAS number 6250-23-3).

No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Yellow 23. However, Disperse Yellow 23 was identified in the ANSES study (2018) as responsible for cases of skin sensitisation reported by patients to physicians after wearing clothing articles or footwear. The Dossier Submitter therefore included the substance in the scope of the restriction proposal.

## 1.2 Anthraquinone dyes

### **CI Disperse Blue 3**

The chemical name of this substance is 9,10-anthracenedione, 1,4-diamino-, N,N'-mixed 2-hydroxyethyl and methyl derivatives. The chemical structure is shown below and its CAS number is 2475-46-9.



Chemical structure of CI Disperse Blue 3 (CAS number 2475-46-9)

CI Disperse Blue 3 is self-classified by 31 notifiers as skin sensitiser category 1; while other 4 notifiers do not classified the substance for skin sensitisation.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding 6 (5 non-occupational and 1 occupational) (3.9%) positive reactions against Disperse Blue 3.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 13 aimed and 3 screening studies with positive results against Disperse Blue 3. The prevalence was 1% (14/1441) and 0.2% (3/2682) in the aimed and screening studies; respectively.

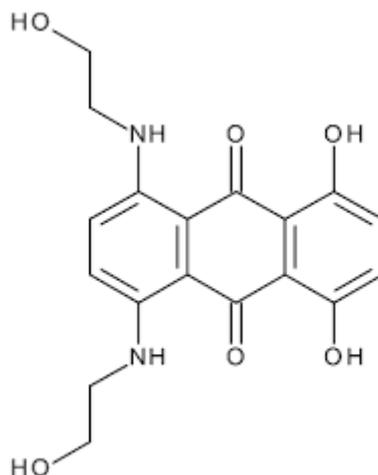
Morrone and co-workers (2014) patched tested 480 consecutive patients in northern Ethiopia exhibiting symptoms of contact dermatitis finding 2.3% of the individuals responding positively to Disperse Blue. However, RAC noted that in this case the allergen were generally identified as Disperse Blue and therefore it is not possible to determine whether these positive reactions were specifically attributable to Disperse Blue 3 or to other substances belonging to the family of the so-called Disperse Blue.

By the other hand, Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding no positive reactions against Disperse Blue 3.

### **CI Disperse Blue 7**

The chemical name of this substance is 1,4-dihydroxy-5,8-bis[(2-hydroxyethyl)amino]anthraquinone. The chemical structure is shown below and its CAS number is 3179-90-6.

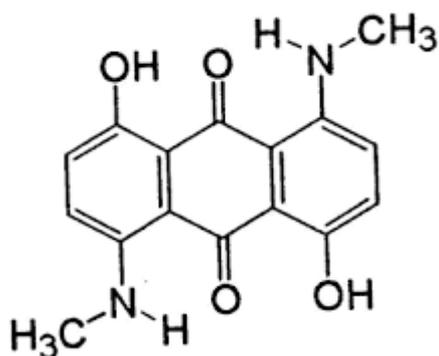
Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 3 aimed studies with positive results against Disperse Blue 7 and a prevalence of 16.7% (2/12).



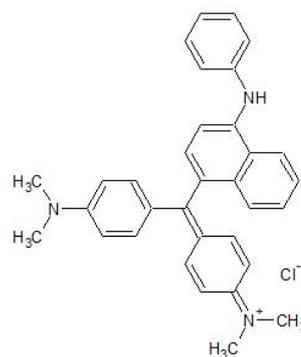
Chemical structure of CI Disperse Blue 7 (CAS number 3179-90-6)

### **CI Disperse Blue 26**

CI disperse Blue 26 is a substance with four different synonyms with chemical names C.I. Disperse Blue 26:1 (CAS number 100357-99-1), 9,10-Anthracenedione, 1,5-bis(dimethylamino)-(CAS number 13324-23-7, chemical structure shown below), 4,8-dihydroxy-1,5-dihydroxy-4,8-bis(methylamino)anthraquinone (CAS number 3860-63-7), and [4-[[4-anilino-1-naphthyl][4-(dimethylamino)phenyl]methylene]cyclohexa-2,5-dien-1 idene]dimethylammonium chloride (CAS number 2580-56-5, chemical structure shown below).



Chemical structure of CI Disperse Blue 26 (CAS number 13324-23-7)



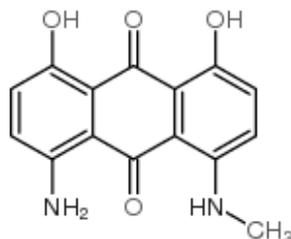
Chemical structure of CI Disperse Blue 26 (CAS number 2580-56-5)

The substance with CAS number 2580-56-5 has been registered under REACH regulation. In the registration dossier, the substance was considered sensitiser based on a valid and reliable QSAR prediction. This substance is self-classified by two notifiers as skin sensitiser category 1; while other 183 notifiers do not classified the substance for skin sensitisation.

The substance with CAS number 3860-63-7 is listed within Annex III of REACH (substances for which it is predicted that they are likely to meet the classification criteria for any health or environmental hazard classes under Regulation (EC) No 1272/2008) as suspected of respiratory sensitiser.

### **CI Disperse Blue 35**

CI disperse Blue 35 is a substance with two different synonyms with chemical names C.I. Disperse Blue 35 (CAS number 12222-75-2) and 1-amino-4,5-dihydroxy-8-(methylamino)anthraquinone (CAS number 56524-77-7, chemical structure shown below).



Chemical structure of CI Disperse Blue 35 (CAS number 56524-77-7)

This substance with CAS number 12222-75-2 is self-classified by 23 notifiers as skin sensitiser category 1.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 13 aimed and 3 screening studies with positive results against Disperse Blue 35. The prevalence was 1.7% (30/1779) and 0.3% (11/4135) in the aimed and screening studies; respectively.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding one non-occupational (0.6%) positive reaction against Disperse Blue 35.

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding five positive reactions (0.8%) against Disperse Blue 35.

Ryberg and co-workers (2006) assessed the prevalence of allergic patch test reactions to different textile dyes in Southern Sweden. Fifty patients (28 men and 22 women) were patch tested and three of them showed positive answer to Disperse Blue 35. In another study only 1/60 patched patients showed positive reaction against Disperse Blue 26 (Ryberg et al., 2009).

Contact allergy to Disperse Blue 35 was tested in two different studies at the Department of Dermatology of the Katholieke Universiteit in Leuven (Belgium). In the first study 6/159 patients (3.8%) were positive; while in the second study 0.4% (2/500) was positive (Morgardt-Ryberg 2009).

Ahuja and co-workers (2010) assessed the sensitising potential of various disperse dyes using a biphasic protocol of the local lymph node assay in mice finding that an administration of 50 µl of a 10 and 30% solution of Disperse Blue 35 on a surface

of 2 cm<sup>2</sup> was able to increase the cell counting in auricular lymph nodes of mice by 24 and 32%; respectively. It allowed to the authors to postulate Disperse Blue 35 as a weak sensitiser.

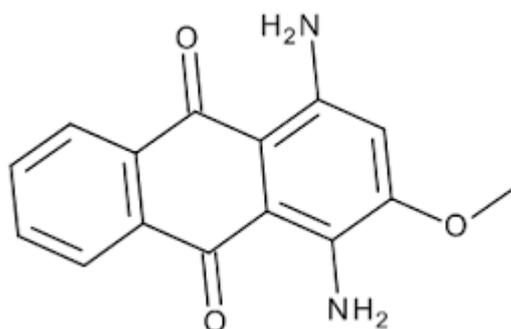
Sonnenburg and co-workers (2012) used the LCSA for combined testing of the sensitising and irritative properties of these substances. It was found that Disperse Blue 26 was considered an extreme sensitiser with an EC<sub>50</sub> of 6 µM.

In Europe, Disperse Blue 35 is included in the textile dye mix used in patch testing includes among others, supporting the scientific evidences presented above.

Finally, the substance with CAS number 56524-77-7 is listed within Annex III of REACH (substances for which it is predicted that they are likely to meet the classification criteria for any health or environmental hazard classes under Regulation (EC) No 1272/2008) as suspected of respiratory sensitiser.

### ***CI Disperse Red 11***

The chemical name of this substance is 1,4-diamino-2-methoxyanthraquinone. The chemical structure is shown below and its CAS number is 2872-48-2.



Chemical structure of CI Disperse Red 11  
(CAS number 2872-48-2)

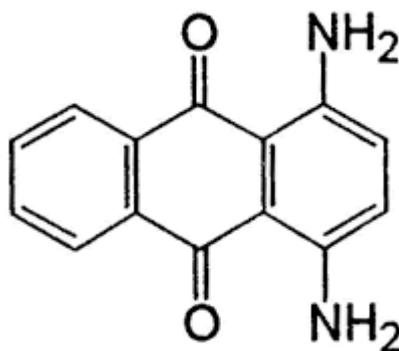
Disperse Red 11 is self-classified by a total of 5 notifiers as skin sensitiser category 1; while 37 other notifiers did not self-classified Disperse Red 11.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding two aimed reporting a prevalence of 0% (0/24).

Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding 11 positive reactions (1.7%) against Disperse Red 11.

### ***CI Disperse Violet 1***

The chemical name of this substance is 1,4-diaminoanthraquinone. The chemical structure is shown below and its CAS number is 128-95-0.



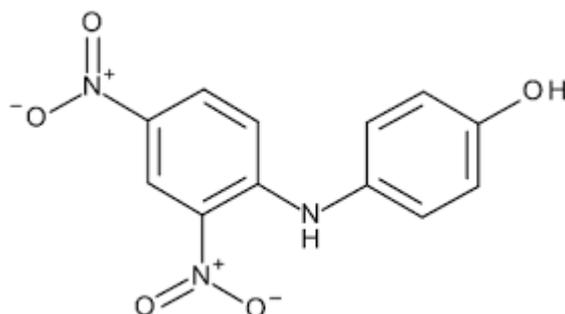
Chemical structure of CI Disperse Violet 1 (CAS number 128-95-0).

Disperse Red 17 is self-classified by a total of 73 notifiers as skin sensitiser category 1; while 32 other notifiers did not self-classify Disperse Violet 1. No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Violet 1.

### 1.3 Nitro dyes

#### ***CI Disperse Yellow 1***

The chemical name of this substance is 4-(2,4-dinitroanilino)phenol. The chemical structure is shown below and its CAS number is 119-15-3.

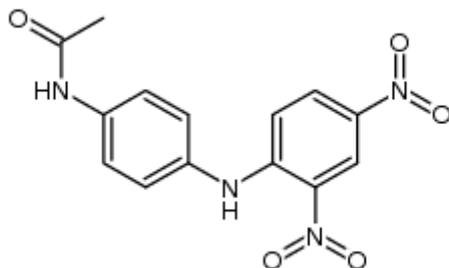


Chemical structure of CI Disperse Yellow 1 (CAS number 119-15-3).

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 1 aimed study with positive results against Disperse Yellow 1 with a prevalence of 5% (2/40).

#### ***CI Disperse Yellow 9***

The chemical name of this substance is N-(2,4-dinitrophenyl)benzene-1,4-diamine. The chemical structure is shown below and its CAS number is 6373-73-5.



Chemical structure of CI Disperse

Yellow 9 (CAS number 6373-73-5).

Disperse Yellow 9 is self-classified by 2 notifiers as skin sensitiser category 1.

Lisi and co-workers (2014) investigated clinical and epidemiological features of textile contact dermatitis in an Italian multicentre study. They studied the positive patch test reactions to textile allergens in 154 (132 non-occupational and 22 occupational) patients affected by allergic textile contact dermatitis finding two non-occupational (1.3%) positive reactions against Disperse Yellow 9.

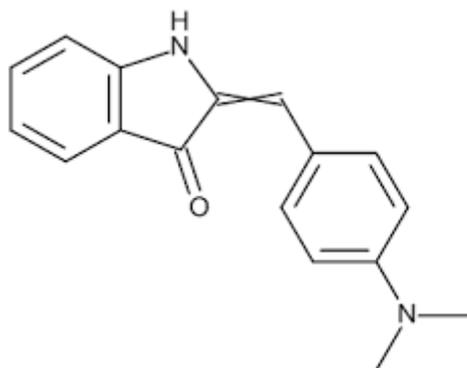
Lazarov (2003) studied in Israel 644 (441 female and 203 male) contact dermatitis patients suspected of having textile allergic contact dermatitis finding one positive reaction (0.2%) against Disperse Yellow 9.

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 13 aimed and 2 screening studies with positive results against Disperse Yellow 9. The prevalence was 1.6% (26/1607) and 0.06% (2/2355) in the aimed and screening studies; respectively.

#### 1.4 Methine dyes

##### **CI Disperse Yellow 39**

The chemical name of this substance is (2Z)-2-{[4-(dimethylamino)phenyl]methylidene}-2,3-dihydro-1H-indol-3-one. The chemical structure is shown below and its CAS number is 12236-29-2.

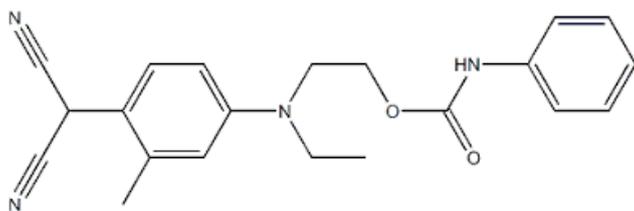


Chemical structure of CI Disperse Yellow 39 (CAS number 12236-29-2).

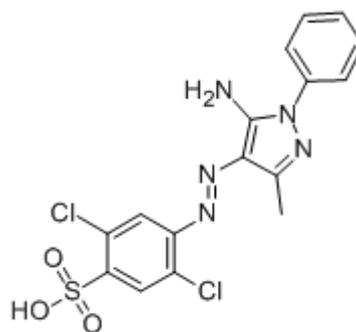
Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 1 aimed studies with a prevalence of 0% (0/6) for Disperse Yellow 39.

##### **CI Disperse Yellow 49**

CI Disperse Yellow 49 is a substance with two different synonyms with chemical names 4-[(5-amino-3-methyl-1-phenyl-1H-pyrazol-4-yl)azo]-2,5-dichlorobenzenesulphonic acid (CAS number 12239-15-5, chemical structure shown below) and Disperse Gelb 49 which is a methine dye corresponding to the CAS number 54824-37-2 (chemical structure shown below).



Chemical structure of CI Disperse Yellow 49 (CAS number 54824-37-2).



Chemical structure of CI Disperse Yellow 49 (CAS number 12239-15-5).

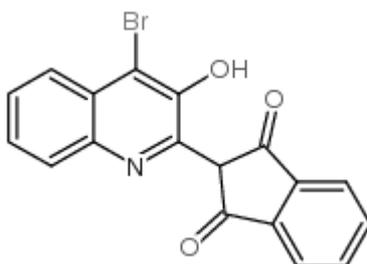
The methine dye with the CAS number 54824-37-2 has no REACH registration dossier or C&L Inventory. No experimental evidences could be found by RAC to support a potential dermal sensitising capability of Disperse Yellow 49.

The substance with the CAS number 12239-15-5 presents the structure of an azo dye and might be related to the class of acid dyes. The REACH registration dossier of the substance with CAS number 12239-15-5 contains a QSAR report performed with OECD QSAR toolbox v3.3 and with log kow as the primary descriptor. According to this report, Disperse Yellow 49 was predicted to be not sensitising to the skin.

### 1.5 Quinoline dyes

#### *CI Disperse Yellow 64*

The chemical name of this substance is p-[[p-(phenylazo)phenyl]azo]phenol. The chemical structure is shown below and its CAS number is 10319-14-9.



Chemical structure of CI Disperse Yellow 64 (CAS number 10319-14-9).

Malinauskiene and co-workers (2013) reviewed studies and reports on contact allergy to disperse dyes during the period 1990–2012 finding 1 aimed studies with a prevalence of 20% (1/5) for Disperse Yellow 64.