Committee for Risk Assessment

RAC

Annex 1

Background document

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

2-[ethyl[3-methyl-4-[(5-nitrothiazol-2-yl)azo]phenyl]amino]ethanol; (Disperse Blue 106)

EC Number: 271-183-4
CAS Number: 68516-81-4

CLH-O-0000007071-84-01/F

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

Adopted

18 March 2022

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification:

2-[ethyl[3-methyl-4-[(5-nitrothiazol-2-yl)azo]phenyl]amino]ethanol

EC Number: **271-183-4**

CAS Number: **68516-81-4**

Index Number: **-**

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Version number: 2.0 **Date: March 2021**

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2-[ETHYL[3-METHYL-4-[(5-NITROTHIAZOL-2-YL)AZO]PHENYL]AMINO]ETHANOL; (DISPERSE BLUE 106)

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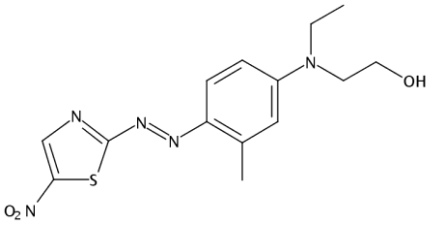
ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON 2-[ETHYL[3-METHYL-4-[(5-NITROTHIAZOL-2-YL)AZO]PHENYL]AMINO]ETHANOL; (DISPERSE BLUE 106)

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

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

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2-[N-ethyl-3-methyl-4-[(5-nitro-1,3-thiazol-2-yl)diazenyl]anilino]ethanol
Other names (usual name, trade name, abbreviation)	Disperse Blue 106; DB106
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	271-183-4
EC name (if available and appropriate)	2-[ethyl[3-methyl-4-[(5-nitrothiazol-2-yl)azo]phenyl]amino]ethanol
CAS number (if available)	68516-81-4
Other identity code (if available)	-
Molecular formula	C14H17N5O3S
Structural formula	
SMILES notation (if available)	CCN(CCO)C1=CC=C(N=NC2=NC=C(S2)[N+]([O-])=O)C(C)=C1
Molecular weight or molecular weight range	335.38 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	Mono-constituent substance; purity not relevant

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3.1 (CLP)	Current self-classification and labelling (CLP)
2-[N-ethyl-3-methyl-4-[(5-nitro-1,3-thiazol-2-yl)diazenyl]anilino]ethanol (CAS No. 68516-81-4)	100 %	None	

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: Proposed harmonised classification and labelling according to the CLP criteria

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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 entry										
Dossier submitters proposal	tba	2-[ethyl[3-methyl-4-[(5-nitrothiazol-2-yl)azo]phenyl]amino]ethanol	271-183-4	68516-81-4	Skin Sens. 1A	H317	GHS07 Wng	H317		Skin Sens. 1A; H317: C ≥ 0.001 %	
Resulting Annex VI entry if agreed by RAC and COM											

Table 4: Reason for not proposing harmonised classification and status under public consultation

<table>
<tr><th>Hazard class</th><th>Reason for no classification</th><th>Within the scope of public consultation</th></tr>
<tr><td>Explosives</td><td rowspan="15">Not assessed in this dossier</td><td rowspan="20">No</td></tr>
<tr><td>Flammable gases (including chemically unstable gases)</td></tr>
<tr><td>Oxidising gases</td></tr>
<tr><td>Gases under pressure</td></tr>
<tr><td>Flammable liquids</td></tr>
<tr><td>Flammable solids</td></tr>
<tr><td>Self-reactive substances</td></tr>
<tr><td>Pyrophoric liquids</td></tr>
<tr><td>Pyrophoric solids</td></tr>
<tr><td>Self-heating substances</td></tr>
<tr><td>Substances which in contact with water emit flammable gases</td></tr>
<tr><td>Oxidising liquids</td></tr>
<tr><td>Oxidising solids</td></tr>
<tr><td>Organic peroxides</td></tr>
<tr><td>Corrosive to metals</td></tr>
<tr><td>Acute toxicity via oral route</td><td rowspan="3">Data lacking</td></tr>
<tr><td>Acute toxicity via dermal route</td></tr>
<tr><td>Acute toxicity via inhalation route</td></tr>
<tr><td>Skin corrosion/irritation</td><td rowspan="2">Not assessed in this dossier</td></tr>
<tr><td>Serious eye damage/eye irritation</td></tr>
<tr><td>Respiratory sensitisation</td><td>Data lacking</td></tr>
<tr><td>Skin sensitisation</td><td>Harmonised classification proposed</td><td>Yes</td></tr>
<tr><td>Germ cell mutagenicity</td><td rowspan="9">Not assessed in this dossier</td><td rowspan="9">No</td></tr>
<tr><td>Carcinogenicity</td></tr>
<tr><td>Reproductive toxicity</td></tr>
<tr><td>Specific target organ toxicity-single exposure</td></tr>
<tr><td>Specific target organ toxicity-repeated exposure</td></tr>
<tr><td>Aspiration hazard</td></tr>
<tr><td>Hazardous to the aquatic environment</td></tr>
<tr><td>Hazardous to the ozone layer</td></tr>
</table>

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

2-[N-ethyl-3-methyl-4-[(5-nitro-1,3-thiazol-2-yl)diazenyl]anilino]ethanol (Disperse Blue 106; DB106) is a pre-registered substance under REACH. It does not have a harmonised classification and labelling in Annex VI to the CLP Regulation.

DB106 is on the Annex III inventory, a substance list that was produced using publicly available databases with experimental data and by using (Q)SAR model results. According to this analysis, DB106 is predicted as likely to meet criteria for category 1A or 1B carcinogenicity, mutagenicity, reproductive toxicity, and is suspected to be persistent in the environment (ECHA, 2020).

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

The dossier submitter considers that for Disperse Blue 106 (DB106) harmonised classification as skin sensitiser with an extreme sensitising potency (Skin Sens. 1A) is warranted, while a small fraction of notifiers in the C&L Inventory self-classified DB106 as skin sensitiser without sub-categorisation.

Harmonised classification as Skin Sens. 1A would ensure an adequate perception of the extreme skin sensitisation hazard associated with DB106, by setting the concentration limit for the classification of mixtures containing DB106 to 0.1 % (Skin Sens. 1A). The harmonised classification would result in even lower concentration thresholds, if the proposed SCL of 0.001 % is agreed by RAC and the Commission. Furthermore, a harmonised classification as Skin Sens. 1A could improve consumer safety in the context of restriction proposals on the use of the substance referring to harmonised classifications as skin sensitiser. In fact, DB106 is listed on the restriction proposal for the placing on the market of textile, leather, hide and fur articles containing skin sensitising substances (ECHA, 2019b) and the restriction proposal for substances in tattoo inks and permanent make up (ECHA, 2019a).

Notably, most of the notifiers self-classified DB106 for Acute Tox. 4 and Resp Sens. 1. However, there were no data available to the DS to address these endpoints.

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Classification affected by Impurities / Additives	Additional Notified Information	Number of Notifiers	Joint Entries
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)						
Acute Tox. 4	H302	H302		GHS08 GHS07 Dgr					38	
Resp. Sens. 1	H334	H334								
Skin Sens. 1	H317	H317		GHS07 Wng				State/Form	2	
Not Classified									1	

Figure 1: Notified classification and labelling according to CLP criteria for DB106[1]

5 IDENTIFIED USES

Disperse dyes, including DB106, are mainly used to dye or print fabrics made of synthetic fibres such as polyester, nylon, triacetate, cellulose, polyamide, and acrylic fibres (Lacasse and Baumann, 2004). These fibres are used in turn to produce garments that are mostly worn directly on the skin, e.g. leggings, bodysuits, suits, dresses, brassieres, tights, and jacket lining (Hausen, 1993; Malinauskiene et al., 2012). Numerous human data, published in particular from the 1980s to the 2000s, provide evidence that DB106 is a common cause of textile dermatitis and is frequently reported to be among the strongest textile dye sensitisers (Hatch

[1] Data were taken from the public ECHA dissemination site (last accessed 18.03.2021).

and Maibach, 1995; Hausen, 1993; Menezes Brandao et al., 1985; Pratt and Taraska, 2000). Because of these findings, the American Contact Dermatitis Society declared disperse blue dyes as the "Contact Allergen of the Year 2000" (Jacob and Ramirez, 2007). Furthermore, the ÖkoTex Standard 100 listed DB106 as an allergenic dye, defining a limit value in textiles produced according to this Standard (OEKO-TEX, 2020). For labelling of textiles with the EU Ecolabel DB106 "shall not be used for dyeing polyester, acrylic, polyamide, or elasticated or stretchable skin contact garments or underwear" (EU Ecolabel, 2015). Furthermore, DB106 was added to the Restricted Substance List that was compiled by a working group of the American Apparel & Footwear Association's (AAFA) Environmental Task Force (AAFA, 2019).

Newer Investigations detected DB106 in textiles "which were bought randomly from a local market" and analysed by ultra-high performance supercritical fluid chromatography combined with tandem mass spectrometry (Zhou et al., 2014). Malinauskiene and colleagues analysed 121 garments from 13 countries for appearance of disperse dyes using high-performance liquid chromatography, detecting DB106 in a pair of light brown women's tights (Malinauskiene et al., 2012). However, in another study DB106 was not detected in 251 samples, including garments and accessories (BVL, 2010). Finally, DB106 was analysed in environmental samples collected from outfalls in three estuaries in China. The analysis of 12 allergenic disperse dyes in 20 river water samples revealed the presence of DB106 in one sample (Zhan et al., 2017).

Beside its use as textile dye, DB106 is suspected to be utilised as a colourant in tattoo inks. Furthermore, the use of DB106 as colourant in ultrasound gel was reported (Skalina and Ramesh, 2018).

6 DATA SOURCES

Data for DB106 were received from the public ECHA dissemination site (ECHA, 2020) and from a thorough search of the published literature in bibliographic databases, including PubMed, Scopus, Web of Science, Embase, Toxnet, Wiley Online library, and Google Scholar. Furthermore, data were taken from a public report of NICNAS assessing Disperse Blue 360, Disperse Blue 124, DB106 and Disperse Blue 96 (NICNAS, 2015).

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20 °C and 101,3 kPa	solid	SDS (AK Scientific, Inc.)	
Melting/freezing point	n.a.		
Boiling point	n.a.		
Relative density	1.38	SDS (AK Scientific, Inc.), Sci Finder	
Vapour pressure	n.a.		
Surface tension			
Water solubility	n.a.		
Partition coefficient n-octanol/water	n.a.		
Granulometry	n.a.		

8 EVALUATION OF PHYSICAL HAZARDS

Not assessed in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Toxicological data giving adequate information on the absorption, distribution, biotransformation, and excretion of DB106 are lacking.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

No data available

10.2 Acute toxicity - dermal route

No data available

10.3 Acute toxicity - inhalation route

No data available

10.4 Skin corrosion/irritation

Not assessed in this dossier

10.5 Serious eye damage/eye irritation

Not assessed in this dossier

10.6 Respiratory sensitisation

No data available

10.7 Skin sensitisation

Skin sensitisation is an immunological process commonly divided into two phases. During the first phase, induction, the naive individual becomes sensitised to the allergenic agent accompanied by the production of allergen-specific memory cells. In the second phase, elicitation, exposure of the sensitised individual to the allergen leads to proliferation and activation of these T-cells, secretion of cytokines and mobilisation of other inflammatory cells resulting in the clinical outcome of allergic contact dermatitis (ECHA, 2017).

Several animal studies are available conducted with DB106 that cover the induction phase and allow placing of the test material into potency groups. Furthermore, a multitude of human studies, including patch test studies and case reports from the literature, cover the elicitation phase and indicate previous sensitisation to DB106 in humans.

There was no Human Repeated Insult Patch Test (HRIPT) or Human Maximisation Test (HMT) performed with DB106 available to the DS.

DB106 is structurally similar to another disperse blue dye, namely Disperse Blue 124 (DB124). In contrast to DB106, DB124 has an acetylated 2-hydroxyethyl group. This acetate should be sensitive to hydrolysis by

esterase activity yielding DB106 as the product (Hansson et al., 1997). Animal data (Ikarashi et al., 1996) and a large number of patch test studies investigated the frequencies of positive reactions to a mix of DB106 together with DB124. Concomitant reactions between DB124 and DB106 have been reported in several human studies (Lisi et al., 2014; Pratt and Taraska, 2000; Slodownik et al., 2011; Uter et al., 2001; Uter et al., 2007). However, these studies were not included in this dossier because a large number of reliable and relevant data on DB106 are available for assessment. Furthermore, the skin sensitising potential of DB124 has already been investigated in a previous CLH proposal (The proposal has been submitted to ECHA in June 2019. The Committee for Risk Assessment has adopted its opinion on the dossier for DB124 in December 2020, agreeing with the proposal to classify this substance as Skin Sens 1A and setting an SCL of 0,001%)[2].

10.7.1 Animal data

Animal studies performed with DB106 are summarised in Table 6.

Table 6: Summary table of animal studies on skin sensitisation for DB106

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Results	Reference
Key Study LLNA (acc. to (Kimber and Basketter, 1992)) Similar to OECD TG 429 No information on GLP Reliability 2: Reliable with restrictions Publication	Mouse, CBA/Ca, male N = 4/dose	**DB106** Purity: 87 % Vehicle: DMSO **DNCB[3]** Purity: 98.9 % Vehicle: DMSO	Concentrations: 0.25, 0.05, 0.025, 0.1, 0.01, and 0.005 % tested in two experiments (A, B) **Substance** / **EC3 (%)** DB106 (A) / 0.012 DB106 (B) / 0.017 DNCB / 0.015	**Positive** **Extreme sensitiser**	(Betts et al., 2005)

[2] https://echa.europa.eu/registry-of-clh-intentions-until-outcome/-/dislist/details/0b0236e1838f2a39

[3] DNCB-dinitrochlorobenzene, positive control

<table>
<tr><th>Method, guideline, deviations if any</th><th>Species, strain, sex, no/group</th><th>Test substance,</th><th>Dose levels duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr><td colspan="6">Supporting studies</td></tr>
<tr>
<td>GPMT modified FCA method
(acc. to (Hausen and Schmalle, 1985))
Similar to OECD TG 406
No GLP

Reliability 2: Reliable with restriction

<u>Deviations:</u>
Intradermal injections at day 0, 5, and 9, instead of intradermal injections at day 0 and topical induction application at day 6-8
No data on performance standard

Publication</td>
<td>Guinea pig Pirbright White, no further information
N = 10</td>
<td>DB106
<u>Vehicle:</u> acetone
<u>Purity:</u> chromato-graphically pure</td>
<td>Threshold of irritation: concentration of 10 %
Intradermal injection: 9 mg dye per guinea pig for the whole procedure in 6 x 0.1 mL emulsion FCA/saline (1:1), corresponding to 1.5 % (w/v)
Challenge concentration: 0.001 % in acetone
<table>
<tr><th></th><th>24 h</th><th>48 h</th><th>72 h</th></tr>
<tr><td>+++</td><td>6</td><td>7</td><td>6</td></tr>
<tr><td>++</td><td>3</td><td>2</td><td>3</td></tr>
<tr><td>+</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>(+)</td><td>-</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td>-</td><td>-</td><td>-</td></tr>
</table>
Reactions for dilutions of 1, 0.3, and 0.1 % were so strong that no reading could be made. One animal died to other causes.</td>
<td>Positive
Moderate sensitiser

Strong or extreme potency cannot be excluded</td>
<td>(Hausen and Menezes Brandao, 1986)</td>
</tr>
<tr>
<td>“Biphasic” LLNA
Non-guideline study
No information on GLP
Reliability 3: Not reliable

Sensitisation phase: Day 1-3, challenge phase: Day 15-17, instead of monophasic sensitisation protocol;
Endpoint analysis: Day 19, instead of two days without treatment;
Analysis of cell-count increase using automated cell counter,
No performance standard;
No SI calculation performed</td>
<td>Mouse, BALB/c, female
N = 10/dose
N = 20/ control</td>
<td>DB106, (CAS no. 68516-81-4)
<u>Vehicle:</u> DMSO
<u>Purity:</u> no information, purchased from Sigma–Aldrich Chemie GmbH, Steinheim, Germany</td>
<td>Significant increase in cell-count (%) compared to vehicle control) for tested concentration (C) of DB106 is shown:
<table>
<tr><th>C (%)</th><th>Cell-count (%)</th></tr>
<tr><td>30</td><td>174</td></tr>
<tr><td>3.0</td><td>124</td></tr>
<tr><td>0.3</td><td>82</td></tr>
<tr><td>0.03</td><td>79</td></tr>
<tr><td>0.003</td><td>37</td></tr>
</table>
30, 3, 0.3, and 0.0 3 % of DB106 resulted in a significant increase in ear-thickness by 26, 13, 17, and 9 %, respectively</td>
<td>Positive

Determi-nation of potency not possible[4]</td>
<td>(Ahuja et al., 2010)</td>
</tr>
</table>

[4] According to the Guidance on the Application of the CLP Criteria, Version 5.0; Table 3.5

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance,**	**Dose levels duration of exposure**	**Results**	**Reference**
Buehler Test According to OECD TG 406 No information on GLP Reliability 4: Not assignable	Guinea pig, Ibm:GOHI N=20/dose N=10/ control	**DB106** Vehicle: PEG 400 Purity: No information	Induction concentration (topical): 50% Challenge concentration (topical): topical: 50% (Maximum non-irritating) Readings 24 h and 48 h after challenge resulted in 16/20 and 15/20 animals with skin reactions (erythema score ≥ 1), respectively.	**Positive** **Moderate sensitiser** Strong or extreme potency cannot be excluded	(NICNAS, 2015)
GPMT According to OECD TG 406 No information on GLP Reliability 4: Not assignable	Guinea pig, Albino Dunkin-Hartley N=20/dose N=10/ control	**DB106** Vehicle: Distilled water Purity: No information	Induction concentration, intradermal: 1%, topical: 75 % Challenge concentration, topical: 50 % and 75 % Number of animals with skin reactions (erythema score ≥ 1): 50 % (24 h): 14/20 50 % (48 h): 12/20 75 % (24 h): 0/20 75 % (48 h): 0/20 There was no response at the challenge concentration of 75 %, due to the suitability of the test substance formulation. Acc. to the study authors, the 75 % formulation did not maintain very good skin contact and the results do not accurately reflect the sensitisation potential of the test material.	**Positive** **Strong sensitiser** Extreme potency cannot be excluded	(NICNAS, 2015)

A significant body of evidence from the published literature indicates that DB106 induces allergic reactions in animal models. Betts and colleagues (Betts et al., 2005) investigated the sensitising potential of DB106 in a LLNA conducted according to a protocol of Kimber and Basketter (1992). Therefore, the authors performed an initial experiment (1 %, 3 %, and 10 % of DB106 formulated in DMF vehicle) to achieve the highest non-toxic concentration of DB106 and the authors investigated different vehicles. For the main study, groups of mice were exposed topically on the dorsum of both ears to 0.25, 0.05, 0.025, 0.1, 0.01, and 0.005 % of DB106 (purity: 87 %) in DMSO, or to the vehicle alone (vehicle control), daily for three consecutive days. The sensitising potency of DNCB (0.01-0.25 % in DMSO) was measured concurrently. Five days after the initiation of exposure, all mice were injected intravenously with (^{3}H)-methyl thymidine (^{3}HTdR) via the tail vein. Five hours later, the draining auricular lymph nodes were excised and pooled for each experimental group. Incorporation of ^{3}HTdR was measured in single-cell suspensions of LNCs. In each case, a stimulation index (SI) relative to the concurrent vehicle-treated control value was derived (A detailed study summary and results are presented in Annex I).

This LLNA shows, that DB106 causes lymph nodes response in mice resulting in very low EC3-values (Experiment A: 0.012 % and Experiment B: 0.017 %). Data indicate an extreme sensitising potency of DB106. This well-documented local lymph node assay does not show obvious deviations from OECD TG 429. The DS considers this LLNA as the key animal study.

Additionally, Hausen and Menezes Brandao (1986) published a guinea pig maximisation test (GPMT) similar to OECD TG 406 performed with DB106. For the main study, guinea pigs were intradermally injected with an 1.5 % (w/v) dye emulsion containing chromatographically pure DB106 dissolved in FCA/saline (1:1), in a semi-circular arc in the shoulder area from the left to the right paw, on days one, five, and nine, according to (Hausen and Schmalle, 1985). Control animals were treated with a FCA/saline (1:1) emulsion. Challenge was performed on the 11th day after the end of the sensitisation procedure by topical application of sub-irritant doses of the dye (The threshold of irritation was determined at a concentration of 10 % in solvent acetone). Readings after 24, 48, and 72 hours resulted in 100 % positively reacting animals due to DB106 treatment. The authors reported that the "*reactions obtained on challenge with dilutions of 1 %, 0.3 %, and 0.1 % were so strong that no reading could be made because the whole flank of the animals became extremely red and swollen"*. One week later, after lesions disappeared, further epicutaneous tests with an additional dilution (0.001 %) were performed on the opposite flank (A detailed study summary and results are presented in Annex I). Since lower concentrations of DB106 ≤ 1.0 % or even ≤ 0.1 % were not tested in this modified FCA method, readings result in a moderate sensitising potency of DB106. However, a strong or an extreme sensitising potency cannot be excluded.

Ahuja and colleagues analysed the sensitising potential of DB106 in a "biphasic" LLNA (Ahuja et al., 2010). The authors used a sensitisation-challenge-protocol and analysed the increase in lymph node cells compared to vehicle controls. Therefore, female mice were treated once daily on their shaved backs from days one to three with 30, 3, 0.3, 0.03 and 0.003 % concentrations of DB106 (no information on purity). On days 15 to 17, mice were challenged with the test solution on the dorsum of both ears. Local lymph nodes were prepared on day 19. The authors investigated the lymph node weight, ear thickness, and ear biopsy weight. Furthermore, single cell suspensions from each single lymph node were counted (million per lymph node) using an automated cell counter. Investigations reveal that treatment with 30, 3, 0.3 and 0.03 % concentrations of DB106 resulted in a significant increase in ear thickness (26, 13, 17 and 9 %, respectively) and enhancement in the ear punch weight (22, 15, 17 and 12 %, respectively), compared to vehicle control. Furthermore, concentrations of 30, 3, 0.3, 0.03 and 0.003 % DB106 increased the cell count by 174, 124, 82, 79, and 37 %, respectively; in contrast to the vehicle control (A detailed study summary and results are presented in Annex I). Altogether, Ahuja and colleagues demonstrated that very low concentrations (0.003 %) of DB106 induced a significant increase in cell-count compared to the vehicle control in this "biphasic" LLNA. However, the test material was insufficiently characterised and this study had not been conducted in accordance with any available OECD testing guideline. Therefore, the experimental data do not allow for determination of a skin sensitising potency of DB106.

Furthermore, the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) published an assessment of DB106 (NICNAS, 2015). Unpublished study reports submitted by notifiers and summarised by NICNAS give evidence that DB106 acts as a skin sensitiser. In a Buehler test (according to OECD TG 406) conducted with DB106 (50 % topical induction, 50 % topical challenge) resulted in 16/20 and 15/20 sensitised animals (24h and 48h after challenge, respectively; erythema score ≥ 1). In an unpublished GPMT of notifiers (according to OECD TG 406), 14/20 and 12/20 animals (24h and 48h after challenge, respectively; erythema score ≥ 1) reacted to DB106 (1 % intradermal induction, 50 % topical challenge). The tested induction concentrations during the Buehler test (50 % for topical induction) and GPMT (1 % for intradermal induction), result in a moderate and strong sensitising potency of DB106, respectively. However, lower concentrations were not tested and an extreme potency cannot be excluded. None of these study reports submitted by notifiers was available to the DS (Reliability 4, not assignable) and data were not considered for potency assessment.

10.7.2 Human data

A large number of human reports documenting dermatological patch test data obtained with DB106 are available from the published literature. Studies considered as reliable and relevant (if not other specified) are summarised in Table 7. In addition, numerous case reports have been found which document sensitisation of individuals exposed to DB106 from various garments. For one case, a correlation of positive patch test reactions to DB106 and working with an ultrasound gel dyed with DB106 was reported. Relevant and reliable case reports are summarised in Table 8. Human studies, including patch test studies and case reports, considered as not reliable or not assignable were excluded from further assessment. A high number of case reports show positive patch test reactions for DB106 in patients, but was not considered relevant, because there is no confirmation that DB106 was present in the suspected source of the lesion, e.g. the textile (Alberta et al., 2005; Batchelor and Wilkinson, 2006; Carrozza and Nestle, 2000; Dejobert et al., 1995; Dwyer and Forsyth, 1994; Escudero et al., 2008; Foussereau, 1986; Goldminz and Scheinman, 2018; Guin, 2001; Guin et al., 1999; Hosteing and Giordano-Labadie, 2015; Jacob et al., 2008; Komericki et al., 2001; Massone et al., 1991; Mohamoud and Andersen, 2017; Nakagawa et al., 1996; Pecquet et al., 1999; Perez-Crespo et al., 2009; Pousa-Martinez et al., 2016; Pratt and Taraska, 2000; Preston et al., 2019; Ramírez et al., 2007; Routheut et al., 2002; Soffer et al., 2015; Ukida et al., 2014; Walker and Beck, 2005; Wong et al., 2011).

Table 7: Summary table of human data on skin sensitisation

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
Consecutive dermatitis patients					
1	Diagnostic patch test analyses from seven allergy departments in Spain	During one year, 1 046 patients were patch-tested with the 34-allergen T.R.U.E. (Thin-layer Rapid Use Epicutaneous) test, to investigate the prevalence of allergens of the test series in all patients presented in seven allergy departments (DB106, 41 µg (50 µg/cm^2) in vehicle povidone).	DB106: **0.6 %** (6/1 046) positive reactions (+++ in 1 patient, ++ in 1 patient, and + in 4 patients) Reaction was considered clinically relevant in 3 patients.	**Positive** **Low/moderate frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Echechipia et al., 2015)
2	Retrospective review of patch test results from dermatological clinic (Mayo clinic)	Electronic patch test database containing demographic information and results from all patients (3 115, mean age 54.9 ± 18.3 years; 2 045 women), tested 01/2006-12/2010, were investigated. On average, patients were patch-tested for 73 allergens, 3 086 subjects were tested to DB106 (1 % in pet.). Data were compared with previous patch test results of the Mayo clinic (2001-2005) and with those in a NACDG[6] report from 2005-2006.	Positive reactions (2006-2010): DB106: **2.8 %** (37.2 % relevant reactions) Irritant reactions (2006-2010): DB106: 0.6 % Positive reactions (2001-2005): DB106: 5.3 **%** (2 096 patients tested) Positive reactions (NACDG, 2005-2006): DB106: 2.1 % (4 426 patients tested)	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Wentworth, 2014)
3	Patch test analyses from 13 dermatological centres from NACDG[6]	01/2007-12/2008, 5 085 patients (3 539 aged >40 years; 1 812 men) with suspected allergic contact dermatitis (598 subjects with occupationally related skin condition) were patch-tested with 65 allergens, including DB106 (1 % in pet.).	DB106: **0.9 %** positive reactions 0 %, 29.2 %, 37.5 %, and 4.2 % definite, probable, possible, and past relevance, respectively	**Positive** **Low/moderate frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Fransway et al., 2013)

[5] Frequency and exposure are rated as relatively high or low in line with Tables 3.2 and 3.3 of the ECHA "Guidance on the Applicability of the CLP criteria", where possible.
[6] NACDG-North American Contact Dermatitis Society

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
4	A retrospective chart review of patch tests from hospital Reliability 4: Not assignable Only abstract available	Within five years, 427 patients (mean age 49.8 years) were patch-tested for "utilization of TRUE® test versus expanded patch test panels for allergic contact dermatitis".	DB106: **2.3 %** positive reactions	**Positive** No sub-categorisation possible	(Mucci et al., 2012)
5	Patch test from dermatological clinic	327 consecutive patients with eczema (mean age 36.5 ± 13.8 years; 100 men) and 205 healthy student volunteers (mean age 25.8±1.5 years, 95 men; non-patient population, recruited by advertisement) were patch-tested with modified European baseline series and textile dye allergens, including DB106, 1 % (vehicle not reported, assumed pet.). No time window reported	DB106: **1.2 %** (4/327) positive reactions in consecutive eczema patients; 0 % among healthy volunteers	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Li, 2010)
6	Patch tests/consumer tests at Department of Occupational and Environmental Dermatology	02-12/2005, 982 dermatitis patients (18 women, mean age 47.3 years and 3 men, mean age 51.0 years) were consecutively patch-tested with a baseline patch test series, including a textile dyes mix and the eight separate components (DB106, 0.1 % in pet. included); 858 patients answered a questionnaire.	DB106: **0.2 %** (2/982) positive reactions	**Positive** **Low/moderate frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Ryberg et al., 2009)
7	Descriptive analysis of patch test data to disperse dyes from the IVDK[7]	07-12/2005, 2 215 consecutive patients were patch-tested with DB106 (0.3 % in pet.), included in the 'monitor series' by a subgroup of IVDK centres. Reliable concentration of 0.3 % for DB106 in patch test preparations were confirmed by HPLC analysis.	DB106: **0.5 %** (11/2 215) positive reactions DB106: 0.2 % (5/2 215) irritant reactions	**Positive** **Low/moderate** frequency Previous exposure to DB106 not documented, no sub-categorisation possible	(Uter et al., 2007)
8	Patch test from dermatological clinic in order to identify emerging allergens and uptake of paediatric series	1995-2001, 1 094 consecutive children (aged: 7 months to 12 years; 509 boys) with suspected contact dermatitis were patch-tested with a "paediatric series" of 30 allergens or with 46 allergens. DB106 was patch-tested in 97 children (1 % in pet.).	DB106: **4.0 %** positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Seidenari et al., 2005)

[7] IVDK- Information Network of Departments of Dermatology

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
9	Patch tests from dermatological clinic	Over a period of one year, 286 consecutive patients (190 women, 96 men) were patch-tested with a standard series (TRUE Tests) and a textile colour and finish series (DB106 assumed 1 % in pet.).	DB106: **4.2 %** (12/286) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Lazarov et al., 2002)
Selected dermatitis patients					
10	Retrospective review of a tertiary health centre regarding the patch test results of contact sensitisation in children without atopic dermatitis	07/2013-07/2017, 178 children aged between 0 and 18 years and who were diagnosed with ACD were investigated. Patients with a known history of atopic dermatitis were excluded from the analysis, resulting in 89 children (30 boys and 59 girls, aged 3 to 18 years). Patients were tested with the TRUE test series (DB106, 50µg/cm^2 of patch, vehicle povidone).	DB106: **5.6 %** (5/89) positive reactions DB106 among the most frequently determined allergens	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Kundak, 2020)
11	Retrospective analysis by IVDK[8] including 56 dermatological departments from Austria, Switzerland, and Germany	2007-2014, among 98 417 patients, 3 207 patients (67.6 % aged ≥ 40 years; 43.8 % men) were identified with a suspected textile allergy due to clothing or textiles (95 210 controls, 72.4 % aged ≥ 40 years; 36.2 % men). 1 628 subjects with ACD were patch-tested with DKG[9] textile and leather dye series, including 1 238 patch-tested to DB106 (0.3 % in pet.).	DB106: **2.0 %** (25/1 238) positive reactions DB106: 0.4 % (5/1 238) irritant reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Heratizadeh et al., 2017)
12	Patch test outcome of ICDRG[10] (representing clinics from nine countries) to textile dye mix (TDM) and patch test reactions to single separate dyes with patients allergic to textile dye mix.	03-12/2013, 2 493 consecutive dermatitis patients were patch-tested with TDM (6 % in pet.), consisting of six disperse dyes (1.0 % each), and DB106 and DB124 (each 0.3 % in pet.). Patients included 917 men (mean age, 38.6 years) and 1 576 women (mean age, 43.4 years). Consideration for inclusion of the TDM into the international baseline series.	3.6 % positive reactions to TDM; 83 positively patch-tested patients were patch-tested with single textile dyes at different concentrations: DB106 (0.3 %): **7.2 %** (6/83) DB106 (1.0 %): **15.7 %** (13/83) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Isaksson et al., 2015)

[8] IVDK-Information Network of Departments of Dermatology
[9] DKG-German Contact Allergy Group
[10] ICDRG-International Contact Dermatitis Research Group

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
13	Retrospective analysis from contact dermatitis clinic and an occupational dermatitis clinic to identify the most relevant allergens	01/2001-12/2010, 5 521 patients (average age 41.0 years) presented, of whom 5 281 were generally patch-tested with an extended European standard series and additional allergens or series based on the dermatologist's assessment (1 174 patients were patch-tested with DB106, 1 % in pet.).	DB106: 5.6 % (66/1 174) positive reactions DB106: **1.4 %** (17/1 174) relevant reactions identified	**Positive** **Low/moderate frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Toholka et al., 2015)
14	Patch test from dermatological clinic Reliability 4: Not assignable	10/2005-12/2009, 50 textile industry workers (34 men) with diagnosis of allergic contact dermatitis were patch-tested with the TRUE test, 36 patients were also tested with textile series allergens (DB106, 1 % in pet.).	DB106: **8.3 %** positive patch test reactions	**Positive** No sub-categorisation possible	(Su et al., 2014)
15	Investigations of the patch test outcome of EECDRG[11] clinics from nine countries to textile dye mix (TDM). Consideration for inclusion of the TDM into the European baseline series.	01-06/2011, 2 907 consecutive dermatitis patients (943 males, mean age 47.7 years, and 1 964 females, mean age 45.7 years) were patch-tested to TDM 6.6 % in pet. (Six disperse dyes, including DB106, 0.3 %). 94 TDM-positive patients were tested with single dyes.	3.7 % (108/2 907) positive reactions to TDM DB106 (0.3 %): **6.4 %** (6/94) DB106 (1.0 %): **13.8 %** (13/94) among TDM-positive patients	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Ryberg et al., 2014)
16	Patch test evaluation of clinical features and epidemiology of textile contact dermatitis	277 selected textile dermatitis patients (187 females and 90 males; mean age 43.5 years) were patch-tested, 154 patients were affected by allergic textile contact dermatitis (non-occupational in 132; occupational in 22 subjects; 104 females, 50 males; mean age 45.2 years). The SIDAPA[12] baseline series, textile series, and suspected garment sample (when available) were used for patch-testing (DB106, 1 % in pet.). Time window unknown	DB106: **28.6 %** (44/154) positive reactions non-occupational: 33.3 % (44/132) occupational: 0 (0/22)	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Lisi et al., 2014)

[11] EECDRG- European Environmental Contact Dermatitis Research Group

[12] SIDAPA-Italian Society of Allergological Dermatology

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
17	Retrospective review of patch tests from department of dermatology	01/2000-09/2011, 671 patients (mean age 56.5±16.3; 442 females, 229 males) were patch-tested with a textile dye series, including 42 dyes and resins, according to NACDG and mayo clinic protocols; 620 patients were generally patch-tested with a standard patch test series. In total, 660 subjects were patch-tested to DB106 (1 % in pet.).	DB106: **8.3 %** positive reactions, 98.2 % total relevant reactions DB106: 0.6 % irritant reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Wentworth et al., 2012)
18	Patch tests from general and occupational contact dermatitis clinics at the Skin and Cancer Foundation Melbourne, Australia	1993-2006, in total 2 069 patients (mean age 39.2 years; 970 male) with suspected textile allergy were tested with an extended European baseline series and textile series (DB106, 1 % pet.). There were 1 040 patients from the contact dermatitis clinic and 1 029 patients from the occupational dermatological clinic.	DB106: **1.0 % (**21/2 069) positive reactions	**Positive** **Low/moderate frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Slodownik et al., 2011)
19	Patch tests from Department of Occupational and Environmental Dermatology, investigation for significance of impurities	21 patients were previously patch-tested in the dermatological departments and reacted positively to DB106; including 18 women (mean age 47.3 years) and 3 men (mean age 51.0 years). Patients were patch-tested with purified and commercial DB106, and with thin-layer chromatography (TLC) strips made from the commercial preparations of dyes.	13/21 patients reacted positively to DB106 TLC-strips, four subjects did not react to main spot; 10 patients reacted to dilution series of purified DB106, and 16 patients tested positively to the dilution series of commercial disperse dye.	**Positive** Frequency unclear Previous exposure to DB106 not documented, no sub-categorisation possible	(Ryberg et al., 2009)
20	Patch tests from Department of Occupational and Environmental Dermatology and Department of Dermatology	01/1999-12/2003, 3 325 patients (58.4 % women (mean age 47.2 years) and 41.6 % men (mean age 45.5 years)) were consecutively patch-tested with the standard series of the departments including a textile dye mix (TDM) of eight disperse dyes (DB106, 0.1 % in pet. included). 47/50 patients who reacted positively to the mix were tested with the eight components separately.	50/3 325 patients reacted positively to TDM DB106: **10.6 %** (5/47) positive reactions among TDM-positive patch test patients Individual readings: (+++) in 1 patient, (+) in 4 patients	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Ryberg et al., 2006)

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
21	Patch test analysis from 37 IVDK[13] dermatological clinics	1998-2002, in total 1 137 patient with suspected textile dermatitis were investigated (640 subjects with age ≥40 years; 41.4 % male). Among subjects, 263 patients were patch-tested with DB106 (1 % in pet.).	DB106: **7.2 %** (19/263) positive reactions DB106: 0.4 % (1/263) irritant reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Bauer et al., 2004)
22	Patch test from dermatological clinic	01/1999-12/2002, 644 patients (441 female and 203 male; mean age 44.4 years) with suspected textile allergic contact dermatitis were patch-tested to a standard series (TRUE Tests), textile colour and finish series (TCFS) and additional series, as well as clothing extracts in 21 cases (DB106, 1 % in pet. included).	DB106: **4.7 %** (30/644) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Lazarov, 2004)
23	Patch test from dermatological clinic, investigation of sensitisation to disperse dyes in children	01/1996-12/2000, 1 098 consecutive children (667 with suspected allergic contact dermatitis and 431 with atopic dermatitis) were patch-tested with a "standard patch test series" and disperse dyes. 51 children (4.6 %; 34 girls and 17 boys) were sensitised to at least one disperse dye. DB106 (no further information) was tested in 12 children.	DB106: **33.3 %** (4/12) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Giusti et al., 2003)
24	Patch test analysis of patients with textile dye allergic contact dermatitis from 10 clinics or physicians representing five countries	09/2000, 20 patients with suspected dyed-fabric allergic contact dermatitis were identified from reports of 10 clinics. Results of 16 patients, patch-tested with 12 commercial disperse dyes from the Textile colour & finishes series (DB106, assumed 1 % in pet.) are presented. Disperse dyes in 32 garments submitted by the patients were analysed using HPLC and confirmed by LC/MS analysis.	DB106: **68.8 %** (11/16) positive reactions In 22/32 garments 35 different disperse dyes were identified; DB106 was identified in nine fabrics.	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Hatch, 2003; Hatch et al., 2003)
25	Retrospective patch test study from department of occupational dermatology	01/1996-12/1999, 577 patients (no information on sex or age) with a possibility for contact allergy to para or azo dyes were analysed. Patch testing with the European standard series and dye series, including DB106 (assumed 1 % in pet.) was performed.	DB106: **5.9 %** (34/577) positive reactions 6/34 positive reactions on day 6 or day 7 (while negative at day	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-	(Koopmans and Bruynzeel, 2003)

[13] IVDK- Information Network of Departments of Dermatology

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
			2 and day 3)	categorisation possible	
26	Patch test analysis from dermatological department	01/1996-12/2000, 6 478 consecutive patients patch-tested to a standard series identified 437 patients allergic to disperse dyes: 130 patients with hand dermatitis (study group, male/female ratio 0.67; mean age 40.7±16.5 years) and 307 without hand involvement (male/female ratio 0.56, mean age 40.5±21.3 years). Patch testing with a standard series supplemented with azo dyes (DB106, no further information) was performed.	DB106: **50 %** (63/130) positive reactions among hand dermatitis patients; **49 %** (133/307) positive reactions among patients without hand involvement	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Giusti et al., 2002)
27	Review of dermatological clinic	04/1997-04/2001, 203 patients (no information on sex or age) with eyelid dermatitis were patch-tested with a "standard" diagnostic series (DB106, 1 % in pet.) and suspected sources of allergic contact dermatitis, if available.	DB106: **4.9 %** (10/203) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Guin, 2002)
28	Patch tests from dermatological clinic	06/1996-12/2000, allergic contact dermatitis to a textile allergen (disperse dyes), was seen in 28 (1.7 %) of 1 638 patients; 18 patients (3 male, 15 female, mean age 41 years) had been patch-tested to a modified British Contact Dermatitis Group standard series, and a series consisting of 18 dyes and four textile chemicals (DB106, 1 % in pet.).	DB106: **22.2 %** (4/18) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Smith and Gawkrodger, 2002)
29	Patch test analysis from 31 participating centres of the IVDK[14], all members of the GCDRG[15]	01/1995-06/1999, in total 49 4931 patients were patch-tested in the participating centres, with 1 986 subjects patch-tested to textile dye series; 1 847 patients were patch-tested to DB106 (1 % in pet.).	DB106: **3.5 %** (64/1 847) positive reactions	**Positive** **High frequency** Previous exposure to D106 not documented, no sub-categorisation possible	(Uter et al., 2001)

[14] IVDK-Information Network of Departments of Dermatology
[15] GCDRG-German Contact Dermatitis Research Group

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
30	Patch testing from dermatological clinic	During five years, 18 out of 1 400 patients with suspected contact dermatitis due to textile fabrics were diagnosed in an allergy section of a hospital (including 14 woman and 4 men; age range from 15 to 62 years). Subjects were patch-tested with the GRDCI[16] standard allergens and with textile dyes (DB106, assumed 1 % in pet.).	DB106: **44.4 %** (8/18) positive reactions	**Positive** **High frequency** Previous exposure to D106 not documented, no sub-categorisation possible	(Fuentes Cuesta et al., 2000)
31	Patch test analysis from a dermatological clinic	During 1998, 103 patients with suspected allergic contact dermatitis to clothing were clinically evaluated and patch-tested with a standard series (TRUE tests) and Textile colour & finish series (DB106, assumed 1 % in pet.). Nine patch-positive patients presented with purpuric patch test reactions[17] (8 female and 1 male, aged from 14 to 62 years).	DB106: **6.8 %** (7/103) positive reactions Purpuric patch tests provoked by DB106	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Lazarov and Cordoba, 2000)
32	Retrospective study of three dermatological clinics on textile dye dermatitis	1991-1997, 55 patients (36 women, 19 men) suspected of having textile contact dermatitis were patch-tested to the European standard series and Textile Colours and Finishes series (DB106, assumed 1 % in pet.).	DB106: **12.5 %** positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Lazarov et al., 2000)
33	Retrospective patch test study from contact dermatitis clinic	09/1997-07/1999, 788 subjects were patch-tested to either the NACDG[18] standard tray or European standard series. 271 patients with clinical suspicion of textile dermatitis were patch-tested with a textile series (including DB106, 1 % in pet.).	DB106: **12.2 %** (33/271) positive reactions	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Pratt and Taraska, 2000)

[16] GRDCI-European Contact Dermatitis Research Group
[17] Uncommon manifestation of allergic contact dermatitis (Lazarov and Cordoba, 2000)
[18] NACDG-North American Contact Dermatitis Group

No.	Type of data/report	Test substance, relevant information about the study (as applicable)	Patch test results for DB106, observation	Results[5], classification	Reference
34	Patch test from dermatological clinic	04/1992-04/1994, 1 236 patients were patch-tested in total, including 26 patients (21 women, mean age 48.5 years and 5 men, mean age 34.4 years) with suspected textile dermatitis. They were tested with the DKG standard series, textile dyes (DB106, 1 % in pet.) and finishing series. In 18 patients, clothes were also tested.	DB106: **15.4 %** (4/26) positive reactions 5 patients reacted positive to their clothes	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Maurer et al., 1995)
35	Patch test analysis from a dermatological department	1987-1991, 3 336 patients were investigated for contact dermatitis and patch-tested with the European standard series. 159 patients were also tested with a textile series (DB106 included, no information on vesicle or concentration). 28 patents with textile dye dermatitis were identified.	DB106 positive reactions: **10.1 %** (16/159) among all patients tested to textile series **57.1 %** (16/28) among patients with textile dye dermatitis	**Positive** **High frequency** Previous exposure to DB106 not documented, no sub-categorisation possible	(Doomsgoossens, 1992)
36	Patch test from dermatological clinic	1990-1991, 32 patients (20 women, mean age 39.9 years and 12 men, mean age 46.6 years) with presumable allergic contact dermatitis and all with a positive patch test reaction to p-aminoazobenzene (PPD; 025 % in pet.) were additionally patch-tested with a series of textile azo dyes (incl. DB106, 1 % in pet.) and one food azo dye.	DB106: **0 %** (0/32) positive reactions among PPD-positively patch-tested patients	**Negative**	(Thierbach et al., 1992)

Table 8: Summary of the reliable and relevant case reports on skin sensitisation for DB106

No.	Clinical data/case history	Patch test results, observation	Reference
1	A 28-year-old woman developed eyelid dermatitis after performing "*research with focused ultrasound on mice in a horizontal laminar flow hood in which the airflow was towards the user*". Seven years before, she had presented with vesicular hand dermatitis and previous patch testing with the ACDS[19] baseline series resulted in a positive reaction for DB106 (no information on conc. or vesicle).	DB106 (+) on day 3 Personal communication with the ultrasound gel manufacturer revealed that the gel was dyed with DB106.	(Skalina and Ramesh, 2018)
2	A 43-year-old woman presented with dermatitis under her breast, across her back and around her waist. Eczematous eruption occurred 24 h after wearing a new navy blue lined dress. Patch-testing with the Skin and Cancer Foundation standard series, textile dye series (DB106, 1 %, assumed in pet.), and samples of her own blue dress was performed.	Strong positive reactions (oedematous and vesicular) to DB106, weak positive reaction to the dress lining (72 h); weak reaction (non-vesicular) to DB106 at 7 days (A generalised eczematous eruption was noted on the back. It centred on the DB106 site and spread out widely from it); other dyes from the textile dye series were negative.	(Dawes-Higgs and Freeman, 2004)
	Five female workers in a ready-to-wear shop presented with 3-month histories of eczema. The garment suspected was a dark blue smock, introduced as a working uniform in the last four months and worn by about 200 employees. Patch tests were performed with the Portuguese standard series, including disperse dye mixes. Furthermore, patients were tested for modified and extended textile series, including 33 dyes (DB106, no further information) and a piece of garment. Thin-layer chromatographic (TLC) analysis was performed on a sample of the smock.	DB106 was identified in smock, using TLC; smock was made of synthetic acetate and polyamide; 5/5 positive reactions to DB106 (individual readings not reported)	(Mota et al., 2000)
3	(Case 1) 34-year-old, presented with eczema around axillae, neck, upper chest, hands (dorsum) and eyelids.	DB106-positive	
4	(Case 2) 25-year-old, presented with eczema around axillae, neck, upper chest, abdominal wall, face	DB106-positive	
5	(Case 3) 34-year-old, presented with eczema around neck, hands (dorsum), antecubital fold, forearm	DB106-positive	
6	(Case 4) 34-year-old, presented with eczema around neck, forearm	DB106-positive	
7	(Case 5) 34-year-old, presented with eczema around neck, fists	DB106-positive	

[19] ACDS-American Contact Dermatitis Society

No.	Clinical data/case history	Patch test results, observation	Reference
8	A 43-year-old female teacher presented in 06/1997. She developed eczematous lesions on her neck, décolleté and crook of her arm (antecubital fossae). Lesions occurred 48 h after wearing the short black coat of a black dress for four to five hours at graduation. The dress had been worn only once before. Patch testing was performed for a standard series (no further information), disinfectants and preserving agents, constituents of nail polish, and 27 disperse dyes (DB106, 1 % in pet.).	DB106-positive patch test reaction (+++) Analysis identified DB106 in extractions from the dress.	(Hausen and Lemke, 1997)
9	Six female patients had allergic contact dermatitis from clothing. Duration of clinical features, including erythema, oedema, papules and severe pruritus, ranged from eight days to four months. Investigations included patch tests using a standard series (Portuguese Contact Dermatitis Group), a textile dye series, two textile resins and pieces cut from the suspected garment (incl. DB106, 1 % in pet.). (Case 4) 58-year-old woman presented with lesions localized around the trunk and abdomen, source of lesion were black underwear.	4/6 women reacted positively to DB106 (individual readings not reported). TLC performed on clothes of three patients identified DB106 in one garment (Case 4)	(Lisboa et al., 1994)
	Nine women with allergic contact dermatitis after wearing black “velvet” fabrics were patch-tested with five purified disperse dyes. Dyes were isolated from patient’s textiles and incorporated in 1 % petrolatum for patch testing.	9/9 textiles revealed presence of DB106 and other disperse dyes, shown by thin-layer chromatography	(Hausen, 1993)
10	(Case 1) A 38-year-old woman presented with severe lesions on the thighs and shins due to leggings worn since 05/1991 on several occasions.	DB106 (+++/+++), fabric (+++/+++)	
11	(Case 2) A 37-year-old woman presented with skin lesions spreading to the arms and legs due to a body worn on several occasions.	DB106 (++/+++) at day 1 and 3, fabric not tested	
12	(Case 3) A 32-year-old woman presented with severe skin lesions due to a body worn less than nine months (since 11/1991), while performing aerobic sports. Lesions occurred where sweat dissolved the black slurry, also involving the arms. Patient showed disability for 3 weeks.	DB106 (+++/+++) at day 1 and 3, own fabric (strongly positive)	
13	(Case 4) A 26-year-old woman presented with severe lesions on the trunk, arms, neck, and décolleté. An emergency treatment was necessary due to a dress “worn sporadically” (lastly 03/1992).	DB106 (-/++) at day 1 and 3, fabric not tested	
14	(Case 5) A 25-year-old woman presented with severe skin lesions occurring around her trunk and arms after wearing a body for 6-7 times (in 02/1991) and after dancing the whole night.	DB106 (++/++) at day 1 and 3, fabric not tested	
15	(Case 6) A 27-year-old woman presented with an outbreak of severe skin lesions, becoming generalised due to a leggings worn several times, in 12/1991.	DB106 (+++/+++) at day 1 and 3, fabric not tested	
16	(Case 7) A 52-year-old woman presented with severe skin lesions on the thighs, spreading also to neck and arms. She showed a disability for 2 weeks. Symptoms occurred after wearing leggings purchased in 11/1991, and worn on several occasions in 01/1992.	DB106 (++/+++) at day 1 and 3 and own fabric (strongly positive)	

No.	Clinical data/case history	Patch test results, observation	Reference
17	(Case 8) A 38-year-old woman presented with severe skin lesions already 12/1991, "burning like sunburn". She bought the textile in 11/1991. She has worn it several times a week.	DB106 (++/++) at day 1 and 3 and own fabric (strongly positive, lasting for weeks)	
18	(Case 9) A 34-year-old woman presented with first lesions on the legs, in 02/1992 and 03/1992, after wearing leggings that was purchased in 12/1991. Lesions worsened after wearing the leggings again.	DB106 (+++/+++) at day 1 and 3 and own fabric (positive)	
	In 1991, four women with allergic contact dermatitis after wearing black "velvet" leggings and bra were reported. Patients were patch-tested with five purified disperse dyes that were isolated from patients own textiles (Disperse Blue124, DB106, Disperse Red 1, Disperse Blue 1, Disperse Yellow 3).	DB106 were identified in patients' garments using TLC. 4/4 women reacted positively to DB106	(Hausen et al., 1991)
19	(Case 1) A 53-year-old woman presented with massive pruritus in areas of the legs and waist after wearing black "velvet" leggings sporadically within four to five months. She bought textile in 02/1991.	DB106 (+++/+++) after 24 and 72 hours	
20	(Case 2) A 25-year-old woman presented in 04/1991 with pruritus and eczema around the legs and buttocks after wearing some black trunks.	DB106 (++/++) after 24 and 72 hours	
21	(Case 3) A 26-year-old woman presented with eczema around the thighs after wearing "velvet" leggings. Symptoms started in 12/1990.	DB106 (0/+/++/++) after 24, 48, 72 and 96 hours	
22	(Case 4) A 41-year-old woman presented with eczema in areas where the bra suits, waist, buttocks after wearing "velvet" leggings and bra. Symptoms started in 12/1990.	DB106 (++) after 24 hours	
	Nine women with textile dye allergy were investigated from 1980-1983. Patch testing with the European standard series, a textile dye series, pieces of different fabrics, and DB106 (1 % in pet.) was performed.	9/9 women reacted positively to DB106 and different textiles.	(Menezes Brandao et al., 1985)
23	(case 1-4) From 1980-1981, four women, aged 36 to 50 years, showed lesions in both axillae, on the sides of the neck, upper back, and inner aspect of the arms after wearing black polyester blouses.	4/4 women reacted positively to different fabrics (reading from + to +++), DB106 (readings from + to +++), and other dyes	
24	(Case 5) March 1982, a 57-year-old woman developed a subacute dermatitis of both axillae, the upper back and elbow flexures, shortly after she began to wear two new dark blue and black blouses.	Positive patch test reaction to several clothes (+++) and DB106 (individual reading not reported	
25	(Case 6) May 1983, a 39-year-old woman showed "*a clinical picture quite similar to that of the 5 preceding patients*" (case 1-5), after wearing new black blouse.	Positive patch test reaction to several clothes (+++) and DB106 ("strong")	
26	(Case 7) A 30-year-old woman presented with "*typical blouse dermatitis*" around the axillae.	Positive reactions to DB106 and blouses (individual reading not reported)	
27	(Case 8) A 41-year-old woman presented with "*typical blouse dermatitis*" around the axillae and	Positive reactions to DB106 and several blouses	

No.	Clinical data/case history	Patch test results, observation	Reference
	neck.	and dresses (individual reading not reported)	
28	(Case 9) A 41-year-old woman presented with "*typical blouse dermatitis*" around the axillae and waist.	Positive reactions to DB106 and several blouses and dresses (individual reading not reported)	

A large body of evidence resulting from human reports indicates that DB106 consistently and repetitively elicits positive reactions in diverse patch tests, in several clinical settings. Human patch test data comprise studies with consecutive or selected dermatitis patients. Tests were performed in dermatological clinics analysing the number of patients sensitised to DB106 compared to all patients tested in a certain time-period.

In studies with unselected, consecutive dermatitis patients patch testing is generally more standardised. In contrast, for a selected (specific) group of patients or workers, usually targeted patch testing with special test series is performed. Data for consecutive patients vary between 0.2 % and 4.2 % positive reactions to DB106, among all patients analysed. Selected dermatitis patients patch-tested positively for DB106 show frequencies between 0 % and 68.8 %. Among all patch test data available, five studies reported skin irritant reactions in a few tested subjects after treatment with DB106. Furthermore, numerous case reports have been published indicating allergic reactions in patients after wearing clothing containing DB106. Reports support that DB106 causes allergic contact dermatitis to textiles, especially at sites where garments fit strongly, at areas of friction and sweating, facilitating allergens to migrate out of the textile.

In general, patch test data or case reports, which aim to determine whether there is a pre-existing sensitisation, do not allow for an estimation of exposure levels.

Altogether, most human studies reveal a relatively high frequency of occurrence of DB106 skin sensitisation in consecutive and selected dermatitis patients.

The purity and concentrations of standard textile dyes used for patch testing were investigated by thin layer chromatography. Investigations revealed that DB106 patch test preparations showed one main spot but also additional weaker, but defined spots in the chromatograms (Everitt et al., 2016; Malinauskiene et al., 2012; Ryberg et al., 2009). Furthermore, analysis showed that the mean concentrations of several commercial DB106 patch test preparations were much lower than labelled (0.35 % (0.3-0.5 %) instead of 1.0 %, 14 preparations (Ryberg et al., 2008). Patch testing with preparations containing impurities and/or a lower concentration than labelled may result in difficulties in diagnosis of individual patients. However, the high frequency of occurrence of positive diagnostic patch test reactions in more than 700 patients, from a high number of dermatological clinics, representing numerous different countries leaves no doubt that DB106 acts as a skin sensitiser.

10.7.3 Other studies relevant for skin sensitisation

Sonnenburg and colleagues published a human cell *in vitro* assay, named loose-fit co-culture-based sensitisation assay (LSCA) (Sonnenburg et al., 2012). This assay shows that treatment with DB106 activates CD86 expression of dendritic cell-related cells (Key event 3 of AOP) compared to vehicle control. Nevertheless, this study was not performed according to an internationally adopted *in chemico*/*in vitro* test guideline (listed in Table R.7.3-3, Endpoint-specific guidance, version 6.0-July 2017) and is precluded from further assessment.

10.7.4 Short summary and overall relevance of the provided information on skin sensitisation

In summary, reliable animal data give strong evidence that DB106 causes skin sensitisation *in vivo*. In a well-documented local lymph node assay without obvious deviations from OECD TG 429, DB106 induced skin sensitisation resulting in very low EC3 values (Experiment A: 0.012 % and Experiment B: 0.017 %; (Betts et al., 2005)). Results indicate that DB106 acts as an extreme sensitiser. Furthermore, in a GPMT (similar to OECD TG 406) 100 % of the tested animals showed positive reactions after DB106 exposure (1.5 % DB106 for intradermal induction, 0.001 % for challenge (Hausen and Menezes Brandao, 1986)). However, results should be taken with care, because the authors had not tested concentrations of DB106 lower than 1 % or even 0.1 % for intradermal induction. Therefore, the possibility of DB106 having a strong or an extreme sensitising potency cannot be excluded from this study. In addition, (Ahuja et al., 2010) demonstrated in a “biphasic” LLNA that DB106 causes skin sensitisation. Very low concentrations (0.003 %) of DB106 induced a significant increase in cell-count compared to the vehicle control. However, this study is of lower reliability, due to an insufficient characterisation of the test material and severe

deviations from OECD TG 429 that do not allow for SI calculation.

A huge human database proves DB106 to be a common source of textile dye allergic contact dermatitis. Results of human patch test studies for consecutive dermatitis patients reveal frequencies between 0.2 % and 4.2 % positive reactions to DB106, among all patients analysed. Selected dermatitis patients, patch-tested for DB106 show frequencies between 0 % and more than 69 %. Altogether, most human studies reveal a relatively high frequency of occurrence of DB106 skin sensitisation. Furthermore, a huge number of case reports indicate allergic reactions to DB106 after wearing clothing containing DB106. Notably, DB106 was reported as "*common causes of textile dermatitis*" (Pratt and Taraska, 2000). Nevertheless, available human data are insufficient for a reliable estimation of exposure levels (and to conclude on potency/SCL setting).

Additionally, in an *in vitro* assay DB106 activated CD86 expression in dendritic cells, representing a main reaction with respect to key event 3 of AOP for skin sensitisation (Sonnenburg et al., 2012). This assay was not performed according to any *in chemico*/*in vitro* tests with regulatory validation and acceptance (listed in Table R.7.3-3, Endpoint specific guidance, version 6.0-July 2017) and therefore is excluded from further assessment.

Finally, the NICNAS published an assessment of DB106. Unpublished study reports of notifiers were summarised, giving evidence of skin sensitisation in a Buehler test and a GPMT (OECD TG 406) conducted with DB106. However, notifiers' study reports were not available to the DS and could not be considered for further evaluation. NICNAS concluded that DB106 is a "*very strong sensitiser from animal studies and human data*" (NICNAS, 2015).

10.7.5 Comparison with the CLP criteria

In Table 9, relevant experiments in animal and human data are compared with CLP criteria, as laid down in the guidance of the Application of the CLP criteria. Only studies with at least reliability 2 are included.

Table 9: Comparison of human and animal data for skin sensitisation of DB106 with CLP criteria

Reference(s)	Criteria acc. to CLP Regulation, as laid out in (ECHA, 2017)	Results	Resulting Classification
Animal data			
LLNA (Betts et al., 2005)	Skin Sens. 1A: EC3 > 0.2 - ≤ 2 %, Strong sensitiser EC3 ≤ 0.2 %, Extreme sensitiser Skin Sens. 1B: EC3 > 2 %, Moderate sensitiser	EC3 = 0.017 %	**Skin Sens. 1A** **Extreme potency**
GPMT (Hausen and Menezes Brandao, 1986)	Skin Sens. 1A - Extreme potency: ≥ 60 % sensitised guinea pigs at ≤ 0.1 % intradermal induction Skin Sens. 1A - Strong potency: ≥ 30 - < 60 % guinea pigs sensitised at ≤ 0.1 % intradermal induction or ≥ 60 % guinea pigs sensitised at > 0.1 - ≤ 1.0 % intradermal induction Skin Sens. 1B - Moderate potency: ≥ 30 - < 60 % guinea pigs sensitised at > 0.1 - ≤ 1.0 % intradermal induction	100 % of guinea pigs responded at 1.5 % of BD106 for intradermal injection.	**Skin Sens. 1** **Extreme potency cannot be excluded**

Reference(s)	Criteria acc. to CLP Regulation, as laid out in (ECHA, 2017)	Results	Resulting Classification
	or ≥ 30 % guinea pigs sensitised at > 1.0 % intradermal induction		
Human data			
Dermatitis patients (unselected, consecutive) (Lazarov et al., 2002; Li, 2010; Seidenari et al., 2005; Wentworth, 2014)	Skin Sens. 1 Relatively low/moderate frequency (< 1.0 %) and relatively low exposure or Relatively high frequency (≥ 1.0 %) and relatively high exposure Skin Sens. 1A Relatively high frequency (≥ 1.0 %) and relatively low exposure Skin Sens. 1B Relatively low/moderate frequency (< 1.0 %) and relatively high exposure	Frequency from "relatively low/moderate to "relatively high" 4/8 studies reveal a relatively high frequency Exposure unclear	**Skin Sens. 1** (not suitable for sub-categorisation)
Selected dermatitis patients (Bauer et al., 2004; Doomsgoossens, 1992; Fuentes Cuesta et al., 2000; Giusti et al., 2002; Giusti et al., 2003; Guin, 2002; Hatch, 2003; Heratizadeh et al., 2017; Isaksson et al., 2015; Koopmans and Bruynzeel, 2003; Kundak, 2020; Lazarov, 2004; Lazarov and Cordoba, 2000; Lazarov et al., 2000; Lisi et al., 2014; Maurer et al., 1995; Pratt and Taraska, 2000; Ryberg et al., 2014; Ryberg et al., 2006; Smith and Gawkrodger, 2002; Toholka et al., 2015; Uter et al., 2001; Wentworth et al., 2012)	Skin Sens. 1 Relatively low/moderate frequency (< 2.0 %) and relatively low exposure or Relatively high frequency (≥ 2.0 %) and relatively high exposure Skin Sens. 1A Relatively high frequency (≥ 2.0 %) and relatively low exposure Skin Sens. 1B Relatively low/moderate frequency (< 2.0 %) and relatively high exposure	Frequency from "negative", "relatively low/moderate" to "relatively high" 22/26 studies reveal a relatively high frequency Exposure unclear	**Skin Sens. 1** (not suitable for sub-categorisation)

Reliable animal data give strong evidence that DB106 causes skin sensitisation *in vivo*. An LLNA according to OECD TG 429 performed by Betts and colleagues (Betts et al., 2005) proves that DB106 acts as an extreme sensitiser (EC3 ≤ 0.2 %; Table 3.6 (ECHA, 2017)). Furthermore, a modified GPMT (Hausen and Menezes Brandao, 1986) performed similar to OECD TG 406, results in a moderate skin sensitising potency of DB106 (≥ 30 % animals responding at > 1.0 % intradermal induction dose; Table 3.7 (ECHA, 2017)). However, the treatment with a concentration of 1.5 % DB106 for intradermal induction elicited skin sensitisation in 100 % animals and results should be taken with care. An extreme sensitising potency of DB106 cannot be excluded in this GPMT, because concentrations for intradermal injection ≤ 0.1 % were not tested.

Available animal data allow classification of DB106 as skin sensitiser with sub-categorisation as Skin Sens. 1A, as laid down in the CLP Regulation (Table 3.4.3). Based on the very low EC3 value obtained from (Betts et al., 2005), DB106 is characterised as an extremely potent skin sensitiser. As a consequence and in line with Table 3.9 of the ECHA Guidance on the Application of the CLP criteria, an SCL of 0.001% (w/v) should be assigned.

There is a substantial body of evidence that DB106 is a common source of textile dye allergic contact dermatitis. DB106 elicits skin sensitisation in more than 700 subjects during patch testing. Furthermore, the majority of patch test studies reveal a relatively high frequency of occurrence of skin sensitisation in consecutive and selected dermatitis patients (Section 3.4.2.2.3.1, Table 3.2 of the Guidance on the Application of CLP criteria (ECHA 2017) (i.e. ≥ 1.0 % for dermatitis patients (unselected/consecutive) or ≥ 2.0 % for selected dermatitis patients), which could justify sub-categorisation 1A. Patch test data and case reports do not give information about exposure levels of DB106 and besides, exposure data are not available to the DS.

In summary, all available studies from animals and humans provide comprehensive data that DB106 acts as skin sensitiser. Furthermore, data are sufficient for sub-categorisation as 1A, according to section 3.4.2.2.1.4 of the CLP Regulation. Results suggest that DB106 should be rated an extreme sensitiser with an SCL setting of 0.001 %.

10.7.6 Conclusion on classification and labelling for skin sensitisation

In conclusion, the DS proposes to classify Disperse Blue 106 as an extremely potent skin sensitiser with sub-categorisation as **Skin Sens. 1A (H317 - May cause an allergic skin reaction)** and an SCL of 0.001% (w/v).

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

2-[ethyl[3-methyl-4-[(5-nitrothiazol-2-yl)azo]phenyl]amino]ethanol (Disperse Blue 106, DB106), is structurally similar to other disperse blue dyes, namely Disperse Blue 124 (DB124). In contrast to DB106, DB124 has an acetylated 2-hydroxyethyl group. This group may be lost by DB124 due to hydrolysis by esterase activity yielding DB106 as the product (Hansson *et al.*, 1997). It has been shown that DB124 is immediately hydrolysed into DB106 at reduced pH, supporting degradation of DB124 into DB106 on the skin surface (Hansson *et al.*, 1997). DB124 has been found to warrant classification as Skin Sens. 1A, H317 with SCL ≥ 0,001 % in the RAC opinion adopted on 10 December 2020.

The DS presented the results of several animal studies conducted with DB106 that cover the induction phase and allow to assess skin sensitising potency of this substance.

There was no Human Repeated Insult Patch Test (HRIPT) or Human Maximisation Test (HMT) performed with DB106, but the DS provided the results of many human patch test studies on consecutive or selected patients with dermatitis and case reports from the literature, covering the elicitation phase and demonstrating occurrence of skin sensitisation to DB106 in humans.

Based on the results of animal and human studies the DS considered that DB106 is an extremely potent skin sensitiser, which warrants classification as Skin Sens. 1A (H317 - May cause an allergic skin reaction) and requires to set a specific concentration limit of ≥ 0.001 %.

Comments received during consultation

Two Member State Competent Authorities (MSCA) commented the proposed

classification.

One MSCA supported the proposed harmonised classification of DB106 as Skin Sens. 1A; H317, with an SCL of 0.001% based on animal data (key study LLNA with EC3 = 0.012-0.017 %). Human evidence further supports classification of DB106 as a potent skin sensitiser.

A second MSCA noted that considering both the animal and human data, there is no doubt that DB106 warrants, at least, a classification as Skin Sens 1. In the studies with consecutive patients with dermatitis, half of the patients showed a high frequency of dermal reaction to DB106 and in the other half, the frequency of skin reaction to DB106 was low or moderate.

Studies on selected dermatitis patients, on the contrary, mainly lead to a high frequency of dermal reaction. In experimental animals, the key study, an LLNA, indicated a very high sensitising potency of DB106 with EC3 values of 0.012 % and 0.017 % in the two experiments. Noting that the CLP guidance indicate that "evidence from animal studies is usually much more reliable than evidence from human exposure", a second MSCA agreed with the proposal to classify DB106 to subcategory 1A, based on having an extreme skin sensitising potency as determined by the LLNA. In parallel, this was supported by the other *in vivo* tests, where a conclusion of strong or extreme sensitiser could not be excluded, therefore a second MSCA proposed to set an SCL of 0.001 %.

Assessment and comparison with the classification criteria

Animal studies

In the key LLNA study (Betts *et al.* 2005), the authors performed a pre-test using DB106 formulated in DMF vehicle at concentration of 1 %, 3 %, and 10 % to determine the highest non-toxic concentration of DB106 and the authors investigated different vehicles. For the main study, groups of mice were exposed topically on the dorsum of both ears to 0.25, 0.05, 0.025, 0.1, 0.01, and 0.005 % of DB106 (purity: 87 %) in DMSO, or to the vehicle alone (vehicle control), daily for three consecutive days. The sensitising potency of 2,4-dinitrochlorobenzene (DNCB) (0.01-0.25 % in DMSO) was measured concurrently. Five days after the initiation of exposure, all mice were injected intravenously with (3*H*)-methyl thymidine (3HTdR) via the tail vein. Five hours later, the draining auricular lymph nodes were excised and pooled for each experimental group. Incorporation of 3HTdR was measured in single-cell suspensions of LNCs (Lymph Node Cells). In each case, a stimulation index (SI) relative to the concurrent vehicle-treated control value was derived. The dye DB106 was found to be an extreme skin sensitiser with the EC3 of 0.012 % in a first experiment and 0.017 % in a second experiment. Data indicate an extreme sensitising potency of DB106. This well-documented LLNA does not show obvious deviations from OECD TG 429 and is considered to be reliable with restrictions. The DS considers this LLNA as the key animal study.

In the GPMT study, (modified FCA method; Hausen and Menezes Brandao, 1986), guinea pigs were intradermally injected with a 1.5 % (w/v) dye emulsion containing chromatographically pure DB106 dissolved in FCA/saline (1:1), in a semi-circular arc in the shoulder area from the left to the right paw, on days one, five, and nine, according to the method of Hausen and Schmalle (1985). Control animals were treated with an FCA/saline (1:1) emulsion. Eleven days after the end of the sensitisation procedure,

challenge was performed by topical application of sub-irritant doses (1 %, 0.3 %, and 0.1 %) of the dye (the threshold of irritation was determined at a concentration of 10 % in solvent acetone). The authors reported that the "reactions obtained on challenge with non-irritant dilutions of 1 %, 0.3 %, and 0.1 % were so strong that no reading could be made because the whole flank of the animals became extremely red and swollen". One week later, after lesions disappeared, further epicutaneous challenge test with an additional dilution (0.001 %) was performed on the opposite flank. Readings after 24, 48, and 72 hours resulted in 100 % positively reacting animals due to DB106 treatment. Since lower concentrations of DB106, ≤ 1.0 % or even ≤ 0.1 %, were not used for intradermal injection, the results of this study using intradermal induction of DB106 at concentration 1.5 % do not provide evidence meeting the classification criteria for subcategory 1A. However, the results indicate a strong or an extreme skin sensitising potency.

In the "biphasic" LLNA (Ahuja *et al.*, 2010) the authors used a sensitisation-challenge-protocol and analysed the increase in lymph node cells compared to vehicle controls. The female mice were treated once daily on their shaved backs from days one to three with 30, 3, 0.3, 0.03 and 0.003 % concentrations of DB106 (no information on purity). On days 15 to 17, mice were challenged with the test solution on the dorsum of both ears. Local lymph nodes were prepared on day 19. The authors investigated the lymph node weight, ear thickness, and ear biopsy weight. Furthermore, single cell suspensions from each single lymph node were counted (million per lymph node) using an automated cell counter. Investigations reveal that treatment with 30, 3, 0.3 and 0.03 % concentrations of DB106 resulted in a significant increase in ear thickness (26, 13, 17 and 9 %, respectively) and enhancement in the ear punch weight (22, 15, 17 and 12 %, respectively), compared to vehicle control. Furthermore, concentrations of 30, 3, 0.3, 0.03 and 0.003 % DB106 increased the cell count by 174, 124, 82, 79, and 37 %, respectively, in comparison to the vehicle control. The results of this "biphasic" LLNA demonstrate that very low concentrations (0.003 %) of DB106 induced a significant increase in cell-count compared to the vehicle control animals. Since the effective concentration inducing skin sensitisation was well below 2 %, DB106 should be considered as strong skin sensitiser. However, the test material was insufficiently characterised, and this study had not been conducted in accordance with any available OECD testing guideline. Therefore, these experimental data do not allow for conclusion on skin sensitising potency of DB106.

The Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) published an assessment of DB106 (NICNAS, 2015). Unpublished study reports submitted by the notifiers and summarised by NICNAS give evidence that DB106 acts as a skin sensitiser:

- in a Buehler test (according to OECD TG 406) conducted with DB106 (50 % topical induction, 50 % topical challenge) resulted in 16/20 and 15/20 sensitised animals (24 h and 48 h after challenge, respectively; erythema score ≥ 1).
- in an unpublished GPMT of notifiers (according to OECD TG 406), 14/20 and 12/20 animals (24 h and 48 h after challenge, respectively; erythema score ≥ 1) reacted to DB106 (1 % intradermal induction, 50 % topical challenge). The tested

induction concentrations during the Buehler test (50 % for topical induction) and GPMT (1 % for intradermal induction), resulted in a moderate and strong sensitising potency of DB106, respectively. However, lower concentrations were not tested, and extreme potency cannot be excluded. None of these study reports submitted by the notifiers was available to the DS (Reliability 4, not assignable) and data were not considered for potency assessment.

Considering only the animal data, DB106 fulfils the criteria given in Regulation (EC) 1272/2008 for classification as Skin Sens. 1A, since in the key LLNA study the EC3 values for BD106, in two experiments were 0.012 % and 0.017 %, both results were well below the criteria of 2 % for subcategory 1A. The other animal studies (Hausen and Menezes Brandao, 1986; Ahuja *et al.*, 2010) also suggest that BD106 has potentially high skin sensitising potency, although due to their specific design, they do not allow for detailed assessment of sensitising potency.

Human studies

According to Regulation (EC) 1272/2008 Annex I: 3.4.2.2.2.1. Human evidence for sub-category 1A can include:

a) positive responses at ≤ 500 μg/cm^2 (HRIPT, HMT – induction threshold);

b) diagnostic patch test data where there is a relatively high and substantial incidence of reactions in a defined population in relation to relatively low exposure;

c) other epidemiological evidence where there is a relatively high and substantial incidence of allergic contact dermatitis in relation to relatively low exposure.

Numerous human data, published from the 1980s to the 2000s, provide evidence that DB106 is a common cause of textile dermatitis and is frequently reported to be among the strongest textile dye sensitisers (Hatch and Maibach, 1995; Hausen, 1993; Menezes Brandao *et al.*, 1985; Pratt and Taraska, 2000). As pointed out by the DS in the background document, DB106 is listed in the restriction proposal for placing on the market of textile, leather, hide and fur articles containing skin sensitising substances (ECHA, 2019b) and on the restriction proposal for substances in tattoo inks and permanent make up (ECHA, 2019a).

The skin sensitisation properties and potency of DB106 were not evaluated in the HRIPT or HMT, therefore an induction threshold for skin sensitisation in humans cannot be established.

However, the incidence of skin sensitisation to DB106 has been assessed in 36 studies with human patch tests using either unselected, consecutive dermatitis patients (9 studies) or selected dermatitis patients (27 studies). In addition, 28 case reports were published demonstrating positive patch test with DB106. The studies are summarised in the background document.

Patch test studies of unselected, consecutive patients with various types of dermatitis

According to Table 3.2 Relatively high or low frequency of occurrence of skin sensitization of the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and

packaging (CLP) of substances and mixtures (Version 5.0, July 2017) the incidence of skin sensitisation to a given substance in the dermatitis patients (unselected, consecutive) detected in patch testing at the level of 1.0 % or above is considered as high frequency of contact allergy.

The frequency of skin sensitisation to DB106 was relatively high:

- in the Wentworth study (2014) 2.8 % of consecutive dermatitis patients had a positive patch test with DB106 (1 % in pet.) out of 3 086 patch tested patients;
- in the Mucci *et al.* study (2012) 2.3 % of consecutive dermatitis patients had a positive patch test with DB106 (1 % in pet.) out of 427 tested patients;
- in the Li study (2010) 1.2 % of consecutive dermatitis patients had a positive patch test with DB106 out of 327 tested patients;
- in Lazarov *et al.* study (2002) 4.2 % out of 286 consecutive dermatitis patients had a positive patch test with DB106 (assumed 1 % in pet.);
- in Seidenari *et al.* study (2005) 4.0 % out of 97 consecutive children with dermatitis had a positive patch test with DB106 (1 % in pet.).

However, in none of these studies was the level or duration of previous dermal exposure to DB106 documented. Thus, these results do not allow subcategorization of skin sensitising potency in humans.

In the 4 other studies summarised in the background document and demonstrating skin sensitisation to BD106, the frequency of positive patch tests with DB106 varied between 0.2 % in 982 consecutive dermatitis patients (Ryberg *et al.* 2009a) to 0.9 % in 5 085 consecutive dermatitis patients (Fransway *et al.* 2013). The level or duration of previous dermal exposure to DB106 was not provided in these studies.

Patch test studies of selected dermatitis patients

According to Table 3.2 *Relatively high or low frequency of occurrence of skin sensitization* of the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Version 5.0, July 2017) the incidence of skin sensitisation to a given substance in the selected dermatitis patients detected in patch testing at the level of 2.0 % or above is considered as high frequency of contact allergy.

A positive response to DB106 was observed in 26 out of 27 patch test studies of selected dermatitis patients carried out in different dermatological clinics and in different countries, the results are summarised in the background document. The frequency of positive response in the patch test to DB106 in three studies was ≥ 50 % of the tested selected dermatitis patients (Hatch 2003 and Hatch *et al.* 2003, Giusti *et al.*, 2002; Doomsgoossens, 1992) and > 2 % of tested patients in 20 studies. The frequency of skin sensitisation to DB106 is above 2 % and that is considered, in line with the recommendation given in table 3.2 as high. However, in none of these studies was the level or duration of the previous dermal exposures to DB106 documented. Thus, these results do not allow subcategorization of skin sensitising potential.

The case reports

The positive patch tests with DB106 in 43 patients (see table 8 of Background Document for details) demonstrated that this dye was responsible for the allergic contact dermatitis diagnosed in these patients.

Conclusion

In the opinion of the RAC, the existing data provides sufficient evidence that DB106 is a strong human skin sensitiser. However, due to lack of data on the level or duration of exposure it is not possible to prove whether the observed cases of allergic contact dermatitis were induced in humans by DB106 at relatively low or at relatively high exposure, therefore human data do not allow for subcategorization of DB106 based on skin sensitising potency. However, considering the animal data that provides evidence that a very low level of exposure was sufficient for induction of sensitisation, RAC considers that **DB106 warrants classification as Skin Sens. 1A with hazard statement H317: May cause an allergic skin reaction.**

Specific concentration limit

The EC3 value of 0.012 % established for DB106 in key LLNA study (Betts *et al.* 2005) is below 0.2 %, therefore DB106 should be considered as meeting the criteria for an extremely potent skin sensitiser and in line with criteria given Table 3.6 the Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures (Version 5.0, July 2017) an **SCL of 0.001 % (w/v) should be set**.

10.8 Germ cell mutagenicity

Not assessed in this dossier

10.9 Carcinogenicity

Not assessed in this dossier

10.10 Reproductive toxicity

Not assessed in this dossier

10.11 Specific target organ toxicity-single exposure

Not assessed in this dossier

10.12 Aspiration hazard

Not assessed in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not assessed in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Not assessed in this dossier

13 ADDITIONAL LABELLING

Not relevant

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