



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

September 21, 2018

Health Council of the Netherlands
Attn: Mrs. B.E. Smink
PO Box 16052
NL-2500 BB The Hague
The Netherlands

Dear Mrs. Smink:

Thank you for the opportunity to review the draft report on *2,4-dichloro-1-nitrobenzene* and *1,4-dichloro-2-nitrobenzene* prepared by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council (DECOS). Comments are enclosed that were prepared by Liying Rojanasakul, Research Biologist, NIOSH/Health Effects Laboratory Division, 1095 Willowdale Road, Morgantown, WV 26506.

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 draft document on 2,4-dichloro-1-nitrobenzene and 1,4-dichloro-2-nitrobenzene

By: Liying Rojanasakul, PhD, Research Biologist, NIOSH/ Health Effects Laboratory Division (HELD), 1095 Willowdale Road, Morgantown, WV 26505

SECTION & PARAGRAPH	COMMENT
General Comments	<p>1) Have all critical studies, which are relevant to the assessment of the health risk, been included? If not, a copy of the reference(s) omitted will have to be provided.</p> <p>Yes, most critical studies were included. Consider adding:</p> <p>Wilkerson MG, Connor TH, Wilkin JK [1988]. Dinitrochlorobenzene is inherently mutagenic in the presence of trace mutagenic contaminants. Arch Dermatol. 124(3):396-398. doi:10.1001/archderm.1988.01670030062023</p> <p>In the abstract, the authors concluded that “DNCB is itself mutagenic, and that contaminants play a minor role in its observed mutagenicity.”</p> <p>2) Are the critical studies presented in sufficient detail to support the conclusions concerning the characterization of risk?</p> <p>Yes.</p> <p>3) Is the presentation of the information sufficiently concise or can the descriptions (of the non-critical studies) be condensed?</p> <p>Yes, the information was described and sufficiently concise.</p>

	<p>4) Are there any limitations of the critical studies which have not been presented?</p> <p>No. Two critical studies were presented. There are limited studies in the literature: only one animal study for each compound is available at present (2,4-dichloro-1-nitrobenzene animal exposure for carcinogenicity by Kano et al. 2012, and 1,4-dichloro-2-nitrobenzene animal exposure for carcinogenicity by Yamazaki et al. 2006). Both studies had been done at the Japan Bioassay Research Center, and were well-designed using two animal species (rat and mouse), and both sexes, for two years.</p> <p>5) Are there alternative interpretations to the overall assessment of the cancer risks?</p> <p>No.</p>
Specific Comments	
	<p>Suggest mentioning that: “The present study was conducted with reference to the OECD Guideline for Testing of Chemicals 451 “Carcinogenicity Studies” (OECD 1981) and were carried out in conformity with the OECD Principle of Good Laboratory Practice (OECD 1998)” where using Ref.#16 Kano et al., page 1764 under “Materials and methods.”</p>
	<p>Reference resource may include the PubChem (https://pubchem.ncbi.nlm.nih.gov), which provides cancer-related information for “compound/2_4-dichloronitrobenzene,” such as Hazards-Identification, and mutation toxicity. For example: “10.1Hazards Identification” (see below “Other resources and relative information 1).</p>
	<p>Reference resource may include: https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+4267. See below “Other resources and relative information 2.”</p>

Other resources and relative information:

1. https://pubchem.ncbi.nlm.nih.gov/compound/2_4-dichloronitrobenzene

2,4-dichloro-1-nitrobenzene

10.1.1 GHS Classification: H350 (23.08%) "May cause cancer [Danger Carcinogenicity]"

11.1.1 NIOSH Toxicity Data:

Measurement	System	Route/Organism	Dose	Effect	Date
Mutation Data	mutation in microorganisms	/Salmonella typhimurium	1 mg/plate (+enzymatic activation step)		March 2014
Mutation Data	mutation in microorganisms	/Salmonella typhimurium	3 µg/plate (-enzymatic activation step)		March 2014

2. https://pubchem.ncbi.nlm.nih.gov/compound/2_5-dichloronitrobenzene

1,4-dichloro-2-nitrobenzene

GHS Classification: H351: Suspected of causing cancer [Warning Carcinogenicity]

3. <https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+4267>



By key word "2,4-DICHLORONITROBENZENE" CASRN: 611-06-3:

0.2.21 CARCINOGENICITY

0.2.21.1 IARC CATEGORY

- A) IARC Carcinogenicity Ratings for CAS98-95-3
(International Agency for Research on Cancer (IARC), 2016; International Agency for Research on Cancer, 2015; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2010a; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2008; IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, 2007; IARC Working Group on the Evaluation of

Carcinogenic Risks to Humans, 2006; IARC, 2004):

1) IARC Classification

a) Listed as: Nitrobenzene

b) Carcinogen Rating: 2B

1) The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure circumstance for which there is inadequate evidence of carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Note: here "a) Listed as: Nitrobenzene"

I checked the IARC which showed that a monograph meeting on these chemicals will be held this October:

Volume 123

Preliminary List of Agents

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

Volume 123: Some Nitrobenzenes and Other Industrial Chemicals

Lyon, France

9–16 October 2018

PRELIMINARY LIST OF AGENTS TO BE REVIEWED:

2-Chloronitrobenzene (CAS No. 88-73-3)

4-Chloronitrobenzene (CAS No. 100-00-5)

1,4-Dichloro-2-nitrobenzene (CAS No. 89-61-2)

2,4-Dichloro-1-nitrobenzene (CAS No. 611-06-3)



Centers for Disease Control and Prevention
National Institute for Occupational
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1090 Tusculum Avenue
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October 2, 2018

Health Council of the Netherlands
Attn: Mrs. B.E. Smink
PO Box 16052
NL-2500 BB The Hague
The Netherlands

Dear Mrs. Smink:

Thank you for the opportunity to review the draft report on *2,4-dichloro-1-nitrobenzene* and *1,4-dichloro-2-nitrobenzene* prepared by the Subcommittee on the Classification of Carcinogenic Substances of the Dutch Expert Committee on Occupational Safety of the Health Council (DECOS). Additional comments were received from Crystal D. Forester, Research Chemist, NIOSH/National Personal Protective Technologies Laboratory, 1095 Willowdale Road, Morgantown, WV 26505 and are enclosed.

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 draft document on 2,4-dichloro-1-nitrobenzene and 1,4-dichloro-2-nitrobenzene

By: Crystal D. Forester, Research Chemist, NIOSH/National Personal Protective Technologies Laboratory, 1095 Willowdale Road, Morgantown, WV 26505

SECTION & PARAGRAPH	COMMENT
General Comments	The Committee's recommendations are appropriate.
General Comments	Literature cited is appropriate, few studies exist for these chemicals.
General Comments	The conclusion of recommending a classification of both chemicals as 1B is appropriate from the limited in vivo and in vitro studies and the lack of human studies.
Specific Comments	A mention of A Report of the Advisory Group to Recommend Priorities for <i>IARC Monographs</i> during 2015-2019 citing these as priority chemicals is suggested.

Att. Thomas J. Lentz, Crystal D. Forester, Liying Rojanasakul
National Institute for Occupational Safety and Health
1090 Tusculum Avenue
Cincinnati, OH 45226-1998
USA

Date: December 11, 2018 Your ref: Letters dated September 21 and October 2, 2018 E-mail: draftOSH@gr.nl
Encl: 1 Our ref: 1455667/BS/pm/246-L21 Phone: 070 340 7520

Subject: Comments on public draft report 2,4-dichloro-1-nitrobenzene and 1,4-dichloro-2-nitrobenzene

Dear Mr. Lentz, Mr/Mrs. Rojanasakul and Mrs. Forester,

Thank you for accepting the invitation to comment on the draft report 2,4-dichloro-1-nitrobenzene and 1,4-dichloro-2-nitrobenzene, which was published for public review in July 2018 by the Subcommittee on the classification of carcinogenic substances of the Dutch Expert Committee on Occupational Safety of the Health Council of the Netherlands. The Subcommittee highly appreciates the comments made by NIOSH, which enabled the subcommittee to modify and improve its report. On behalf of the President of the Health Council, I give you a reply.

General comment Mr/Mrs. Rojanasakul:

Most critical studies were included. Consider adding: Wilkerson MG, Connor TH, Wilkin JK [1988]. Dinitrochlorobenzene is inherently mutagenic in the presence of trace mutagenic contaminants. Arch Dermatol. 124(3):396-398.

Reply: The aim of the study of Wilkerson et al. was to characterize the effects of traces of known mutagens, e.g., 2,4-dichloronitrobenzene, on a new, commercially available grade of 2,4-dinitrochlorobenzene in the Ames assay. After careful consideration, the Subcommittee decided that this study was not relevant in view of the evaluation of the genotoxicity of the two dichloronitrobenzenes.

Specific Comments Mr/Mrs. Rojanasakul:

- Suggest mentioning that: "The present study was conducted with reference to the OECD Guideline for Testing of Chemicals 451 "Carcinogenicity Studies" (ORCD 1981) and were carried out in conformity with the OECD Principle of Good Laboratory Practice (OECD 1998) where using Ref.#16 Kano et al.."
- Reference resource may include the PubChem (<https://pubchem.ncbi.nlm.nih.gov>), which provides cancer-related information for "compound/2_4-dichloronitrobenzene," such as Hazards Identification, and mutation toxicity.
- Reference resource may include: <https://toxnet.nlm.nih.gov/cgi-bin/sis!search/a?dbs+hsdb:@term+@DOCNO+4267>.

Reply: Thank you for your suggestions. A modification has been made under "5.2.1 Non-human information."

Specific comments Mrs. C. Forester:

A mention of a report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015-2019 citing these as priority chemicals is suggested.

Reply: A modification has been made under “2.3 International classifications”.

The final advisory report ‘2,4-dichloro-1-nitrobenzene and 1,4-dichloro-2-nitrobenzene’ was published on December 11, 2018. It can be found on the website of the Health Council. Also your comments and this letter can be found on the website. The comments and replies by the Committee are available for the public.

Best regards,

Beitske E. Smink, Ph.D.
Scientific secretary