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'*-methylenediacrylamide**

EC Number: 203-750-9
CAS Number: 110-26-9

CLH-O-0000007157-72-01/F

Adopted

15 September 2022

ANNEX 2 - COMMENTS AND RESPONSE TO COMMENTS ON CLH PROPOSAL ON *N,N'*-METHYLENEDIACRYLAMIDE

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'*-methylenediacrylamide
EC number: 203-750-9
CAS number: 110-26-9
Dossier submitter: Sweden

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
04.02.2022	Germany		MemberState	1
Comment received				
In section 2 Table 5 of the CLH report the hazard pictogram GHS06 is erroneously used instead of GHS08. This means that in Table 5 in the cell of - Row "Dossier submitter's proposal" and column "Labelling - Pictogram, Signal Wordcode(s)" - Row "Resulting Annex VI entry if agreed by RAC and COM" and column "Labelling - Pictogram, Signal Word Code(s)" the coding "GHS06" has to be deleted and replaced by "GHS08". In addition, in Table 5 in the cell of - Row "Dossier submitter's proposal" and column "Classification - Hazard Class and category code(s)" - Row "Resulting Annex VI entry if agreed by RAC and COM" and column "Classification - Hazard Class and Category Code(s)" H340 behind the expression "Muta. 1B" has to be deleted - H340 has to be named in a separate cell ("Labelling – Hazard statement Code(s)") in Table 5.				
Dossier Submitter's Response				
Thank you for noticing these mistakes made for the incorrect hazard pictogram in Table 5, as well as the incorrect placement of the category code H340. These errors in Table 5 need to be corrected.				
RAC's response				
RAC concurs with the DS.				

MUTAGENICITY

Date	Country	Organisation	Type of Organisation	Comment number
11.02.2022	France		MemberState	2

Comment received

Two in vitro studies, one conducted according OECD TG 471 and the second following a protocol similar to OECD TG 471 are available. The first one showed negative results with and without metabolic activation, while in the other study, N,N'-methylenediacrylamide was found to be mutagenic with metabolic activation.

Page 9: In the CLH report, for the test conducted according OECD TG 471 (Hashimoto and Tanii, 1985), it is indicated that the cytotoxicity is unspecified. However, on the ECHA's dissemination site, it is specified that the substance showed no cytotoxicity. Is it a mistake or could you please explain this discrepancy?

In vivo, MBA was seen to induce dominant lethal effects in male mice. However, in the study, only one dose was tested and it seems that some results could be due to cytotoxicity. The study also showed an increase in the incidence of semisterile offspring and heritable reciprocal translocations were pointed out.
Micronuclei assay conducted in mice via intraperitoneal injection showed a statistically significant increase of micronuclei in the bone marrow.
Comet assay showed that MBA administered by oral route can reach the gonads of male mice and induce testicular DNA damages.

The other studies available (Reproductive Assessment by Continuous Breeding (RACB), study on sperm count and morphology and testicular histopathology in mice and Sex-linked recessive lethal test in Drosophila) demonstrated that MBA affected spermatocytes, sperm and the morphology of the male reproductive organs. Developmental effects were also seen in mice. In drosophila, sex-linked recessive lethal mutations were demonstrated, but in this study, MBA did not induce reciprocal translocations.

Moreover, MBA is a structural analogue of acrylamide, which has a harmonised classification as Muta. 1B, and whose mutagenic effects are well documented. These data support the previous results on the mutagenicity of MBA.

Given positive results from in vivo heritable germ cell mutagenicity tests in mammals available, MBA fulfill the criteria for a classification in category 1B. Moreover, the positive results with the other studies available support this conclusion, along with the similarity with the muta. 1B substance acrylamide.

Therefore, FR agrees with the classification Muta. 1B, H340.

Dossier Submitter's Response

Thank you for your comments, and for your support.

Regarding the cytotoxicity issue in the study of Hashimoto and Tanii, summarised in the table on page 9, we agree that the statement "Cytotoxicity was not specified" should be changed to "No cytotoxicity". The original article does not explicitly mention cytotoxicity for this substance, but we agree it is clear from the context that no cytotoxicity was involved in this case.

RAC's response

RAC concurs with the DS.

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Date	Country	Organisation	Type of Organisation	Comment number
04.02.2022	Germany		MemberState	3
Comment received				
The DE-CA agrees that classification of N,N'-methylenediacrylamide as Muta. 1B, H340 is warranted. The proposal is mainly based on positive results from an in vivo heritable germ cell mutagenicity test (similar to OECD TG 478), an in vivo somatic cell mutagenicity test (OECD TG 474), as well as results from an in vivo comet assay. Both in vivo mutagenicity tests were performed as i. p. studies, what is not a regular route of human exposure (Guidance: chapter 3.5.2.4, p. 367). However, the results of the positive comet assay prove that N,N'-methylenediacrylamide given by the oral route reaches also the gonads and induces DNA damage in testicular cells of mice. Thus, the effects of the i. p. studies should be considered relevant. Furthermore, the data from a similar substance (acrylamide) give additional support for the proposed classification.				
Dossier Submitter's Response				
Thank you for your support.				
RAC's response				
RAC concurs with the DS.				