Attn: Ms Berg, Ms Rojanasakul and Ms Whittaker
CDC/National Institute for Occupational Safety and Health
1090 Tusculum Avenue, M/S C-34
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Gezondheidsraad
Health Council of the Netherlands

Date:	6 December 2021	Your ref:	E-mails of June, 2021	Our ref:	-
Phone:	+31 70 340 75 20	E-mail:	GR_OSH@gr.nl	Encl:	1

Subject: Comments on public draft advisory report *1-bromopropane*

Dear Ms Berg, Ms Rojanasakul and Ms Whittaker,

Thank you for accepting the invitation to comment on the draft advisory report on the classification of 1-bromopropane as a mutagenic and carcinogenic substance, which was published for public review in May 2021 by the Subcommittee on the classification of carcinogenic substances of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. The Subcommittee appreciates the valuable comments made by NIOSH, which enables the Subcommittee to modify and improve its report.

On behalf of the President of the Health Council, I would like to inform you about the Subcommittee's replies, which are given on the next pages of this letter.

The final advisory report *1-bromopropane* was published on the website of the Health Council (www.healthcouncil.nl) on 6 December 2021. Also on the website, you can find your comment and this letter, as well as all other comments and replies

Best regards,

Emma E.J. Kasteel, PhD (Ms)
Scientific Secretary

Comments on DECOS draft document on 1-bromopropane

By Shannon Berg, Associate Service Fellow

Page Number, Line Number	NIOSH Comment	Reply by the Subcommittee
Page 4, lines 28-29 Page 5, line 1	NIOSH does not agree with the statement in the Executive Summary concerning insufficient evidence for malignant tumour development in rats. NIOSH recommends reviewing the 1-bromopropane carcinogenicity information discussed in the Report on Carcinogens, Fourteenth Edition [NTP 2016] and the Report on Carcinogens: Monograph on 1-Bromopropane [NTP 2013].	The Subcommittee reviewed the two NTP reports, which are both based on the NTP study from 2011. The Subcommittee agrees with the NTP that there is an increase in intestine adenomas in female rats, and that there is evidence from literature for progression of these adenomas into carcinomas. However, no carcinomas were detected in the NTP study, and the classification system used by the Subcommittee (based on the Globally Harmonized System, GHS) does not allow for classification in category 1B when there is no direct evidence for malignant tumour development in rats; no evidence of intestine carcinomas was found in male or female rats. Also, indeed an increase in combined skin neoplasms is seen, but this (significant) increase is not seen for the two carcinomas included in this combination (basal cell carcinoma and squamous cell carcinoma) and mostly based on an increase in adenomas (keratoacanthomas). The evaluation of the Subcommittee is partly based on the European Union's regulation on classification, labelling and packaging of chemical substances and mixtures (CLP regulation), see 'Guideline to the classification of carcinogenic substances', published by the Health Council in 2010. According to the CLP Annex, "the induction of only benign tumours usually provides a lower strength of evidence for carcinogenicity than the induction of malignant tumours and will usually support Category 2". The Subcommittee also noted the arguments of the NTP for carcinogenicity of 1-bromopropane's metabolites. As no significant increase in carcinomas is detected in rats after 2 years of exposure, the Subcommittee believes that metabolite exposure was possibly insufficient. Altogether, the Subcommittee does agree with the reasoning of NIOSH and NTP, but there is insufficient evidence for classification in category 1B. An explanation has also been added to the advisory report (section 4.4).
Page 13, Table 1	Please verify, as NIOSH was not able to, that cytotoxicity in some trials was seen in the +/- S9 10,000 μg/plate for the Ames test using *E.*	At page 152-153 in the NTP rapport, the results of the Bacterial Mutagenicity study are depicted. Here, it is indicated that 10,000 μg/plate was 'Toxic' in some trials.

	Coli strain discussed in the 2011 NTP Study.	
Page 26, lines 11-13	Respectfully, NIOSH does not agree with the Category 2 classification of 1-Bromopropane discussed in the evaluation of carcinogenicity section. NIOSH believes a Category 1B classification is warranted based on the carcinogenicity information discussed in the following studies: NTP [2011], Morgan et al. [2011], NTP [2013], and NTP [2016].	See the reply above. The Subcommittee acknowledges the findings reported in these studies and agrees with them, but believes this is circumstantial evidence for 1-bromopropane causing malignant tumours in rats. Hence, as the Subcommittee follows the criteria as laid down in the CLP regulation, classification in Category 1B requires a causal relationship between the substance and an increased incidence of *malignant* neoplasm in two or more animal species. Therefore, the Subcommittee believes category 2 classification is appropriate. A remark about the significant concern on the intestine adenomas has been added to the advisory report.

By Liying Rojanasakul, PhD. Research Biologist

PAGE NUMBER, LINE NUMBER	NIOSH COMMENT	Reply by the Subcommittee
Page 19, table 4 and lines 3-5	Page 19, lines 3-5 state: "Effects of 1-bromopropane on DNA single strand breaks and DNA repair were measured in a human hepatoma cell line (HepG2) at concentrations of 25 to 500 ppm (236 to 2,515 mg/m^3)." Question: The "(236 to 2,515 mg/m^3)" is not shown in the original ref.. Are the ppm doses in vitro (in liquid) comparable to the mg/m^3 doses in vivo (in air)? Please explain.	The units have been changed into the units as reported in the orignial reference (ppm). The prefarable (international) unit for *in vitro* studies would be mg/mL or mM, but this is not indicated in the original reference.

Page 19, lines 6-7	"Cytotoxicity was observed at 2,515 mg/m^3." Since this statement is in the same paragraph as the HepG2 cell test, is it based on data of "500 ppm: ±75% cell survival" (see below highlight in table 4)? If so, the unit of "500 ppm" should be included. The mg/m^3 unit suggests animal inhalation concentration but is not common in in vitro studies.	Yes, it is. It is changed to the unit reported in the original reference (ppm).
An additional reference suggestion	"Report on carcinogens monograph on 1-bromopropane". National Toxicology Program Rep Carcinog Monogr. 2013 Sep;(13-5982):1-168. https://pubmed.ncbi.nlm.nih.gov/24810716/ It provides useful information as indicated in the abstract that "Also noted was that 1 bromopropane, either directly or via reactive metabolites, caused molecular alterations that typically are associated with carcinogenesis, including genotoxicity, oxidative stress, and glutathione depletion. These alterations, observed in mainly in vitro and toxicity studies in rodents, are relevant to possible mechanisms of human carcinogenicity and support the relevance of the cancer studies in experimental animals to humans."	This reference has been included in the advisory report.