
Gezondheidsraad

Health Council of the Netherlands



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Subject : Comments on 4,4'-Methylenedianiline
Your reference : August 31, 2015, Letter + Comments on 4,4'-Methylenedianiline
Our reference : U-868769/BvdV/cn/459-G72
Enclosure(s) : 2
Date : November 17, 2015

Dear dr. Lentz,

Thank you and your colleagues dr. C. B'Hymer and dr S. Reynolds for accepting the invitation to comment on the draft report '4,4-Methylenedianiline', which was published for public review in July 2015 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands.

The Committee highly appreciates the detailed comments presented by the NIOSH reviewers. The Committee has incorporated most comments in its final report. In the Annex to this letter the responses by DECOS to all recommendations made by NIOSH are specified.

The Committee expresses its appreciation for the meticulous review of the document which allows us to improve the final report.

Enclosed you find a copy of the final report on '4,4'-Methylenedianiline'.

Yours sincerely,

G.B. van der Voet, PhD, ERT, Scientific secretary

Enclosures:

Detailed response by DECOS to NIOSH comments
Final report on '4,4'-Methylenedianiline'

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RESPONSES BY THE COMMITTEE

**NIOSH review comments on DECOS 4,4'-Methylenedianiline by:
Clayton B'Hymer, Research Chemist, NIOSH/Division of Applied
Research and Technology (DART), 1090 Tusculum Avenue,
Cincinnati, OH45226-1998 and Steven Reynolds, Research
Pharmacologist, NIOSH/Health Effects Laboratory Division (HELD),
1095 Willowdale Rd., Morgantown, WV 26505-2888**

SECTION & PARAGRAPH	COMMENT	RESPONSE by the Committee
General Comments	<p>Overall the work is general and lacking specific information on the health effects documented in humans.</p> <p>The work tends to cite secondary sources (if any reference is given), instead of the primary source. As such, the work requires extensive revision on referencing the primary sources of experimental results.</p>	<p>The Committee updates its previous report (2000) in view of the recent advice of the AGS published in 2010 and the SCOEL published in 2012. The Committee points out that the report has a focus on the carcinogenic effects of MDA and that the toxicological information regarding other health effects is kept limited.</p> <p>The Committee agrees with this view and added primary sources. The Committee points out that the core document is based on the primary studies on carcinogenicity all mentioned and tabulated in Annex G.</p>
Specific Comments		
Page 4, lines 11-12	<p>The last line which describes the uses for 4,4-methylenedianiline (MDA) is non-specific, which leaves the reader asking how often this chemical is encountered in the work place or the environment. Specifically, MDA is used in the production of polyurethanes which most readers would know. It is also used in the production of Spandex fiber. This sentence should be expanded.</p>	<p>The sentence was expanded.</p>
Page 4, lines 14-18	<p>The Committee's conclusion of the compound should be stated as based on the limited bacteria and animal data collected in the document (Section E). The work seems questionable owing to the Committee's own comments in section 2.2 on page 8 for humans.</p>	<p>The sentence was modified.</p>
Page 7, section 2.1.1	<p>Again, the work cites secondary sources instead of citing primary studies or documents. The hepatic health effects of MDA were first documented in England from 1965 poisoning of 84 people from contaminated bread flour in Kopelman H et al. 1966; <i>The Epping Jaundice</i> Brit Med J 1:514-516; and <i>The Epping Jaundice after two years</i></p>	<p>These references were included in paragraph 2.1.1. The Committee points out that the report has a focus on the carcinogenic effects of MDA and that the toxicological information</p>

	Kopelman H 1968, Postgrad Med J 44:78-80. The Epping poisoning was the first documented human incidence of MDA health effects and is worth citing.	is kept limited.
Page 8, lines 11-13	The primary reference for this study was not cited, only the mention that it was related to NTP.	The primary references were cited.
Page 8, lines 15-25	The primary references for the animal studies are not given.	These are details of the NTP studies, referenced above.
Page 8, Section 2.2, line 22	“The Committee is of the opinion that epidemiological studies of MDA do not provide a reliable starting point for quantitative risk assessment.” This is an important statement; however, the Committee proceeds to calculate lifetime cancer risks which are stated in the initial summary.	Yes, the Committee agrees that this seems paradoxical and added a sentence to clarify the issue.
<p>Relevant data were extracted from reports on MDA from the AGS and SCOEL published in 2010 and 2012, respectively. Data for calculations were obtained from the online databases Toxline, Medline, and Chemical Abstracts (CABplus), using “4,4-methylenedianiline” and “4,4-methylenedianiline carcinogenicity” as keywords in May 2015. An August 14, 2015 search using OVID and Scopus with “4,4-methylenedianiline” and “4,4-methylenedianiline carcinogenicity” as keywords provided no additional relevant information other than what is currently contained in the report. All critical studies relevant to the derivation of health-based occupational cancer risk values for 4,4-methylenedianiline seem to have been included in the report.</p> <p>OK, the Committee appreciates the NIOSH view that no relevant recent publications are missing in the report.</p> <p>The critical studies are presented in sufficient detail to support the conclusions regarding the derivation of health-based occupational cancer risk values for 4,4-methylenedianiline.</p> <p>OK</p> <p>The presentation of the material is sufficiently concise.</p> <p>OK</p> <p>The limitations of the critical studies were discussed.</p> <p>OK</p> <p>There are no obvious alternative interpretations regarding the overall assessment of the cancer risks.</p> <p>The Committee appreciates this NIOSH observation.</p>		