



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

April 18, 2017

The Health Council of the Netherlands
Attn: S.R. Vink
PO Box 16052
2500 BB The Hague
the Netherlands

Dear Mr. Vink:

Thank you for the opportunity to review the draft report on *1,2Dibromoethane* prepared by the Dutch Expert Committee on Occupational Safety (DECOS). Comments are enclosed that were prepared by Todd Stueckle, Research Biologist, NIOSH/Health Effects Laboratory Division (HELD), 1095 Willowdale Road, Morgantown, WV 26505 and Kevin Hanley, Industrial Hygienist, NIOSH/Division of Surveillance, Hazard Evaluations and Field Studies (DSHEFS), 1090 Tusculum Ave., Cincinnati, OH 45226.

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,

A handwritten signature in black ink, appearing to read "T. J. Lentz".

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

1 Enclosure

**Review Comments on DECOS draft document on 1,2-Dibromoethane
 By: Todd Stueckle, Ph.D., Research Biologist, NIOSH/Health Effects
 Laboratory Division, 1095 Willowdale Road, Morgantown, WV 26505;
 and Kevin Hanley, MSPH, CIH, REHS/RS, Industrial Hygienist,
 NIOSH/Division of Surveillance, Hazard Evaluations and Field
 Studies, 1090 Tusculum Ave., Cincinnati, OH 45226-1998**

SECTION & PARAGRAPH	COMMENT
<p>General Comments</p>	<p>The Committee's recommendations are appropriate. The addition of the Skin Notation (Section 4) is well-justified.</p> <p>All critical and supporting studies are included and presented in sufficient detail.</p> <p>The DECOS document, "Health-based recommendation on occupational exposure limits for 1, 2-Dibromoethane (DBE)," is an update to their previous publication on this topic (no. 1999/070SH).</p> <p>The Committee's recommendations for an estimated excess cancer risk from DBE in air from occupational exposure and the derived exposure limits (OELs) are appropriate. These are the same values as those previously published in 1999, however, the update document is vastly improved from 18 years ago.</p> <p>The most apparent improvement is inclusion of a skin notation for DBE in addition to the air OELs.</p> <p>In section 2 & 3, more details are provided in the text for the supporting studies beyond reporting the information in an Annex table. This document has 46 references, 25 more than in 1999.</p> <p>One weakness of this assessment is the minimal amount of <i>current</i> production/use data and number of exposed workers. The reported data are 20+ years old. Is there any more recent information from US EPA or EU? Where is it manufactured – Europe, Americas, Asia?</p>

	<p>The European Commission has estimated that 7600 workers are exposed to DBE (presumably in the EU): (http://europa.eu/rapid/press-release MEMO-17-4_en.htm). The high volume uses of DBE have been discontinued (anti-knock agent and pesticides) but the amount of DBE in chemical intermediates and solvents for use in making resins, gums, waxes, pharmaceuticals and vinyl chloride is not estimated in this document. Further, how many workers are potentially affected and is there data regarding exposure levels?</p>
Specific Comments	
Section 2.1, Page 8, line 7	“banning...in <i>many</i> countries” ? Suggest changing this to ‘...nearly all...’
Page 5, Lines 12 and 13	“... as chemical . . .” should read “as a chemical”; also “as solvent” . . . should read “as a solvent”
Section 2.2, Page 9, Line 4	<p>“IARC...2A (probably...).⁴” After this sentence, recommend adding more detail because it is important information. Insert: ‘This evaluation was based on sufficient evidence in animals but inadequate evidence in humans. However, IARC considered that DBE is genotoxic in a broad range of in vitro and in vivo assays and binds covalently with DNA in vivo to elevate the overall evaluation from 2B (possibly carcinogenic...) to 2A.’</p> <p>There are many other organizations which evaluate cancer classifications. Should NTP be listed in this paragraph?</p> <p>Consider including an Annex table which provides a more comprehensive listing of these with their terminology without excessive text, just an introduction of the table.</p> <p>Per ACGIH 2015 Guide to Occupational Exposure Values – carcinogenicity codes include: EPA-L; IARC-2A; MAK-2; NIOSH-Ca; NTP-R; TLV-A3.</p>
Section 2.3.1, Page 9, Line 24	“Sing” should be ‘Singh.’ Ref 12
Page 10, Line 11	“... less than 0.5 ppm” This is unclear from an industrial hygiene perspective. Is this the limit of detection (LOD)? If yes, report ‘non-detectable (ND; < 0.5 ppm).’ If no, report the value in lieu of “less than 0.5 ppm.” Also insert ‘<’ symbol in front of “(< 3.8 – 38 mg/m3).”

Page 10, Lines 15 & 22	“(8-hr time-weighted average 8 ppb [0.062 mg/m ³]).” It is unclear what this phrase is reporting. Is this just from one measurement-day? An “8-hr TWA” is calculated from a single work shift. Do you mean ‘average 8-h TWA’ from multiple workers (or ‘GM 8-h TWA’)? Recommend that the authors review references 15 & 16 for clarification.
Page 11, Lines 23–26	In the cited rat inhalation study, it is not clear why mortality occurred at a lower dose (20 ppm) than growth retardation (40 ppm). This contradicts Appendix F and the NTP report. Also, the 1545 mg/m ³ appears to be a typo. 20 ppm is equivalent to 154 mg/m ³ . Did growth retardation occur at 20 ppm (154 mg/m ³) and mortality at 40 ppm (308 mg/m ³)? The same issue occurs again on Lines 25-26. Please clarify and/or revise.
Page 11, Line 24	“20 & 40 ppm (1545 & 308 mg/m ³)” There is an apparent error. It probably should be ‘15.4 & 308 mg/m ³ ’
Page 11, Lines 32–36	Suggest that doses used for the oral gavage and drinking water exposures be briefly stated to help establish non-tumor dose-response relationships for gastrointestinal tissues.
Page 14, Line 6	“1, 2-Dichloroethane” Is this correct? The cited article has DBE in the title.
Page 14 Line 11; Page 15, Line 3, etc.	After the 1 st sentence in these paragraphs, insert the reference citations and check to see if the study is listed in the References section. After reviewing these study descriptions again, it appears that citations are missing when introducing some of the studies.
Page 14, Lines 28 –29	Suggest this revision – “Positive . . . micronucleus assay” would be better stated as “1,2 dibromoethane tested positive in the comet assay and negative in the micronucleus assay.”
Page 18, Line 6	“10, 40 ppm” should read “10 or 40 ppm”
Page 15, Line 22; Page 26, Line 23	This reference entry seems incomplete. Is there a report no.? Journal citation?
Page 15, Line 22	“In 2008,...” Ref 6 is “2011.”
Section 2.4, Pages 15 & 16	Descriptions of OELs in the paragraph and in the table appear outdated. Refer to GESTIS International Limit Values @ http://www.dguv.de/ifa/gestis/gestis-stoffdatenbank/index-2.jsp for additional information. European Commission shows (in a graph) an OEL for DBE of 0.001 mg/m ³ : (http://europa.eu/rapid/press-release_MEMO-17-4_en.htm).

Section 2.4, Pages 15 & 16 (con't)	<p>Should the ACGIH TLVs be included in section 2.4? Although it doesn't have a value for the TLV, ACGIH lists DBE as an A3 (known animal carcinogen with unknown relevance to humans) and a skin notation.</p> <p>OSHA PEL (20 ppm; 29 CFR 1910.1000, Table Z-2) was promulgated via reference to an existing consensus standard – ANSI Z37.31 (1970).</p> <p>CalOSHA PEL for DBE is 130 ppb; it appears it was promulgated in 1981.</p>
Sections 2 & 3	Nearly all of the studies are 30 (+) years old. Are there any more recent studies available?
Section 3.3, Page 20, Line 12	“...NTP study was not available...used Gold et al. (1984)”. The NTP study (ref 17) is dated ‘1982.’ This seems inconsistent. Is there a typo here? Further, DECOS previous report was dated 1999. Still unavailable after 17 years?
Section 3.4.2, Page 21, Line 24	“...assumed no difference between animals & humans...” Can this assumption be supported? No evidence for this rationale is presented. Should a safety factor be applied for extrapolation from animals to humans?
Section 4, Page 23	This is a very important addition to this document.
	Octanol:water partition coefficient ($\text{Log}_{oc/w}$) = 1.96 per pg 8. What are the implications of this coefficient? Should it be discussed in Section 4?
Page 23, Line 16	“50 mg.” How was this quantity selected for this model calculation? Is 50 mg reasonably expected to occur in industry operations that still use DBE?
References	
Page 24, Line 7	“NTP, Report on Carcinogens, 12 th edition.” In 2016, NTP completed the NTP RoC, 14 th edition and it includes DBE assessment. Preference is to use the most current edition.
Page 24, Line 8	No ‘year’ is listed for this dossier, nor is there any report number to track/retrieve it. If it can't be retrieved, it should not be a reference citation.
Page 25, Line 7	Ref 17 is incomplete. Is there a NTP report no.? Is the report retrievable?
Annex E & F, Pages 34-44	These tables would benefit by the inclusion of the reference citations for each of the studies presented here.

Thomas J. Lentz, PhD, M.P.H.
Branch Chief
Document Development Branch
Education and Information Division
Centers for Disease Control and Prevention
National Institute for Occupational Safety and Health
(NIOSH)
1090 Tusculum Avenue

Date: December 1, 2017 Your ref: Email, dated april 20th, 2017 E-mail: sr.vink@gr.nl
Encl: 1 Our ref: 1262803/SV/jh/459-Q74 Phone: +31 6 52781584
Subject: Comments on concept report on 1,2-dibromoethane


Dear dr. Lentz,

Thank you and your colleagues mr. Stueckle and mr. Hanley for accepting the invitation to comment on the draft report '1,2-Dibromoethane', which was published for public review in February 2017 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands.

The Committee expresses its appreciation for the thorough review and comments presented by NIOSH. The responses by DECOS to these comments are specified in the Annex to this letter.

In the accompanying e-mail you can find a link to a copy of the final report on 1,2-dibromoethane.

Yours sincerely,



S.R. Vink, PhD
Scientific secretary

Annex 1: Specific responses by DECOS on comments made by NIOSH on the draft report '1,2-Dibromoethane'

SECTION & PARAGRAPH	COMMENT	RESPONSE BY DECOS
General comment	<p>One weakness of this assessment is the minimal amount of current production/use data and number of exposed workers. The reported data are 20+ years old. Is there any more recent information from US EPA or EU? Where is it manufactured — Europe, Americas, Asia?</p> <p>The European Commission has estimated that 7600 workers are exposed to DBE (presumably in the EU): (http://europa.eu/rapidJpress_release_MEMO-17-4_en.htm). The high volume uses of DBE have been discontinued (anti-knock agent and pesticides) but the amount of DBE in chemical intermediates and solvents for use in making resins, gums, waxes, pharmaceuticals and vinyl chloride is not estimated in this document. Further, how many workers are potentially affected and is there data regarding exposure levels?</p>	DECOS' reports do not include detailed information on use and exposure. Review documents are generally used, in this case the most recent available (SCOEL 2011).
Scientific Comments		
Section 2.1, Page 8, line 7	"banning. . . in many countries"? Suggest changing this to 'nearly all...'	The report has been changed accordingly
Page 5, Lines 12 and 13	". . . as chemical. . ." should read "as a chemical"; also "as solvent" . . . should read "as a solvent"	The report has been changed accordingly
Section 2.2, Page 9, Line 4	<p>"IARC. . . 2A (probably. . .)." After this sentence, recommend adding more detail because it is important information. Insert: 'This evaluation was based on sufficient evidence in animals but inadequate evidence in humans. However, IARC considered that DBE is genotoxic in a broad range of in vitro and in vivo assays and binds covalently with DNA in vivo to elevate the overall evaluation from 2B (possibly carcinogenic...) to 2A.'</p> <p>There are many other organizations which evaluate cancer classifications. Should NTP be listed in this paragraph?</p> <p>Consider including an Annex table which provides a more comprehensive listing of these with their terminology without excessive text, just an introduction of the table.</p> <p>Per ACGIH 2015 Guide to Occupational Exposure Values — carcinogenicity codes include: EPA-L; IARC-2A; MAK-2; NIOSH-Ca; NTP-R; TLV-A3.</p>	The reports of the Health Council should be readable as a stand-alone documents. Although reports of other organisations can be informative, DECOS only refers to them when documents contain information of particular relevance. DECOS considers this only the case for the information on the IARC classification, which has been added to the report.
Section 2.3.1, Page 9, Line 24	"Sing" should be 'Singh.' Ref 12	The report has been changed accordingly
Page 10, Line 11	". . . less than 0.5 ppm" This is unclear from an industrial hygiene perspective. Is this the limit of detection (LOD)? If yes, report 'non-detectable (ND; < 0.5 ppm).' If no, report the value in lieu of "less than 0.5 ppm." Also insert '<' symbol in front of "< 3.8 —38 mg/m3)."	The text has been clarified. In the end, it remains unclear from the publication whether or not the 0.5 ppm exposure level represents the LOD.
Page 10, Lines	"(8-hr time-weighted average 8 ppb [0.062 mg/m3])." It is	As these studies are

15&22	unclear what this phrase is reporting. Is this just from one measurement-day? An "8-hr TWA" is calculated from a single work shift. Do you mean 'average 8-h TWA' from multiple workers (or 'GM 8-h TWA')? Recommend that the authors review references 15 & 16 for clarification.	not critical for the evaluation, DECOS only provides short summaries without details on the exposure assessment strategy.
Page 11, Lines 23—26	In the cited rat inhalation study, it is not clear why mortality occurred at a lower dose (20 ppm) than growth retardation (40 ppm). This contradicts Appendix F and the NTP report. Also, the 1545 mg/m ³ appears to be a typo. 20 ppm is equivalent to 154 mg/m ³ . Did growth retardation occur at 20 ppm (154 mg/m ³) and mortality at 40 ppm (308 mg/m ³)? The same issue occurs again on Lines 25-26. Please clarify and/or revise.	This section has been rephrased. Overall, increased mortality was seen at lower concentrations than growth retardation, which is in line with the carcinogenic effects observed.
Page 11, Line 24	"20 & 40 ppm (1545 & 308 mg/m ³)" There is an apparent error. It probably should be '15.4 & 308 mg/m ³ '	This has been corrected.
Page 11, Lines 32—36	Suggest that doses used for the oral gavage and drinking water exposures be briefly stated to help establish non-tumor dose-response relationships for gastrointestinal tissues.	The doses applied have been added.
Page 14, Line 6	"1, 2-Dichloroethane" Is this correct? The cited article has DBE in the title.	This has been corrected.
Page 14 Line 11; Page 15, Line 3, etc.	After the "1" sentence in these paragraphs, insert the reference citations and check to see if the study is listed in the References section. After reviewing these study descriptions again, it appears that citations are missing when introducing some of the studies.	As noted at the beginning of the paragraph, the references used are IARC and EPA; unless specified otherwise.
Page 14, Lines 28—29	Suggest this revision — "Positive... micronucleus assay" would be better stated as "1,2-: dibromoethane tested positive in the comet assay"	The text has been modified.
Page 18, Line 6	"10, 40 ppm" should read "10 or 40 ppm"	The text has been modified.
Page 15, Line 22; Page 26, Line 23	This reference entry seems incomplete. Is there a report no.? Journal citation?	This has been corrected.
Page 15, Line 22	"In 2008,..." Ref 6 is "2011."	This has been corrected.
Section 2.4, Pages 15 & 16	Descriptions of OELs in the paragraph and in the table appear outdated. Refer to GESTIS International Limit Values @ http://www.dguv.de/ifaLgestis/gestjsstoffdatenbank/index-2.jsp for additional information. European Commission shows (in a graph) an OEL for DBE of 0.001 mg/m ³ : (http://europa.eu/rapid/press-release_MEMO-17-4_en.htm).	DECOS has checked and included the GESTIS database, which is in line with the report. A confirmation of an EC OEL was not found.
Section 2.4, Pages 15 & 16 (con't)	Should the ACGIH TLVs be included in section 2.4? Although it doesn't have a value for the TLV, ACGIH lists DBE as an A3 (known animal carcinogen with unknown relevance to humans) and a skin notation. OSF1A PEL (20 ppm; 29 CFR 1910.1000, Table Z-2) was promulgated via reference to an existing consensus standard—ANSI Z37.31 (1970). CalOSHA PEL for DBE is 130 ppb; it appears it was	In this section only limit values are included; (and when applicable a skin notation). The table is not an exhaustive list, without details on the origin of the OELs.

	promulgated in 1981. supported?	
Sections 2 & 3	Nearly all of the studies are 30 (+) years old. Are there any more recent studies available?	The sections were based on review documents. DECOS did not find new relevant data for deriving cancer risk values for 1,2-dibromotethane.
Section 3.3, Page 20, Line 12	“...NTP study was not available.. .used Gold et al. (1984)”. The NTP study (ref 17) is dated ‘1982.’ This seems inconsistent. Is there a typo here? Further, DECOS previous report was dated 1999. Still unavailable after 17 years?	In the report of 1999, it was stated that the NTP study was not available. It is not clear why not. Alternatively, the tumour incidences derived from the database of Gold were used. This has been clarified in the text.
Section 3.4.2, Page 21, Line 24	“...assumed no difference between animals & humans...” Can this assumption be supported? No evidence for this rationale is presented. Should a safety factor be applied for extrapolation from animals to humans?	This assumption is not correct. When no specific data are available, DECOS does not apply an uncertainty factor according to the guideline used. The text has been changed accordingly.
Section 4, Page 23	This is a very important addition to this document. Octanol:water partition coefficient (Log oc/w)=1.96 per pg 8. What are the implications of this coefficient? Should it be discussed in Section 4?	DECOS acknowledges that the Log oc/w is an important parameter for dermal absorption. However, this parameter is taken into account by the model used and DECOS decided not to further explain the model.
Page 23, Line 16	“50 mg.” How was this quantity selected for this model calculation? Is 50 mg reasonably expected to occur in industry operations that still use DBE?	Exposure to 50 mg can, equivalent to a large drop, be considered a reasonable worst scenario.
References		
Page 24, Line 7	“NTP, Report on Carcinogens, 12edition.” In 2016, NTP completed the NTP RoC, 14” edition and it includes DBE assessment. Preference is to use the most current edition.	This has been corrected.
Page 24, Line 8	No ‘year’ is listed for this dossier, nor is there any report number to track/retrieve it. If it can’t be retrieved, it should not be a reference citation.	This has been corrected.
Page 25, Line 7	Ref 17 is incomplete. Is there a NTP report no.? Is the report retrievable?	This has been corrected.
Annex E & F, Pages 34_44	These tables would benefit by the inclusion of the reference citations for each of the studies presented here.	This has been corrected.