



Centers for Disease Control and Prevention
National Institute for Occupational
Safety and Health
1090 Tusculum Avenue
Cincinnati OH 45226-1998

August 31, 2015

The Health Council of the Netherlands
Attn: Mr. G.B. van der Voet
PO Box 16052
2500 BB
The Hague
the Netherlands

Dear Mr. van der Voet:

Thank you for the opportunity to review the draft report on *4,4-Methylenedianiline* prepared by the Dutch Expert Committee on Occupational Safety (DECOS). Comments are enclosed that were prepared by Clayton B'Hymer, Research Chemist, NIOSH/Division of Applied Research and Technology, 1090 Tusculum Avenue, Cincinnati, OH 45226-1998 and Steven Reynolds, Research Pharmacologist, NIOSH/Health Effects Laboratory Division (HELD), 1095 Willowdale Road, Morgantown, WV 26505-2888.

If you have any questions regarding the comments, please contact me at 513-533-8260 (telephone) or by Email at tbl7@cdc.gov.

Sincerely yours,

Thomas J. Lentz, Ph.D., M.P.H.
Branch Chief
Document Development Branch
Education and Information Division

1 Enclosure

**Comments on DECOS 4,4'-Methylenedianiline by:
Clayton B'Hymer, Research Chemist, NIOSH/Division of Applied
Research and Technology (DART) 1090 Tusculum Avenue,
Cincinnati, OH 45226-1998 and Steven Reynolds, Research
Pharmacologist, NIOSH/Health Effects Laboratory Division (HELD),
1095 Willowdale Road, Morgantown, WV 26505-2888**

SECTION & PARAGRAPH	COMMENT
General Comments	Overall the work is general and lacking specific information on the health effects documented in humans. 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.
Specific Comments	
Page 4, lines 11-12	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.
Page 4, lines 14-18	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.
Page 7, Section 2.1.1	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 the 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> 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.
Page 8, lines 11-13	The primary reference for this study was not cited, only the mention that it was related to NTP.
Page 8, lines 15-25	The primary references for the animal studies are not given.
Page 8, Section 2,2, line 22	"The Committee is of the opinion that the 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.

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 (CAPlus), using "4,4-methylenedianiline" and CAS No. 101-77-9 as key words 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.

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.

The presentation of the material is sufficiently concise.

The limitations of the critical studies were discussed.

There are no obvious alternative interpretations regarding the overall assessment of the cancer risks.