Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

barium bis[2-chloro-5-[(2-hydroxy-1-naphthyl)azo]toluene-4-sulphonate]; C.I. Pigment Red 53:1

EC Number: 225-935-3

CAS Number: 5160-02-1

CLH-O-0000007323-79-01/F

Adopted

8 June 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BARIUM BIS[2-CHLORO-5-[(2-HYDROXY-1-NAPHTHYL)AZO]TOLUENE-4-SULPHONATE]; C.I. PIGMENT RED 53:1

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties. Journal articles are not confidential; however they are not published on the website due to Intellectual Property Rights.

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Substance name: barium bis[2-chloro-5-[(2-hydroxy-1-naphthyl)azo]toluene-4-sulphonate]; C.I. Pigment Red 53:1
EC number: 225-935-3
CAS number: 5160-02-1
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2022	Germany	<confidential>	Company-Manufacturer	1
Comment received				
The available toxicological data of barium bis[2-chloro-5-[(2-hydroxy-1-naphthyl)azo]toluene-4-sulphonate]; C.I. Pigment Red 53:1 in the CLH report Proposal for Harmonised Classification and Labelling by BAUA, do not justify a classification as Carc 2. The pigment has been assessed by several expert groups in the past concluding that Pigment Red 53:1 has no genotoxic potential and does not act as a primary carcinogen. Instead, the adverse effects seen in liver and spleen result most likely from metabolites leading to hemosiderosis in both target organs and to fibrosis and promotion of tumour formation in spleen. The material is handled safely by workers and professionals to minimize the risk of exposure. The CLH report states on page 9 (chapter 5.2 Consumers) that the described information regarding the possible uses of PR53:1 leads to the conclusion that exposure of consumers over the three routes (inhalation, dermal, oral) is possible. It should be stated here that the pure compound is not handled by the general population. In consumer articles the material is included at very low concentrations, embedded in a matrix. Uptake of the substance at dose level relevant for adverse toxic effects can be excluded. We support that the pigment may not be used in sensitive applications like food contact or finger paint as indicated in the uses of some registrants (see pages 6 and 7 of the CLH report). ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment comments.pdf				

Dossier Submitter's Response
Thank you for your comment on the CLH proposal. In general, chemicals are defined as carcinogenic if they induce tumours, increase tumour incidence and/or malignancy, or shorten the time to tumour occurrence (Guidance 7a, R 7.7.8.1). Therefore, it is not relevant for the classification as carcinogenic whether the substance acts as a genotoxic carcinogen or via other modes of action. Overall, there is evidence of a carcinogenic potential of PR53:1 based on an increased incidence of splenic sarcomas in male rats, a rare type of tumour in this organ (CTFA, 1982b; CTFA, 1982a; NTP, 1982). The increased incidence was statistically significant in the NTP study but not in the CTFA study. Results from the CTFA study are considered as supportive evidence because similar patterns of non-neoplastic splenic lesions were observed in both studies. In addition, the high incidence of splenic sarcomas in the rat study (NTP, 1982), the diversity of sarcomas that all originated from mesenchymal tissue with different cell types as most prominent tumour cells (leio-, osteo-, and fibrosarcomas) and the frequently observed metastases are indicating a high malignancy. The study by Davis and Fitzhugh (1962) was also assessed by the DS. There is no tumour development, but severe splenic effects are observed. However, the study is only of limited reliability because of the following: limited reporting, no data on individual animals, only six animals from each group examined histopathologically, incidences only on a limited number of findings, no body weight information, and no historical control data. The same holds true for the dermal study published by Carson (1984) with the following limitations: limited reporting, such as no data on individual animals, only six animals from each group examined histopathologically, incidences only on a limited number of findings, no body weight information, and no historical control data. As stated above, for classification it is not relevant whether the substance acts via a genotoxic or non-genotoxic mode of action. However, in contrast to genotoxic modes of action, for non-genotoxic modes of action, a threshold can be presumed. In the present case, a GCL for a carcinogen of medium potency is proposed. Medium potency can be concluded from a T25 value of 69 mg/kg bw, which was calculated according to Dybing et al (1997)[1] using the incidences of splenic sarcoma in the high-dose group (NTP, 1982). As discussed in the dossier, the available data do not suggest a genotoxic mode of action of Pigment Red 53:1 in tumour formation with splenic lesions as the most likely starting point of tumour formation. However, the DS comes to the conclusion that the available data does not allow to draw a final conclusion on the mode of action with certainty. The DS proposes classification of Pigment Red 53:1 as carcinogen, Category 2. According to Regulation (EC)1272/2008 category 2 is fulfilled, when there is **limited evidence of carcinogenicity**. Limited evidence is given, if data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. the evidence of carcinogenicity is restricted to a single experiment. The criteria for sufficient evidence you cited in your comment refer to a classification of the substance as a carcinogen fulfilling criteria Category 1B.

[1] Dybing E., Sanner T., Roelfzema H., Kroese D., and Tennant R.W. (1997): T25: A Simplified Carcinogenic Potency Index: Description of the System and Study of Correlations between Carcinogenic Potency and Species/Site Specificity and Mutagenicity. Pharmacology & Toxicology 80 (6), 272-279. DOI: 10.1111/j.1600-0773.1997.tb01973.x

In addition, please note that for substances fulfilling criteria of carcinogenicity, cat. 1A, 1B or 2 there is no requirement for justification that action is needed at Community level. Pursuant to Article 36(1) of Regulation (EC)1272/2008 they shall normally be subject to harmonised classification. The identified uses are therefore for information only and it is not required to evaluate exposure levels of the substance. Harmonised classification is based on intrinsic hazard properties of the substance.

RAC's response

Thank you for your comment.
According to the CLP regulation, Annex I, Table 3.6.1, criteria for classification of substances as carcinogens in category 2: Suspected human carcinogens "is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived either from limited (1) evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies."

One animal study on F344 rats showed a statistically significant increase in splenic sarcomas in males with incidences above the historical control data (HCD), with high malignancy and metastasis potential and low spontaneous incidence (NTP, 1982a). The effects are supported by another study on Charles-River CD Sprague-Dawley male rats with a similar trend without statistical significance (CTFA, 1982b; CTFA, 1982a). There is no possibility of confounding effects of excessive toxicity at test doses. The effects were observed only in males. In females, an increasing trend of non-neoplastic spleen lesions was reported, the lesions being also reported in studies with mice. Splenic lesions are considered as starting point for tumour formation. The possibility of a genotoxic mode of action is dismissed based on the available negative *in vitro* and *in vivo* genotoxicity data. The non-genotoxic mode of action starting from splenic lesions is plausible and its relevance to humans cannot be excluded. Similar findings and modes of action are described also for aniline and other aromatic amines and aromatic azo compounds that are structurally related to PR 53:1. Taking everything into consideration, the increasing incidence of splenic sarcoma in male rats is considered limited evidence of carcinogenicity and in this way, the criteria for classification in Category 2 are met and RAC proposes this classification in agreement with the DS proposal. The generic concentration limit (GCL) of ≥ 1.0 % shall apply.

Date	Country	Organisation	Type of Organisation	Comment number
07.11.2022	Germany	Eurocolour e.V.	Industry or trade association	2

Comment received

Eurocolour e. V. is the umbrella association for manufacturers of pigments, dyes, fillers, frits, ceramic and glass colours, and ceramic glazes in Europe. We would like to use this opportunity to provide input as a harmonized classification is from our point of view neither necessary nor justified but would only undermine the science-based classification system and thus weaken the hazard communication.

Initial concerns on the safety of bis[2-chloro-5-[(2-hydroxy-1-naphthyl)azo]toluene-4-sulphonate] (CAS 5160-02-1) – more commonly known as C.I. Pigment Red 53:1 –

expressed by Germany's Federal Institute for Occupational Safety and Health (BAuA) during the substance evaluation have already been addressed in the REACH dossier.

Please also consider the attached document as well as the more detailed input provided by manufacturers of Pigment Red 53:1.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Eurocolour_Input_PigmentRed53-1.pdf

Dossier Submitter's Response

Thank you for your comment on the CLH proposal.

Please see response to comment no. 1.

RAC's response

Thank you for your comment.

Please see RAC response to comment no. 1.

Date	Country	Organisation	Type of Organisation	Comment number
17.11.2022	Switzerland	ETAD	Industry or trade association	3

Comment received

C.I. Pigment Red 53:1 has previously been assessed by a number of different expert groups, including ETAD (ETAD, 1994). We would like to reiterate the key references we considered in our assessment:
- There have been eight independent long-term studies on C.I. Pigment Red 53:1. Only in one of those studies did the pigment cause splenic tumours in rats at a dose of 150 mg/kg bodyweight, which is a dose known to have visible toxic effects to this organ. Considering this, our toxicologist concluded that tissue toxicity of this non-genotoxic substance is a prerequisite for tumour development. The affected animals were restricted to one strain of male rats. It seems that Fischer rats are especially sensitive to these effects considering higher doses in other strains of rats did not cause fibrosarcoma.
- C.I. Pigment Red 53:1 was neither carcinogenic nor mutagenic in mice after oral or dermal exposure

Besides ETAD's assessment mentioned above, there are other studies conducted by other expert groups (e.g. Myhr, Caspary 1991; Zeiger 1988) concluding that Pigment Red 53:1 has no genotoxic potential and does not act as a primary carcinogen (CFTA report 1982; SIDS report 1999).

Based on these studies and available toxicological data, C.I. Pigment Red 53:1 is not classifiable as carcinogenic (Carc 2. as given in the CLH report) and mutagenic to humans, unless there are other supporting data available providing new knowledge on the pigment's toxicological properties.

Dossier Submitter's Response

Thank you for your comment on the CLH proposal.

Please, see response to comment no. 1.

RAC's response
Thank you for your comment. Please see RAC response to comment no. 1.

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
10.10.2022	Germany	<confidential>	Company-Manufacturer	4
Comment received				
The substance was tested for its carcinogenic potential in several studies. In one study with rats [NTP Technical Report, 1982], high dose male animals developed splenic sarcomas and neoplastic nodules of the liver. Female animals and mice had no tumours. In the course of another feeding study [Davis, Fitzhugh, 1962], similar or higher doses of the substance were administered in the diet for 2 years. Splenomegaly was detected however, formation of tumours was not observed. In addition, a chronic dermal study was performed [Carson, 1984] and mice were painted with 1% solution twice a week for 18 months. Development of neoplasias was not observed. At last, two studies sponsored by the Cosmetic, Toiletry and Fragrance Association of New Zealand (CTFA) [CFTA Report, 1982 a and b] were conducted to determine repeated dose toxicity and carcinogenicity in rats and mice after chronic exposure and after in utero and in life exposure to low concentrations of the test item. There was no increased incidence for tumours in any tissue. According to EC 1272/2008 (CLP) sufficient evidence for carcinogenicity is evident if "a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols." In case of Pigment Red 53:1, formation of neoplasms was observed in one species and in one sex only. The evidence is therefore restricted to a single experiment and has to be regarded as insufficient. ECHA note – An attachment was submitted with the comment above. Refer to confidential attachment comments.pdf				
Dossier Submitter's Response				
Thank you for your comment on the CLH proposal. Please, see response to comment no. 1.				
RAC's response				
Thank you for your comment. Please see RAC response to comment no. 1.				

Date	Country	Organisation	Type of Organisation	Comment number
07.11.2022	Germany	Eurocolour e.V.	Industry or trade association	5

Comment received

Pigment Red 53:1 (CAS 5160-02-1) was tested for its carcinogenic potential in several studies. Several expert groups concluded that Pigment Red 53:1 does not act as a primary carcinogen or a genotoxic carcinogen. According to the CLP Regulation (EC 1272/2008) sufficient evidence for carcinogenicity is evident if "a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols." Such evidence is not given for Pigment Red 53:1. A detailed overview of relevant studies and the respective results are given in the input provided by the manufacturers.

The material is handled safely by worker and professionals. Personal precautions, protective equipment as well as protective clothing are established to minimize the risk of exposure in manufacturing and processing processes by inhalation or dermal contact, and by accidental oral exposure.

Additionally, the pure substance is not handled by the general population. In consumer articles the material is included at very low concentrations, usually embedded in a matrix, e.g. a polymer matrix or binders matrix. Uptake of the substance at dose level relevant for adverse toxic effects is not expected.

Without a sufficient justification of the classification and no evidence for a potential danger for worker, user, or consumer, a classification as proposed is not appropriate and would only undermine the science-based classification system and thus weaken the hazard communication. On this basis, Eurocolour does not support any classification.

Please also consider the attached document as well as the more detailed input provided by manufacturers of Pigment Red 53:1.

ECHA note – An attachment was submitted with the comment above. Refer to public attachment Eurocolour_Input_PigmentRed53-1.pdf

Dossier Submitter's Response

Thank you for your comment on the CLH proposal.

Please, see response to comment no. 1.

RAC's response

Thank you for your comment.

Please see RAC response to comment no. 1.

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON BARIUM BIS[2-CHLORO-5-[(2-HYDROXY-1-NAPHTHYL)AZO]TOLUENE-4-SULPHONATE]; C.I. PIGMENT RED 53:1

Date	Country	Organisation	Type of Organisation	Comment number
18.11.2022	France		MemberState	6
Comment received				
FR agrees with the classification proposal Carc. 2 – H351 and the GCL of ≥ 1%, based on the increase of the incidence of splenic sarcoma observed in rats in the NTP study. The relevance of these tumors is supported by non-neoplastic splenic lesions observed in CTFA (Cosmetics, Toiletry, and Fragrance Association) studies and as other studies report adverse effects on the spleen following exposure to the substance. FR agrees that, based on the available mutagenic data, the substance is not likely to exhibit a genotoxic mode of action. The MOA proposed seems consistent with the decrease of blood parameters observed in CTFA studies and haemosiderosis of the spleen observed in CTFA studies, NTP study and in Davis and Fitzhugh (1962) study.				
Dossier Submitter's Response				
Thank you for your support of the CLH proposal.				
RAC's response				
Thank you for your comment. RAC agrees with the proposal to classify the substance as Carc. 2 – H351 and the GCL of ≥ 1 %.				

PUBLIC ATTACHMENTS
1. Eurocolour_Input_PigmentRed53-1.pdf [Please refer to comment No. 2, 5]

CONFIDENTIAL ATTACHMENTS
1. comments.pdf [Please refer to comment No. 1, 4]