Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

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

***N*-1-naphthylaniline; *N*-phenylnaphthalen-1-amine**

EC Number: 201-983-0
CAS Number: 90-30-2

CLH-O-0000007248-69-01/F

Adopted

16 March 2023

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *N*-1-NAPHTHYLANILINE; *N*-PHENYLNAPHTHALEN-1-AMINE

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: *N*-1-naphthylaniline; *N*-phenylnaphthalen-1-amine
EC number: 201-983-0
CAS number: 90-30-2
Dossier submitter: Germany

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	1
Comment received				
Acute toxicity by oral route: FR agrees with the proposed classification as Acute Tox 4 and the ATE of 1231 mg/kg bw. This value is associated with high uncertainties considering that only one animal died at 1000 mg/kg bw and all animals at 2000 mg/kg bw. However, it is the lowest LD50 value and it should have been over-conservative to retain the cATpE of 500 mg/kg bw considering the overall dataset. Acute toxicity by dermal route: Based on available data, FR agrees that the substance does not warrant a classification.				
Dossier Submitter's Response				
We thank the FR CA for the support.				
RAC's response				
The proposal to classify as Acute Tox 4, H302 with the ATE of 1231 mg/kg bw is supported.				

OTHER HAZARDS AND ENDPOINTS – Skin Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	2
Comment received				
Skin irritation: Based on available data, FR agrees that the substance does not warrant a classification.				
Dossier Submitter's Response				
We thank the FR CA for the support.				

RAC's response
Agreed, no classification required

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	3
Comment received				
Eye irritation: Based on available data, FR agrees that the substance does not warrant a classification.				
Dossier Submitter's Response				
We thank the FR CA for the support.				
RAC's response				
Agreed, no classification required				

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	4
Comment received				
Skin sensitisation: Skin sensitisations are reported in 3 in vivo studies. Occurrence of reactions are clearly above the threshold for classification. However, it is highly regrettable that all studies tested a high intradermal induction dose that prevent any subcategorisation. Is there any justification of the chosen concentration? Since only few case reports are available, this does not contribute to propose a category 1A. Nevertheless, it would have been useful to provide a comparison to criteria according to CLP guidance. Overall, FR agrees that a classification for subcategory 1A cannot be excluded based on experimental data and thus the substance should be classified as Skin Sens. Cat. 1.				
Dossier Submitter's Response				
We thank the FR CA for the support. There are only 5 case reports available, in which NPNA was tested using patch tests in a non-standardised way on single human patients. There are neither data from Human Repeated Insult Patch Tests (HRIPT), Human Maximization Tests (HMT) and Diagnostic patch tests nor from epidemiological studies available, which however are necessary to conclude on the appropriate sub-categorisation according to CLP Annex I, 3.4.2.2.2.1 and 3.4.2.2.2.2. We therefore considered it inappropriate to draw any conclusions from these few individual reportings on the general frequency of occurrence of skin sensitisation in humans and the likelihood of exposure (as forseen in the CLP Guidance, section 3.4.2.2.2.: "When considering human evidence, it is necessary to take into account the size of the population exposed and the extent of exposure and frequency, and thus the consideration is on a case by case basis."). This is why we did not provide a comparison of these data to the criteria for human data listed in the CLP Guidance.				
RAC's response				
RAC support the opinion of the Dossier Submitter and classification as Skin Sens. 1.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Single Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	5
Comment received				
STOT SE: Available data do not allow proposing a classification for STOT SE.				
Dossier Submitter's Response				
We thank the FR CA for the support.				
RAC's response				
Agreed, no classification required				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
08.07.2022	France		MemberState	6
Comment received				

STOT RE:
According to CLP guidance: "The guidance developed for classification of substances inducing haemolytic anaemia according to 67/548/EEC (Muller A. et al., 2006) cannot directly be used under CLP because of the changes in criteria (see CLP Annex I, 3.9.2.7.3 c and 3.9.2.8.b, d). The major criterion for haemolytic anaemia changed:
From 'Any consistent changes in haematology which indicate severe organ dysfunction.'
To 'Any consistent and significant adverse changes in haematology.' This indicates that less adverse effects are considered for classification according to CLP".

The overall data clearly show that the substance induces haemolytic anaemia with impact on liver and kidney, especially.

Regarding haematology, a significant decrease of haemoglobin is reported in the 90-day study at 125 mg/kg/d. Even if the dose is slightly above the cut-off for STOT RE 2 (100 mg/kg/d), it should be noted that the lower tested dose is very low (25 mg/kg bw/d). This is not in accordance with OECD guidance that recommends a 2 to 4 interval between tested doses. The large interval creates uncertainties on results that can be expected at a dose close to the CLP cut-off. At 125 mg/kg/d, reticulocytes are significantly increased and total bilirubin is increased at all tested doses. This supports the relevance and significance of haemolytic anaemia. Significant decrease of haemoglobin is also reported in a 28 day study at 80 mg/kg/d (CLP cut-off for STOT RE 2: 30 < C ≤ 300 mg/kg/d) and in a prenatal developmental toxicity study at 150 mg/kg/d (CLP cut-off for STOT RE 2: 60 < C ≤ 600 mg/kg/d). Even if the threshold of 10% for a decrease of haemoglobin set by Muller et al. 2006 is not reached, the decreases observed at these doses are statistically significant and can correspond to the more flexible criteria set in the CLP guidance. The effects can fulfil the CLP criteria: "any consistent and significant adverse change in clinical biochemistry, haematology, or urinalysis parameters".

Concerning liver: increased weight associated with centrilobular hypertrophy is reported in the 90-day study. These effects cannot be considered as an adaptive reaction especially at the dose of 125 mg/kg bw/day: the increase of liver weight is clearly higher than 10% and almost all animals present an hypertrophy of slight to moderate severity.

Even if the dose is slightly above the cut-off for STOT RE2, similar results can be expected at a dose close to or below 100 mg/kg bw/day. Indeed, increased liver weight and hypertrophy are already observed at 25 mg/kg/d, reaching statistically significance, even if these findings are of lower significance.

Concerning kidney: Chronic nephropathy is observed from 25 mg/kg/d in males only in the 90-day study. Study authors considered that this lesion may not be of relevance for humans as CNP is a frequently observed effect in the male aging rat, (only) exacerbated by the chemical treatment. However, the relevance of this tumour to humans cannot be neither completely excluded since (1) these effects occurred in animals that cannot be considered as aged at the end of the study, (2) a clear-dose response is observed for severity and (3) haemolytic anaemia can lead to secondary effects on the kidney. In addition, degeneration/regeneration of tubules is reported in males and mostly at the dose of 125 mg/kg/d. Even if the dose is slightly above the cut-off for STOT RE2, similar results can be expected at a dose close to or below 100 mg/kg bw/day. These effects can fulfil to the CLP criteria: "significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination."

Finally, it has to be noted that these results are consistent with those reported with an analoguous substance, diphenylamine classified as STOT RE 2 (RAR, 2008). Data from this substance can support the need to classify NPNA, accordingly.

Dossier Submitter's Response

We thank the FR CA for the comment.

As indicated in the dossier, we agree that the effects on blood parameters and histomorphology have to be seen as borderline with respect to the criteria as laid down in Muller et al. (2006) and the ECHA Guidance on the Application of the CLP Criteria (ECHA, 2017)(e.g. regarding Hb reduction of ≥ 10 %) and further considering that several haematotoxic effects were observed at a dose only slightly above the upper limit value for STOT RE 2 classification (i.e. at 125 mg/kg bw/d).

In addition and as noted in the dossier, regarding the chronic progressive nephropathy (CPN) frequently observed in males in the subchronic study starting at a dose of 5 mg/kg bw/d with higher incidence at ≥ 25 mg/kg bw/d and the clear dose-response relationship regarding severity (BASF, 2016b), it is not possible to fully exclude a relevance for humans, although the study authors suggested this. However, as no specific histopathological findings with respect to CPN were reported in the study report, final assessment of the relevance of this finding is hampered and it is neither possible to fully exclude nor to verify a potential impact of the observed haematotoxicity on the progression of the reported CPN in the treated rats, as additional kidney effects elicited by haemolysis were observed as well.

Disucussion in RAC, whether classification of NPNA as STOT RE 2, H373 (blood system) is warranted, is welcome.

We further agree as indicated in the dossier that based on the available data the liver is to be identified as target organ for NPNA toxicity and, thus, classification as STOT RE, H373 (liver) may be warranted as well. Discussion in RAC is welcome.

RAC's response

RAC supports the classification as STOT RE 2, H373: May cause damage to organs (blood system, liver) through prolonged or repeated exposure. Please see RAC opinion for details.