Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

**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**

CLH-O-0000003528-69-03/F

Adopted

14 March 2014

14 March 2014

CLH-O-0000003528-69-03/F

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

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

Chemicals 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: 154242-58-5

The proposal was submitted by **Germany** and received by the RAC on **26 February 2013.**

In this opinion, all classifications are given in the form of CLP hazard classes and/or categories, the majority of which are consistent with the Globally Harmonised System (GHS). The classification notation for 67/548/EEC, the Dangerous Substances Directive (DSD) is no longer provided.

PROCESS FOR ADOPTION OF THE OPINION

Germany has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation*** on **26 March 2013**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **10 May 2013.**

ADOPTION OF THE OPINION OF THE RAC

Rapporteur, appointed by RAC: **Boguslaw Baranski**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation.The RAC opinion on the proposed harmonised classification and labelling was reached on **14 March 2014** and the comments received are compiled in Annex 2. The RAC Opinion was adopted by **consensus**.

OPINION OF THE RAC

The RAC adopted the opinion that **Direct Blue FC 57087** should be classified and labelled as follows:

Classification and labelling in accordance with the CLP Regulation

	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 state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	609-066-00-0	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	418-870-9	154212-58-5	Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT SE 2 **	H332 H312 H302 H371 **	GHS08 GHS07 Dgr	H332 H312 H302 H371 **			
Dossier submitters proposal					**Remove** Acute Tox. 4 * Acute Tox. 4 * Acute Tox. 4 * STOT SE 2 **	**Remove** H332 H312 H302 H371 **	**Remove** GHS08 GHS07 Dgr	**Remove** H332 H312 H302 H371 **			
RAC opinion					~~Acute Tox. 4 *~~ ~~Acute Tox. 4 *~~ ~~Acute Tox. 4 *~~ ~~STOT SE 2 **~~	~~H332~~ ~~H312~~ ~~H302~~ ~~H371 **~~	~~GHS08~~ ~~GHS07~~ ~~Dgr~~	~~H332~~ ~~H312~~ ~~H302~~ ~~H371 **~~			
Resulting Annex VI entry if agreed by COM	None										

SCIENTIFIC GROUNDS FOR THE OPINION

HUMAN HEALTH HAZARD ASSESSMENT

RAC general comment

The IUPAC name of the substance is:

lithium
sodium3-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. It will be referred to as **Direct Blue FC 57087** throughout this opinion.

Any references used in this opinion are listed in the accompanying Background Document

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.

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.

ANNEXES:

Annex 1 Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the Dossier Submitter; the evaluation performed by RAC is contained in RAC boxes.

Annex 2 Comments received on the CLH report, response to comments provided by the Dossier Submitter and rapporteurs' comments (excl. confidential information).