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,*N*-dimethyl-*p*-toluidine

EC Number: 202-805-4
CAS Number: 99-97-8

CLH-O-0000007005-83-01/F

Adopted

10 June 2021

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,N-dimethyl-p-toluidine
EC number: 202-805-4
CAS number: 99-97-8
Dossier submitter: Germany

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2020	France		MemberState	1
Comment received				
It would have been appreciated to investigate if the update of existing classification for N,N-dimethyl-p-toluidine can also be applicable to N,N-dimethyl-m- toluidine and N,N-dimethyl-o- toluidine.				
Dossier Submitter's Response				
Data, especially the NTP study data, are only available for the para isomer of the substance. Ortho-, meta- and para-substituted substances can have quite different toxicological properties and/or potency. Therefore, a simple read-across to meta- and ortho-isomers is not possible. The eMSCA is not aware of data that would support a read-across to the other isomers.				
RAC's response				
RAC only evaluates the information in the CLH report.				

CARCINOGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
20.08.2020	Sweden		MemberState	2
Comment received				
The Swedish CA thanks DE for the proposal to classify N,N-dimethyl-p-toluidine (CAS No. 99-97-8) as Carc. 2. However, we consider that a Carc. 1B classification may be more appropriate. An increased incidence of tumors is observed mainly in animals exposed to the highest dose, with simultaneous general toxicity, including the weight gain clearly reduced.				

However, preneoplastic lesions are observed at all lower doses, in a dose-dependent manner, where animals show no signs of general toxicity. Furthermore, in female mice, liver tumors were statistically increased at lower doses without simultaneous general toxicity. We consider that the effects seen at the lower doses should be given more weight as the general toxicity appears to "obscure" the carcinogenic effect of this chemical at this high dose level. Some rare tumors were also observed in rats (nasal cavity, liver) and mice (hepatoblastoma), which adds further evidence to the carcinogenic potential of the substance.
Dossier Submitter's Response
The eMSCA generally agrees with the comment by SE that the observed effects, low-dose pre-neoplasia and rare/uncommon tumour findings could also be considered for classification as Carc 1B. However, in the CLH dossier, the eMSCA weighted the arguments for Carc 1B or Carc 2 and came to the conclusion that a classification as Carc 2 would be more appropriate: A number of confounding factors are present, e.g. most neoplastic lesions only appeared at the highest dose, with likely excessive general toxicity. The proposed mode of action, i.e. non-genotoxic carcinogen with induction of severe methaemoglobinaemia, and the generally high number of spontaneous incidences of mice liver tumours are further factors that should be considered, as well as the limitation of neoplasms (nose, lung, forestomach) to single species and sexes.
RAC's response
Treatment-related cancer incidences occurred at the high dose (60 mg/kg bw/day) in both species in combination with a reduced survival (especially in rats and female mice). Although general toxicity is present at the highest dose in the form of lower body weight and higher mortality, this occurs only at the end of the study period. This means that these effects are likely to coincide with the induction of tumours, and may be secondary to the carcinogenic effects. For this reason, RAC considers the tumours occurring at the high dose relevant for classification. Further, as noted above, cancer incidences were also increased at the mid dose in mice. RAC concludes that, based on the dose-dependent induction of liver carcinomas in two species (mice and rats) in both sexes, dose-dependent progression to neoplasms, pre-neoplastic lesions in all organs with neoplasms, the induction of rare hepatoblastomas in mice and nasal cavity tumours in rats (above HCD) and the presence of a plausible mode of action which is relevant to humans, DMPT fulfils the criteria for category 1B.

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2020	France		MemberState	3
Comment received				
The substance induces various tumours in the NTP studies: - Liver tumours, mainly carcinomas, occurred in both sexes of rats and mice. These tumours occurred in rats at a dose associated with excessive toxicity (survival < 50%). B6C3F1 mice are known to be very sensitive to liver tumorigenesis. It should be noted that in mice, the increased incidence of hepatoblastoma is statistically significant. This type of tumour is very rare and may not be combined with adenoma and hepatocarcinoma. - Nasal cavity tumours occurred only in male rats, principally as adenomas, at a dose				

associated with excessive toxicity. - Thyroid tumours occurred only in male rats, at a dose associated with excessive toxicity. - Lung tumours occurred in mice, principally as adenomas. - Forestomac tumours – squamous cell papilloma - occurred only in female mice. Overall, the clearest evidence of carcinogenicity is principally driven by the malignant liver tumours in both sexes and both species (all other tumours are rather benign). This can fulfil criteria for Carc. 1B. However, considering the excessive toxicity at the highest tested dose in rats and the high sensitivity of mice, we agree with that the proposed classification as Carc. 2 seems more appropriate.
Dossier Submitter's Response
The eMSCA acknowledges the comment by FR.
RAC's response
See response to comment 2.

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2020	France		MemberState	4
Comment received				
There is no study on germ cells. In vitro studies report mostly negative results or, at the best, equivocal results. In vivo studies report mostly negative results. However, it should be highlighted that there is no study in full accordance with OECD guideline. In addition, in most in vivo studies, there is no data on general toxicity and thus it cannot be confirmed that the exposure was sufficient to identify mutagenicity. Therefore, we agree with the proposal of no classification for this endpoint.				
Dossier Submitter's Response				
The eMSCA acknowledges the comment by FR.				
RAC's response				
RAC agrees with the evaluation of the DS and the commenting MSCA.				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2020	France		MemberState	5
Comment received				
Acute toxicity by oral route: We agree with the proposed classification as Acute. Tox. 3. Considering the overall quality of the dataset, we question the relevance of the ATE of 139 mg/kg bw which is the lowest LD50 identified but issued from a study for which there is no detail on protocol and results. Instead, the generic ATE of 100 mg/kg bw can be retained. Acute toxicity by dermal route: Based on the study presented, we agree that no classification is required for this substance. Did you find the rationale of the existing harmonised classification as Acute Tox 3* - H311 for the grouping entry?				

Acute toxicity by inhalation:
We agree with the proposed classification as Acute. Tox. 4. Considering the overall quality of the dataset, we question the relevance of the ATE of 1.4 mg/L based on a study for which there is no detail on protocol and results. However, we note that this ATE is very close to the generic ATE of 1.5 mg/kg bw. In this context, we can agree with the proposed ATE.

Dossier Submitter's Response

The eMSCA acknowledges the comments by FR.

1) The eMSCA agrees that the reliability of the LD_{50} data underlying the proposed classification for acute toxicity by oral route is not assignable. However, the LD_{50} value for a study in mice of 139 mg/kg bw listed in RTECS and used to set the ATE value falls into the range of estimated toxicity values from a 3-month study in mice (NTP): In mice treated with 125 mg/kg bw/day, only 2/10 (m) or 1/10 (f) died within the first 2 weeks of dosing, therefore 125 mg/kg bw is considered as below the LD_{50} value. Therefore, 139 mg/kg bw/day are considered reasonable. In the 3-month study, with 250 mg/kg bw, 10/10 (m) or 9/10(f) died within 10 days of dosing.

2) For the dermal route, no data except the single study listed in the dossier was identified, i.e. a study in rabbits with reliability not assignable and a listed LD_{50} value of > 2000 mg/kg bw. The basis for the existing classification is not known to the eMSCA.

3) The eMSCA acknowledges the comment regarding the inhalation route.

RAC's response

Acute toxicity by oral route:
RAC agrees with the proposed classification as Acute. Tox. 3. Although no detailed information is available on the LD_{50} studies, the results are supported by information from a toxicokinetic study and two 3-month NTP studies. Results show that mice are more sensitive than rats. RAC supports the ATE based on the lowest LD50 of 139 mg/kg bw, rounded off to 140 mg/kg bw.

Acute toxicity by dermal route:
RAC agrees with no classification.

Acute toxicity by inhalation:
RAC agrees with the proposed classification as Acute. Tox. 4 and ATE of 1.4 mg/L.

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
21.08.2020	France		MemberState	6
Comment received				
STOT RE: We agree with the proposed classification as STOT RE 2. Nevertheless, we question the				

need to adjust the effective dose considering the frequency of exposure (from 5 days/week to continuous administration), even if there is no impact on overall conclusion.
Dossier Submitter's Response
According to OECD Test Guideline 408, "the animals are dosed with the test chemical daily seven days each week for at least 90 days". Dosing in the NTP protocol is five days per week, on average over the study period, the animals received a lower dose per week than reported. The eMSCA considers it therefore necessary to calculate the corrected dose and to use these values for classification.
RAC's response
RAC agrees with the DS and MSCA on STOT RE 2. However the organs designated are blood system and respiratory tract. RAP considers the need for adjusting the dose in this case not necessary.