Gezondheidsraad

Reactie Gezondheidsraad op commentaar conceptadvies Methylisobutylketon

Response Health Council to comments on draft report Methyl isobutyl ketone

Inhoud

1 Reactie op commentaar NIOSH
Response to comments NIOSH

Op 8 december 2020 heeft de Gezondheidsraad per brief gereageerd op het commentaar van het *National Institute for Occupational Safety and Health* (NIOSH) op het concept van het advies *Methylisobutylketon*. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On December 8, 2020, the Health Council sent a letter to the National Institute for Occupational Safety and Health (NIOSH) in response to the comments on the draft report on Methyl isobutyl ketone*. The response is cited below.*

“Thank you for accepting the invitation to comment on the draft advisory report on the classification of methyl isobutyl ketone as a mutagenic and carcinogenic substance, which was published for public review in December 2019 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 like to inform you about the Subcommittee’s replies, which are given on the next pages of this letter.

The final advisory report *Methyl isobutyl ketone* was published on the website of the Health Council (www.healthcouncil.nl) on December 8, 2020. Also on the website, you find your comment and this letter, as well as all other comments and replies.”

By: Robert Streicher, Supervisory Research Chemist

SECTION & PARAGRAPH	**NIOSH COMMENT**	**Reply by the Subcommittee**
General Comments	My background is chemistry, so my technical comments will be limited to the chemistry aspects of this document.	
Specific Comments		
Pg. 10, line 3	Are all the synonyms intended to be English synonyms? All of them are except for “methylisobutylacetone.” Also, the NIOSH Pocket Guide uses “Hexone” as its primary name for MIBK (reference 11 in the draft). This is not a good scientific name, but it suggests that it may be a very common synonym.	The synonyms are added in Section 2.1 of the final advisory report.
Pg. 10, line 7	Surface tension values for MIBK are available in the PubChem entry for MIBK: 23.6 dynes/cm = 0.0236 N/m at 20.0 °C. Link: https://pubchem.ncbi.nlm.nih.gov/	Data on surface tension are added in Section 2.3 of the final advisory report.

	compound/Methyl-isobutyl-ketone#section=Surface-Tension. PubChem cites another source as presumably the primary source of the data: http://cameochemicals.noaa.gov/. However, following the Cameo Chemicals link, and then the search that brings you to the methyl isobutyl ketone page (https://cameochemicals.noaa.gov/chemical/3943) I do not see the surface tension data. Perhaps the values provided on PubChem are not accurate? The surface tension given is quite reasonable for this compound, but the Cameo Chemicals source may be incorrect.	
Pg. 11, line 1	The units for viscosity should be "mPa·s," not "mmPa.s."	Adapted.
Pg. 13, lines 6-7	NIOSH is the National Institute for (not of) Occupational Safety and Health. There is an additional ketones method in the latest (5th) edition of the NIOSH Manual of Analytical Methods: Method 2027. Link: https://www.cdc.gov/niosh/docs/2014-151/pdfs/methods/2027.pdf. We suggest that the other two methods should still be listed, just add 2027. The three methods (1300, 2555, and 2027) use different sorbents for collection of air samples (coconut charcoal, carbon molecular sieve, and silica gel, respectively).	Adapted. Reference is made of NIOSH Method 2027 in Section 4.1 of the final advisory report.
Pg. 15, line 9	"…uptake via de dermal route…" should probably be "…uptake via the dermal route…"	Adapted.
Pg. 15, line 21	The word "in" is missing; suggest changing to "…detectable in the brain…"	Adapted
Pg. 15, line 31	"The metabolite, MIBK,…". Should this be "MIBC?"	Adapted.
Pg. 24, line 30	Should be National Institute for (not of) Occupational Safety and Health.	Adapted.

By: Bingbing Wu, ORISE Fellow

SECTION & PARAGRAPH	**NIOSH COMMENT**	**Reply by the Subcommittee**
General Comments	The Committee's recommendations are appropriate.	
Specific Comments		
Pg. 13, lines 9-10	No biological exposure monitoring data available for MIBK noted in this document. Suggest additional search for biological monitoring studies of MIBK and adding the data if applicable. An example for your reference: Kawai et al. [2003]. Methyl isobutyl ketone	A literature search has been performed on biological monitoring of MIBK. Data are added in the Sections 4.2

	and methyl ethyl ketone in urine as biological markers of occupational exposure to these solvents at low levels. International Archives of Occupational and Environmental Health Vol 76(1):17–23. https://link.springer.com/article/10.1007/ s00420-002-0374-9. Recommend listing the exclusion criteria for studies not included in the review process.	and 6.1 of the final advisory report.
Pg. 15, line 24	Recommend collecting more information from different studies on MIBK elimination route. In this document, it is reported that “0.04% of the total dose was eliminated unchanged through the urine.” However, Kawai et al. [2003] found that approximately 0.12% of MIBK absorbed in the lungs will be excreted in urine.	The study results by Kawai et al. (2003) on urinary excretion are added in Section 6.1.
Pg. 21, line 23	Change “and” to “or” or “nor” in the sentence “not in female rats and in mice.”	Adapted.
Pg. 19, lines 10-11	Suggest rephrasing this sentence to “a statistically significant increase of the incidence of hepatic adenomas and 10 carcinomas (combined) was observed at the highest exposure level.”	Adapted.

2 Reactie op commentaar MIBK REACH Consortium

Response to comments MIBK REACH Consortium

Op 8 december 2020 heeft de Gezondheidsraad per brief gereageerd op het commentaar van het *MIBK REACH Consortium* op het concept van het advies *Methylisobutylketon*. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On December 8, 2020, the Health Council sent a letter to the MIBK REACH Consortium in response to the comments on the draft report on Methyl isobutyl ketone*. The response is cited below.*

"Thank you for accepting the invitation to comment on the draft advisory report on the classification of methyl isobutyl ketone as a mutagenic and carcinogenic substance, which was published for public review in December 2019 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 comments made by the MIBK REACH consortium, which enables the Subcommittee to modify and improve its report.

On behalf of the President of the Health Council, I like to inform you about the Subcommittee's replies, which are given below.

Remaining uncertainties related to CAR/PXR MOA

1) *Relevance for humans has not been investigated*. The ongoing in vitro experiment by the MIBK Consortium could give more insight in the CAR-PXR mode of action for MIBK. However, to assess the relevance of this possible mode of action in MIBK-related tumour development, in vivo carcinogenicity data are needed. For instance by using CAR knock-out mice, and comparing these data with the tumour development in wild type mice. In addition, data are needed which show that the exposure-response relationships of the different endpoint characteristics to a CAR/PXR mode of action are in line with the exposure-response relationships of tumour development. For this reason, the Subcommittee does not expect this in vitro experiment to lead to a final conclusion about its relevance to humans. Therefore, the Subcommittee decided not to wait for the outcome of the experiment. In the event that new data in the public literature becomes available in the future that is relevant to the recommendations, the advice may be updated at the request of the Ministry of Social Affairs and Employment.
2) *CAR/PXR MoA has insufficiently been investigated*. The Subcommittee took notice of the eight points in the RAC opinion to address the limitations of the CAR/PXR mode of action, and your reply on these points to show that there is substantial weight of evidence to support this mode of action. Overall there are indications for a CAR/PXR mode of action for MIBK. However, the point is that this information is almost exclusively based on the study by Hughes et al. (2016), and this is a small base for a strong conclusion. In the Hughes study, the link between the in vitro data of the KO-mice/wild-type mice and the actual

presence of tumours (in vivo) is lacking. For a minimum set of data robust dose concordance between the dose levels that produce each of the early key events (in the short-term study), and those that produce the eventual adverse outcome (in the carcinogenicity study) is needed. In the Hughes study only one dose is included and this information is lacking. Overall, the Subcommittee did not change its opinion.

Evidence related to other uncertainties
The Subcommittee took notice of your letter to the DG Employment regarding the RAC opinion In this letter, the consortium addresses also uncertainties on the relevance of kidney tumours in rats, in particular on the relevance of chronic progressive nephropathy (CPN) as a mode of action, and the relevance of renal mesenchymal tumours in female rats. The Subcommittee considers neither effects of relevance to humans. This is clarified in the Sections 8.1 and 8.2 in the final advisory report.

The final advisory report *Methyl isobutyl ketone* was published on the website of the Health Council (www.healthcouncil.nl) on December 8, 2020. Also on the website, you find your comment and this letter, as well as all other comments and replies."