Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonized classification and labelling at Community level of

Direct Blue FC 57087

EC Number: 418-870-9
CAS Number: 154212-58-5

CLH-O-0000003528-69-03/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 public 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

14 March 2014

Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland | Tel. +358 9 686180 | Fax +358 9 68618210 | echa.europa.eu

CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name: lithium sodium 3-amino-10-{4-(10-amino-6,13-dichloro-4,11-disulfonatobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-3-ylamino)-6-[methyl(2-sulfonato-ethyl)amino]-1,3,5-triazin-2-ylamino}-6,13-dichlorobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-4,11-disulfonate (Direct Blue FC 57087)

EC Number: 418-870-9

CAS Number: 154212-58-5

Index Number: 609-066-00-0

Version number: 01 **Date:** January 2013

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PART A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	lithium sodium 3-amino-10-{4-(10-amino-6,13-dichloro-4,11-disulfonatobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-3-ylamino)-6-[methyl(2-sulfonato-ethyl)amino]-1,3,5-triazin-2-ylamino}-6,13-dichlorobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-4,11-disulfonate
EC number:	418-870-9
CAS number:	154212-58-5
Annex VI Index number:	609-066-00-0
Degree of purity:	63.0 % (w/w) (53.0 — 73.0 % (w/w))
Impurities:	Not relevant for classification and labelling. Confidential information. For more information please refer to the IUCLID file

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	CLP Regulation		**Directive 67/548/EEC (Dangerous Substances Directive; DSD)**
Current entry in Annex VI, CLP Regulation	Acute Tox. 4 Acute Tox. 4 Acute Tox. 4 STOT SE 2	H332 H312 H302 H371	Xn; R20/21/22-68/20/21/22
Current proposal for consideration by RAC	remove classification		remove classification
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Not classified		Not classified

1.3 Proposed harmonised classification and labelling based on CLP Regulation and/or DSD criteria

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	**EXPLOSIVES**	not classified		not classified	conclusive but not sufficient for classification
2.2.	**FLAMMABLE GASES**	not classified		not classified	conclusive but not sufficient for classification
2.3.	**FLAMMABLE AEROSOLS**	not classified		not classified	conclusive but not sufficient for classification
2.4.	**OXIDISING GASES**	not classified		not classified	conclusive but not sufficient for classification
2.5.	**GASES UNDER PRESSURE**	not classified		not classified	conclusive but not sufficient for classification
2.6.	**FLAMMABLE LIQUIDS**	not classified		not classified	conclusive but not sufficient for classification
2.7.	**FLAMMABLE SOLIDS**	not classified		not classified	conclusive but not sufficient for classification
2.8.	**SELF-REACTIVE SUBSTANCES AND MIXTURES**	not classified		not classified	conclusive but not sufficient for classification
2.9.	**PYROPHORIC LIQUIDS**	not classified		not classified	conclusive but not sufficient for classification
2.10.	**PYROPHORIC SOLIDS**	not classified		not classified	conclusive but not sufficient for classification
2.11.	**SELF-HEATING SUBSTANCES AND MIXTURES**	not classified		not classified	conclusive but not sufficient for classification

2.12.	**SUBSTANCES AND MIXTURES WHICH IN CONTACT WITH WATER EMIT FLAMMABLE GASES**	not classified		not classified	conclusive but not sufficient for classification
2.13.	**OXIDISING LIQUIDS**	not classified		not classified	conclusive but not sufficient for classification
2.14.	**OXIDISING SOLIDS**	not classified		not classified	conclusive but not sufficient for classification
2.15.	**ORGANIC PEROXIDES**	not classified		not classified	conclusive but not sufficient for classification
2.16.	**SUBSTANCE AND MIXTURES CORROSIVE TO METALS**	not classified		not classified	conclusive but not sufficient for classification
3.1.	**ACUTE TOXICITY - ORAL**	not classified		Acute Tox. 4 H302: Harmful if swallowed	conclusive but not sufficient for classification
	ACUTE TOXICITY - DERMAL	not classified		Acute Tox. 4 H312: Harmful in contact with skin.	conclusive but not sufficient for classification
	ACUTE TOXICITY – INHALATION	not classified		Acute Tox. 4 H332: Harmful if inhaled.	data lacking
3.2.	**SKIN CORROSION / IRRITATION**	not classified		not classified	conclusive but not sufficient for classification
3.3.	**SERIOUS EYE DAMAGE / EYE IRRITATION**	not classified		not classified	conclusive but not sufficient for classification
3.4.	**RESPIRATORY SENSITISATION**	not classified		not classified	data lacking
3.4.	**SKIN SENSITISATION**	not classified		not classified	conclusive but not sufficient for classification
3.5.	**GERM CELL MUTAGENICITY**	not classified		not classified	conclusive but not sufficient for classification
3.6.	**CARCINOGENICITY**	not classified		not classified	data lacking
3.7.	**REPRODUCTIVE**	not classified		not classified	data lacking

	TOXICITY				
3.8.	**SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE**	not classified		STOT Single Exp. 2 H371: May cause damage to organs	conclusive but not sufficient for classification
3.9.	**SPECIFIC TARGET ORGAN TOXICITY – REPEATED EXPOSURE**	not classified		not classified	conclusive but not sufficient for classification
3.10.	**ASPIRATION HAZARD**	not classified		not classified	data lacking
4.1.	**HAZARDOUS TO THE AQUATIC ENVIRONMENT**	not classified		not classified	data lacking
5.1.	**HAZARDOUS TO THE OZONE LAYER**	not classified		not classified	conclusive but not sufficient for classification

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: Signal word: No signal word
Hazard statements: -
Precautionary statements: -

Proposed notes assigned to an entry:

-

Table 4: Proposed classification according to DSD

Hazardous property	Proposed classification	Proposed SCLs	Current classification [1)]	Reason for no classification [2)]
Explosiveness	not classified		not classified	conclusive but not sufficient for classification
Oxidising properties	not classified		not classified	conclusive but not sufficient for classification
Flammability	not classified		not classified	conclusive but not sufficient for classification
Other physico-chemical properties *[Add rows when relevant]*	not classified		not classified	conclusive but not sufficient for classification
Thermal stability	not classified		not classified	conclusive but not sufficient for classification
Acute toxicity	not classified		Xn; R20/21/22 Harmful; Harmful by inhalation, in contact with skin and if swallowed.	conclusive but not sufficient for classification
Acute toxicity – irreversible damage after single exposure	not classified		Xn; R68/20/21/22 Harmful; Harmful: possible risk of irreversible effects through inhalation, in contact with skin and if swallowed.	data lacking
Repeated dose toxicity	not classified		not classified	conclusive but not sufficient for classification
Irritation / Corrosion	not classified		not classified	conclusive but not sufficient for classification
Sensitisation	not classified		not classified	conclusive but not sufficient for classification
Carcinogenicity	not classified		not classified	data lacking
Mutagenicity – Genetic toxicity	not classified		not classified	conclusive but not sufficient for classification

Toxicity to reproduction – fertility	not classified		not classified	data lacking
Toxicity to reproduction – development	not classified		not classified	data lacking
Toxicity to reproduction – breastfed babies. Effects on or via lactation	not classified		not classified	data lacking
Environment	not classified		not classified	conclusive but not sufficient for classification

[1)] Including SCLs
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification

Labelling: None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

2000	Risk assessment: Conclusions of the risk assessment: „No immediate concern for man and the environment“ Comment: “Harmful, Xn, R20/22 if the methanol content is ≥ 3 %“
2004	Entry to Annex I DSD (29 ATP). The former notifier informed the German CA that the methanol content in the registered substance is below 3% (0% to 1.5%; mean < 0.5%) and asked to remove the classification due to the fact by the German CA.
2005	After checking the documents the registrant was informed that classification is not longer justified and was asked to deliver a corrected SNIF-File of the substance. The German-CA delivered the revised SNIF-file to ECB.
2006	A further update of the SNIF-file was send to ECB. The revision of Direct Blue has not been discussed in the TC&CL.

2.2 Short summary of the scientific justification for the CLH proposal

The current classification was due to a possible methanol content of ≥ 3% at time of registration. "Harmful, Xn, R20/22 if the methanol content is ≥ 3%." (see confidential attachment in IUCLID).

The first step of the synthesis is done in a mixture of methanol and water. In the further steps of synthesis, no methanol is used or can be formed during the reaction process. Due to this fact, it is most unlikely that a reasonable amount of methanol could be present in the final synthesis product.

The most recent analysis performed on 06. April 2011 showed that the methanol content of a current batch is < 0.001% (10 mg/kg.)

2.3 Current harmonised classification and labelling

2.3.1 Current classification and labelling in Annex VI, Table 3.1 in the CLP Regulation

Classification		Labelling		
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Pictogram Signal Word Code(s)**	**Hazard Statement Code(s)**	**Suppl. Hazard statement code(s)**
Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT SE 2 **	H332 H312 H302 H371 **	GHS08 GHS07 Dgr	H332 H312 H302 H371 **	

Specific Concentration Limits and M Factors	
Concentration	**Classification**
-	-

Pictogram(s)	
 Health hazard	 Exclamation mark

2.3.2 Current classification and labelling in Annex VI, Table 3.2 in the CLP Regulation

Classification	Risk phrases	Safety phrases	Indication(s) of danger
Xn; R20/21/22-68/20/21/22	20/21/22 68/20/21/22	2 36/37	Xn

Concentration Limits	
Concentration	**Classification**
-	-

Seveso Data				
Seveso Substance	**Main Seveso Category**	**Other Seveso Categories**	**Seveso Concentration**	**Categories**
	-	-	-	-

Symbol(s)
 Harmful

2.4 Current self-classification and labelling

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

Due to the fact that the methanol content in Direct Blue FC 57087 is below 3%, no classification is necessary.

The data from all available registration dossiers and NONS (notification of new substance) notifications has been taken into account.

PART B.

SCIENTIFIC EVALUATION OF THE DATA

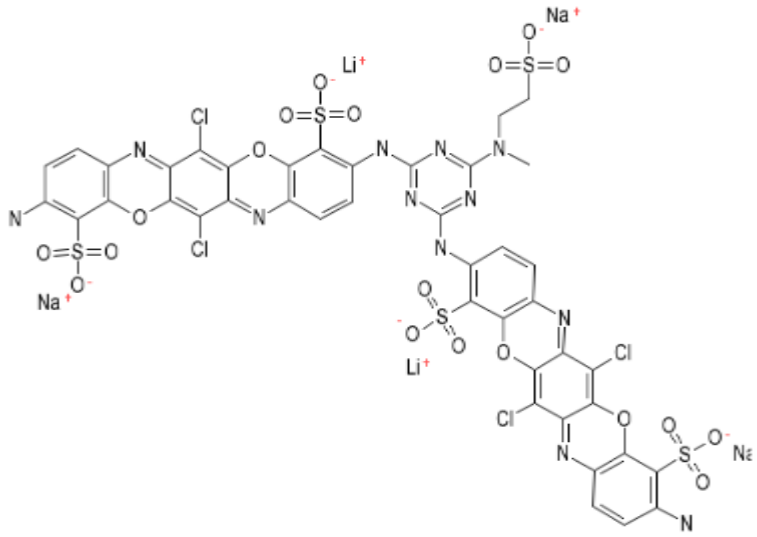
1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 5: Substance identity

EC number:	418-870-9
EC name:	lithium sodium 3-amino-10-{4-(10-amino-6,13-dichloro-4,11-disulfonatobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-3-ylamino)-6-[methyl(2-sulfonato-ethyl)amino]-1,3,5-triazin-2-ylamino}-6,13-dichlorobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-4,11-disulfonate
CAS number (EC inventory):	
CAS number:	154212-58-5
CAS name:	4,11-Triphenodioxazinedisulfonic acid, 3,3'-[[6-[methyl(2-sulfoethyl)amino]-1,3,5-triazine-2,4-diyl]diimino]bis[10-amino-6,13-dichloro-, lithium sodium salt (1:?:?)
IUPAC name:	lithium sodium 3-amino-10-{4-(10-amino-6,13-dichloro-4,11-disulfonatobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-3-ylamino)-6-[methyl(2-sulfonato-ethyl)amino]-1,3,5-triazin-2-ylamino}-6,13-dichlorobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-4,11-disulfonate
CLP Annex VI Index number:	609-066-00-0
Molecular formula:	Hill formula: C42H(26-x)Cl4N12(Li,Na)xO19S5 (x > 0, x < 5) CAS formula: C42H26Cl4N12O19S5.xLi.xNa SMILES Code, molecular weight and structure given for: C42H21Cl4Li2N12Na3O19S5
Molecular weight range:	ca. 1382.66

Structural formula:



1.2 Composition of the substance

Table 6: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
lithium sodium 3-amino-10-{4-(10-amino-6,13-dichloro-4,11-di sulfonatobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-3-ylamino) -6-[methyl(2-sulfonato-ethyl)amino]-1,3,5-triazin-2-ylamino} -6,13-dichlorobenzo[5,6][1,4]oxazino[2,3-b]phenoxazine-4,11- disulfonate EC no.: 418-870-9	63.0% (w/w)	53.0 — 73.0% (w/w)	

Current Annex VI entry: none for compound itself (see reason for dossier)

Table 7: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
methanol EC no.: 200-659-6	< 0.5 % (w/w)	<= 1.5 % (w/w)	Not relevant for classification and labelling. Confidential information. For more information please refer to the IUCLID file.

Current Annex VI entry: Acute Tox. 4, STOT SE 2: H332, H312, H302, H371 for >3% methanol

Table 8: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
				Not relevant for classification and labelling. Confidential information. For more information please refer to the IUCLID file.

Current Annex VI entry: none for additives

1.2.1 Composition of test material

1.3 Physico-chemical properties

Table 9: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	solid, blue		measured
Melting/freezing point	> 300°C		no melting point is measured up to 300°C
Boiling point	NA		No boiling point measurable
Relative density	1.86 at 20°C		measured
Vapour pressure	NA		The determination of the vapour pressure was not necessary because of the substance structure (salt)
Surface tension	33.4 nM/m at 20°C, 999.95 mg/L		measured
Water solubility	forms a sol		The water solubility of the test item cannot be determined according to EU Guideline A.6, as the test item does not form a proper solution, but a colloidal solution. Investigations from transmission electron microscopy and electron diffraction showed a disperse distribution of the test item (sol) in water at a concentration of 2.9 /L with particle sizes of 200 to 500 nm in diameter.
Partition coefficient n-octanol/water	log Pow < -4		measured
Flash point	In accordance with Section 2 of REACH Annex XI, information requirement section 7.9, this study does not need to be conducted based on the physical state of the substance.		*Data Waiver*
Flammability upon ignition (solids)	non flammable	Mix (1994)	Measured, 84/449/EWG, A.10
Flammability on contact with water	Substance does not evolve highly flammable gases in contact with water.	Mix (1994)	Measured, 84/449/EWG, A.12
Flammability: pyrophoric properties	non pyrophoric	Mix (1994)	Measured, 84/449/EWG, A.13
Explosive properties	non explosive	Mix (1994)	Measured, 84/449/EWG, A.14
Self-ignition temperature	No self ignition up to	Mix (1994)	Measured, 84/449/EWG, A.16

	the melting point		
Oxidising properties	no oxidising properties	Mix (1994)	Measured, 84/449/EWG, A.17
Granulometry	NA		The substance is marketed or used in a granular form. The substance is isolated by spray drying into the composite micro granular form. As such, the particle size is not a function of the chemical but a function of the spray dryer used.

2 MANUFACTURE AND USES

2.1 Manufacture

The dyestuff is condensed from cyanuric chloride and methyltaurine in the presence of a lithium hydroxide solution and an emulsifier at different temperatures and pH-values. Thereafter, the dye is spray-dried in the presence of a suspending agent.

2.2 Identified uses

Table 10: Uses by workers in industrial settings

Confidential	IU number	Identified Use (IU) name	Substance supplied to that use	Use descriptors
	1	Formulation	in a mixture	**Process category (PROC):** PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) **Market sector by type of chemical product:** PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids PC 18: Ink and toners **Environmental release category (ERC):** ERC 2: Formulation of preparations **Sector of end use (SU):** SU 5: Manufacture of textiles, leather, fur SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys)

Confidential	IU number	Identified Use (IU) name	Substance supplied to that use	Use descriptors
				Subsequent service life relevant for that use?: no
	2	Handling - transfer to/from vessels	in a mixture	**Process category (PROC):** PROC 8a: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at non-dedicated facilities PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) **Market sector by type of chemical product:** PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids PC 18: Ink and toners **Environmental release category (ERC):** ERC 5: Industrial use resulting in inclusion into or onto a matrix **Sector of end use (SU):** SU 5: Manufacture of textiles, leather, fur **Subsequent service life relevant for that use?:** no
	3	Textile application	in a mixture	**Process category (PROC):** PROC 13: Treatment of articles by dipping and pouring PROC 6: Calendering operations PROC 10: Roller application or brushing **Market sector by type of chemical product:** PC 34: Textile dyes, finishing and impregnating products; including bleaches and other processing aids PC 18: Ink and toners **Environmental release category (ERC):**

Confidential	IU number	Identified Use (IU) name	Substance supplied to that use	Use descriptors
				ERC 5: Industrial use resulting in inclusion into or onto a matrix **Sector of end use (SU):** SU 5: Manufacture of textiles, leather, fur **Subsequent service life relevant for that use?:** yes **Article category related to subsequent service life (AC):** AC 5: Fabrics, textiles and apparel

Table 11. Uses by consumers

Confidential	IU number	Identified Use (IU) name	Use descriptors
	4	Service life stage of textile products	**Environmental release category (ERC):** ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release ERC 10a: Wide dispersive outdoor use of long-life articles and materials with low release **Subsequent service life relevant for that use?:** yes **Article category related to subsequent service life (AC):** AC 5: Fabrics, textiles and apparel

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in this dossier

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Not evaluated in this dossier

4.2 Acute toxicity

Table 12: Summary table of relevant acute toxicity studies

Method	Results	Remarks	Reference
rat (Wistar) male/female oral: gavage EU Method B.1 (Acute Toxicity (Oral))	LD50: > 2000 mg/kg bw (male/female)	1 (reliable without restriction) key study experimental result	Bomhard E (1994a)
rat (Wistar) male/female Coverage: occlusive EU Method B.3 (Acute Toxicity (Dermal)) OECD Guideline 402 (Acute Dermal Toxicity)	LD50: > 2000 mg/kg bw (male/female)	1 (reliable without restriction) key study experimental result	Bomhard E (1994b)

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

Acute toxicological investigations of male and female Wistar rats were conducted after single oral administration of Direct Blue FC 57087. The LD_{50} for male and female rats was greater than 2000 mg/kg and was not exactly determined. Blue coloration of the feces in correspondence with the colour of the dye was observed after administration of 2000 mg/kg body weight. Body weight development of male and female rats was not affected. No deaths occurred. None of the animals sacrificed at the end of study showed any noticeable gross pathological findings. (Bomhard E (1994a))

4.2.1.2 Acute toxicity: inhalation

No data available.

4.2.1.3 Acute toxicity: dermal

Acute toxicological investigations of male and female Wistar rats were conducted after dermal exposure to Direct Blue FC57087. The LD_{50} for male and female rats was greater than 2000 mg/kg and was not exactly determined. No signs of systemic poisoning were observed. Local skin changes included blue coloration in correspondence with the colour of the dye and inflammation in the area

of the application site. Body weight development of male and female rats was not affected. No deaths occurred. None of the animals sacrificed at the end of study showed any noticeable gross pathological findings. (Bomhard E (1994b))

4.2.1.4 Acute toxicity: other routes

No data available

4.2.2 Human information

No data available

4.2.3 Summary and discussion of acute toxicity

No deaths or systemic clinical signs occurred after oral or dermal single administration of 2000 mg/kg body weight.

The LD_{50} for oral and dermal administration is above 2000 mg/kg body weight.

4.2.4 Comparison with criteria

According to criteria of the CLP Regulation and to DSD criteria, no classification is necessary.

4.2.5 Conclusions on classification and labelling

The following information is taken into account for any hazard / risk assessment:

Single dose toxicity

Value used for CSA:

LD_{50} (oral): 2000 mg/kg bw

LD_{50} (dermal): 2000 mg/kg bw

Justification for classification or non classification

No classification necessary

RAC evaluation of acute toxicity
Summary of the Dossier submitter's proposal The current harmonised classification of Direct Blue FC 57087 under DSD was Xn, R20/21/22 and was based on a possible methanol content in the substance of ≥ 3% at the time of Notification of New Substance (NONS) registration. The current classification according to the CLP regulation was obtained by translating (using the translation table in Annex VII to CLP Regulation) from the classification under DSD to classification under CLP as follows – minimum classifications as Acute tox. 4 (H332, H312 and H302) and STOT SE 2; H371. As early as 2004 the former (NONS) notifier informed the German CA that the methanol content in the registered substance was below 3% (0% to 1.5%; mean < 0.5%) and asked to remove the classification. After checking the documents the registrant was informed that classification was no longer justified. However, the revision of the

classification for Direct Blue FC 57087 was not discussed in the Technical Committee on Classsification and Labelling (TC C&L).

The most recent analysis performed on 06 April 2011 showed that the methanol content of a current batch of Direct Blue FC 57087 is <0.001% (<10 mg/kg) according to results contained in a confidential attachment to the IUCLID file for Direct Blue FC 57087.

Oral acute toxicity

One acute oral toxicity study was included in the CLH proposal (Bomhard, 1994a).

The acute oral toxicity study in male and female Wistar rats was conducted with Direct Blue FC 57087. The oral LD_{50} for male and female rats was greater than 2000 mg/kg, as no deaths occurred up to that dose. Blue coloration of the faeces corresponding to the colour of the dye was observed after administration of 2000 mg/kg body weight. The body weights of male and female rats were not affected. None of the animals sacrificed at the end of study showed any noticeable gross pathological findings (Bomhard, 1994a).

Dermal acute toxicity

One acute toxicity study was included in the CLH proposal (Bomhard, 1994b), in which male and female Wistar rats were dermally exposed to Direct Blue FC 57087. The dermal LD_{50} for male and female rats was greater than 2000 mg/kg as no deaths occurred up to that dose. No signs of systemic poisoning were observed. Local skin changes included blue coloration corresponding to the colour of the dye and inflammation at the application site. The body weights of male and female rats were not affected. None of the animals sacrificed at the end of study showed any noticeable gross pathological findings (Bomhard E (1994b)).

Inhalation acute toxicity

No data were available.

The current classification for acute inhalation toxicity was due to a possible methanol content of ≥ 3% at time of registration "Harmful, Xn; R20 if the methanol content is ≥3%."
As the methanol content in Direct Blue FC 57087 is below 3%, the DS proposes no classification for inhalation toxicity.

Comments received during public consultation

Comments on classification for acute toxicity were received from two MS during public consultation.

One Competent Authority (CA) supported removal of classification for acute toxicity and specific target organ toxicity-single exposure.

Another CA questioned the possibility for removal of the classification for Acute Tox. 4, STOT SE and STOT RE for the following reasons:

- The upper limit of the methanol concentration range in Direct Blue FC 57087 mentioned in the Dossier (<1.5% w/w) is still above the generic cut-off value from Annex I, Table 1.1. of the CLP Regulation, which would in some cases imply a possibility for classification based on the toxicity of methanol.
- Direct Blue FC 57087 itself has no acute toxicity according to the CLP criteria (LD_{50} > 2000 mg/kg bw) and no target organ toxicity was observed in acute (Bomhard,

1994a,b) and repeated dose toxicity studies (Jekat and Sander, 1995), all of which confirms the conclusion that no classification is warranted. However, it was noted that the rat is an insensitive species with respect to methanol toxicity due to a different effect/mode of action by comparison with humans, hence no effects from methanol toxicity at the dose ranges applied in the presented studies would have been expected. In order to verify the reliability of these studies, the CA wished to ask whether some additional information from studies on other species could be provided by the Dossier Submitter.

In their reply, the Dossier Submitter clarified that:

- In the process previously used for Direct Blue FC 57087 synthesis, the first step of the synthesis was done in a methanol/water mixture, and therefore the final product could contain methanol at concentrations higher than 3%. However in the current process of Direct Blue FC 57087 synthesis, this first step is done in water only, and therefore the end product should not contain methanol. According to current analytical results of a typical substance batch, the concentration of methanol is <0.001% (<10 mg/kg). Therefore in the new specification for Direct Blue FC 57087, the upper limit for methanol is <0.1%; however typical concentrations are <0.01%.
- Regarding the provision of new information or studies on other species, the DS informed that the only other available studies are for skin and eye irritation in the rabbit, in which neither systemic nor local toxicity was observed. According to the IUCLID 4 file for methanol available in ESIS, the oral LD_{50} values of methanol for all tested species (rat, mouse, rabbit, dog) were above 5000 mg/kg.

Assessment and comparison with the classification criteria

According to data given in the IUCLID file for Direct Blue FC 57087, the sample of this dye used for assessment of oral and dermal toxicity (Bomhard E. 1994 a,b) contained 1.2% methanol, but the LD_{50} values were still above 2000 mg/kg, and thus above both the DSD and CLP classification criteria of 2000 mg /kg bw. Since the oral and dermal values for Direct Blue FC 57087 are above this value and no data were available to support the classification for acute inhalation toxicity, RAC is of the opinion that this substance should not be classified for acute toxicity, and that the current harmonised classification should be removed.

However, in any case where Direct Blue FC 57087 does contain methanol, the manufacturer and importer placing this Direct Blue FC 57087 on the market would, in line with articles 10 and 11 of the CLP regulation, need to consider the impact of this impurity for the self-classification of their Direct Blue FC 57087.

According to article 11 of the CLP regulation, the presence of methanol in Direct Blue FC 57087 as an impurity in concentrations greater than a generic cut-off value of 0.1% should be taken into account in setting the acute toxicity category, because methanol has been classified as category 3 for acute toxicity. Cut-off values indicate when the presence of a substance needs to be taken into account for the purposes of classification of a substance or a mixture containing that hazardous substance, whether as an identified impurity, additive, or individual constituent.

Therefore the current classification of Direct Blue FC 57087 as Acute Tox. 4; H332, H312, H302 should be removed.

4.3 Specific target organ toxicity – single exposure (STOT SE)

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

No target organ toxicity observed (Bomhard E (1994a), Bomhard E (1994b)).

4.3.2 Comparison with criteria

According to criteria of the CLP Regulation and to DSD criteria, no classification is necessary.

4.3.3 Conclusions on classification and labelling

No classification necessary

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)
Summary of the Dossier submitter's proposal The current harmonised classification of Direct Blue FC 57087 under DSD is Xn, R68/20/21/22 and this has been based on a possible methanol content of ≥3% at the time of registration. The current classification according to the CLP regulation was obtained by translating (using the translation table in Annex VII to the CLP Regulation) from classification under DSD to classification under CLP, as follows: STOT SE 2, H371. As indicated under "RAC evaluation of acute toxicity" (above) the synthesis of Direct Blue FC 57087 no longer involves a methanol-step and therefore in the new specification for this substance the upper limit for methanol is <0.1 %; however typical concentrations are <0.01%. Based on the SCLs for methanol given in Annex VI of the CLP Regulation, the properties of this substance are not taken into account for classification of a mixture as STOT SE 2 when its concentration in the mixture is below 3%. The current methanol concentration in Direct Blue FC 57087 is well below this limit. In the studies of acute oral and dermal toxicity on rats no target organ toxicity was observed (Bomhard, 1994a,b). Therefore the DS proposes removal of the classification. **Comments received during public consultation** One comment was received. The Belgian CA questioned the possibility for removal of the classification for specific target organ toxicity - single exposure (STOT SE). This issue has been considered jointly with comments on acute toxicity in the previous section. **Assessment and comparison with the classification criteria** According to the CLP Regulation substances are classified as STOT SE when they have produced significant toxicity in humans or when, on the basis of evidence from studies in experimental animals, they can be presumed to have the potential to produce significant toxicity in humans following single exposure. Since no human data on Direct Blue FC 57087 were provided, and the acute oral and

dermal toxicity studies in rats (Bomhard, 1994a,b) with Direct Blue FC 57087 did not produce any effects indicating specific target organ toxicity, this substance should not be classified as STOT SE 2, H371 under CLP. Hence, the current classification should be removed.

4.4 Irritation

Not evaluated in this dossier

4.5 Corrosivity

Not evaluated in this dossier

4.6 Sensitisation

Not evaluated in this dossier

4.7 Repeated dose toxicity

Table 13. Overview of experimental studies on repeated dose toxicity after oral administration

Method	Results	Remarks	Reference
rat (Wistar) male/female subacute (oral: gavage) 60, 250, 1000 mg/kg (nominal in water) 6, 25, 100 mg/mL (nominal in water) Exposure: 30 days (daily) OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity in Rodents) EU Method B.7 (Repeated Dose (28 Days) Toxicity (Oral))	NOAEL: 1000 mg/kg bw/day (nominal) (female) based on: test mat. NOAEL: 250 mg/kg bw/day (nominal) (male) based on: test mat. (Histopathology: increased incidence of low grade inflammatory infiltrations of the submucosa of the stomach and at the basis of the mucosa in males at 1000 mg/kg/day)	1 (reliable without restriction) key study experimental result	Jekat FW, Sander E (1995)

Discussion

Five male and female rats each received Direct Blue FC 57087 by gavage in dosages of 0 (vehicle control), 60, 250 and 1000 mg/kg body weight for 30 days. In addition, 5 male and female rats per group were treated with the application vehicle or 1000mg/kgand observed for reversibility, continuance or delayed occurrence of toxic effects during a recovery period of 14 days. Appearance and general behaviour were not influenced by treatment up to and including 1000 mg/kg. Growth, mortality, food and water intake were not affected by the test substance. Animals from all treatment groups showed blue discoloration, corresponding to the colour of the test substance, of the feces.

Hematological and histopathological investigations gave no indication of toxicologically relevant damage to blood, hematopoietic organs or coagulability of the blood up to and including 1000 mg/kg. Neither clinico-chemical nor gross pathological or histopathological investigations produced any evidence of treatment-related metabolic or organ damage. However, a higher incidence of low rate inflammatory infiltrations of the submucosa of the stomach and at the basis of the mucosa was observed in males at 1000 mg/kg as adaptive reaction to the substance overload.

Under the conditions described, Direct Blue FC 57087 was tolerated without adverse effects in dosages of up to and including 250 mg/kg. (Jekat FW, Sander E (1995))

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT RE)

No target organ toxicity observed (Jekat FW, Sander E (1995))

4.9 Germ cell mutagenicity (Mutagenicity)

Not evaluated in this dossier

4.10 Carcinogenicity

Not evaluated in this dossier

4.11 Toxicity for reproduction

Not evaluated in this dossier

4.12 Other effects

Not evaluated in this dossier

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in this dossier

6 OTHER INFORMATION

Not evaluated in this dossier

7 REFERENCES

Bomhard E (1994a). Acute Oral Toxicity Study in Male and Female Wistar Rats. Testing laboratory: BAYER AG, Institute of Industrial Toxicology Friedrich-Ebert-Str. 217-333 42096 Wuppertal. Report no.: 23572. Owner company: DyStar Colours Deutschland GmbH. Study number: T3058019. Report date: 1994-12-27.

Bomhard E (1994b). Acute Dermal Toxicity Study in Male and Female Wistar Rats. Testing laboratory: BAYER AG, Institute of Industrial Toxicology Friedrich-Ebert-Str. 217-333 42096 Wuppertal. Report no.: 23573. Owner company: DyStar Colours Deutschland GmbH. Study number: T9058051. Report date: 1994-12-27.

Jekat FW, Sander E (1995). Subacute Toxicity Study in Wistar Rats (Administration by Gavage for 30 Days with a Subsequent Recovery Period of 14 Days). Testing laboratory: BAYER AG, Fachbereich Toxicology Friedrich-Ebert-Str. 217-333 D-42096 Wuppertal. Report no.: 23627. Owner company: DyStar Colours Deutschland GmbH. Report date: 1995-01-09.

Mix (1994). Untersuchung der sicherheitstechnischen Kennzahlen. Testing laboratory: BAYER AG 51368 LEVERKUSEN. Report no.: 94/00137. Owner company: DyStar Colours Deutschland GmbH. Report date: 1994-07-18.