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-DIMETHYLACETAMIDE (DMAC)

EC number: 204-826-4
CAS number: 127-19-5

CLH-O-0000004716-69-03/F

Adopted

12 September 2014

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in this table as submitted by the webform. Please note that some attachments received may have been copied in the table below. The attachments received have been provided in full to the dossier submitter and RAC.

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Substance name: N,N-dimethylacetamide
CAS number: 127-19-5
EC number: 204-826-4
Dossier submitter: The Netherlands

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2014	France		MemberState	1
Comment received				
Based on the fact that DMAC shows an ED10 > 4 mg/kg bw/day, and < 400 mg/kg bw/day, (medium potency); the GCL of 0.3% relevant for substances classified in category 1 is considered to be appropriate for DMAC. Consequently, FR agrees with the removal of the current Specific Concentration Limit for reproductive toxicity.				
Dossier Submitter's Response				
Thank you for your comments.				
RAC's response				
Noted.				

TOXICITY TO REPRODUCTION

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2014	Germany		MemberState	2
Comment received				
The DE CA can follow the dossier submitter's proposal regarding N,N-Dimethylacetamide to remove the current SCL of ≥ 5 % and apply the GCL of ≥ 0.3 % according to the CLP regulation. However, we would like to comment on some ED10-values derived by the dossier submitter. The CLP guidance defines ED10-values shall be based on adverse effects fulfilling the classification criteria for reproductive toxicity. Taking this into account, it appears questionable to derive an ED10-value for the BASF 1976a-study based on cleft palates in mice offspring which are known to be readily inducible by maternal stress in this species. The study results described in the CLH dossier do not allow for a final assessment as to whether the increased occurrence of cleft palates in the high dose group should be considered an unspecific reaction to maternal toxicity in the mice offspring or an indication for specific teratogenicity caused by fetal exposure to N,N-dimethylacetamide. If clear maternal toxicity was observed in this study, this type of malformation would be considered irrelevant for classification and consequently for the derivation of an ED10-value as well.				

The dossier submitter also derived ED10-values based on sums of malformations which refer to observations in different fetal organs and body parts. We are challenging these values since classification for teratogenicity is normally based on incidences of single types of malformation and not on sums thereof. In our opinion ED10-values should be derived following the same rationale. Consequently, we rate those ED10-values, which are based on incidences of single types of malformation, as being the most significant when it comes to determining the lowest ED10-value from all prenatal developmental toxicity studies. Thus in the case of N,N-Dimethylacetamide we consider the ED10-values based on heart and great vessels malformations being the most appropriate.

Dossier Submitter's Response

We agree that cleft palate in mice can be induced by maternal stress. However, as both of the early studies in mice (BASF 1975, BASF 1976a and 1976b) show, DMAC produces a range of teratogenic effects, even after single application. In these studies a teratogenic response was present already at dose levels that induced no maternal toxicity according to the available reports of these studies. Cleft palate was among the effects seen without reported maternal toxicity (in the BASF 1975 study after single dose of 3000 and 1200 mg/kg bw, in the BASF 1976a and 1976b study at 400 mg/kg bw at which no maternal toxicity was reportedly present; note that in the latter study at 1200 mg/kg bw cleft palate occurred together with only slight maternal toxicity). Thus, in our evaluation cleft palate as seen in these studies cannot plausibly be explained as resulting from maternal stress and can therefore appropriately be used for ED10 calculation.

As to the relevance of sum of malformations as parameter for ED10 calculation it should be noted that (as already indicated above), DMAC has been shown to produce a range of malformations in multiple studies. In our evaluation these malformations are a unequivocal exponent of DMAC's developmental toxicity and using them together for quantitative potency analysis is a valid approach in our view. We consider the different malformations as clearly compound-related and see no reason to exclude them from our quantative analysis. Combining effects is also in line with the guidance. See paragraph 3.7.2.5.3 stating: "Determining exactly which effect or combination of effects is the one that fulfils the classification criteria may seem difficult.".

RAC's response

Noted.

Date	Country	Organisation	Type of Organisation	Comment number
27.01.2014	Sweden		MemberState	3

Comment received

The Swedish CA supports the proposal to remove the current specific concentration limit (SCL), 5%, for N,N-dimethylacetamide (CAS no 127-19-5), a compound that has a harmonized classification for reproductive toxicity in Cat 1B (H360D).
According to the Guidance on the application of the CLP criteria the ED10 value (as used for reprotoxicity SCLs) is the lowest dose which induces reproductive toxic effects that fulfill the criteria for reproductive toxicity with an incidence or magnitude of 10% after correction for the spontaneous incidence. In the current dossier, the dossier submitter has from several developmental toxicity studies calculated ED10 values for developmental toxicity endpoints that all fulfill the criteria for classification. Overall, the lowest ED10 value identified (i.e. the one that according to the guideline should be used for deciding on potency level) was 217 mg/kg bw/day (sum of malformations (head, whole body, heart, vessels, skeleton)) using

the benchmark dose (BMD) method or 185 mg/kg bw/day using the linear interpolation method. Both these values are clearly within the range (4≤ ED10 ≤ 400 mg/kg bw/day) that the CLP guidance document defines for a Repro Cat 1B compound of medium potency. The identified ED10 values are not close to the lower or upper boundaries of the medium potency group and therefore there is no need to modify the potency group due to the severity of the effect. In conclusion, based on available data N,N-dimethylacetamide is a medium potency Cat 1B (H360D) developmental toxicant and according to the CLP guidance the SCL for this potency group is 0.3%, i.e. the general concentration limit for a Cat 1B reproductive toxicant, and thus there is no need to assign a SCL.
Dossier Submitter's Response
Thank you for your comments.
RAC's response
Noted.