Gezondheidsraad

Reactie Gezondheidsraad op commentaar conceptadvies Koolmonoxide

Response Health Council to comments draft report Carbon monoxide

Inhoud

1 Reactie op commentaar Mrs. Alexander and Mrs. Estill (NIOSH)

Response to comments Mrs. Alexander and Mrs. Estill (NIOSH)

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Mrs. Alexander and Mrs. Estill (NIOSH) op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 3rd 2024 the Health Council sent a letter to Mrs. Alexander and Mrs. Estill (NIOSH) in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Mrs. Alexander and Mrs. Estill,,

Thank you for accepting the invitation to comment on the draft report ‘carbon monoxide’, which was published for public review by the Health Council in December 2023. The Dutch Expert Committee on Occupational Safety (DECOS) appreciates the thorough review of the report.

The majority of your comments deal with grammatical, editorial and punctuation errors. Where appropriate, the necessary corrections have been made. You further noted that the recommended OEL can in some cases be lower than ambient levels of carbon monoxide. As you mention yourself, the Committee indeed notes that the feasibility is not taken into account.

The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public. In the accompanying email you will find a link to a copy of the final report.

2 Reactie op commentaar Mr. Frank (NIOSH)

Response to comments Mr. Frank (NIOSH)

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Mr. Frank (NIOSH) op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).
On September 3rd 2024 the Health Council sent a letter to Mr. Frank (NIOSH) in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Mr. Frank,

Thank you for accepting the invitation to comment on the draft report 'carbon monoxide', which was published for public review by the Health Council in December 2023. The Dutch Expert Committee on Occupational Safety (DECOS) appreciates the thorough review of the report.

The Committee has supplemented the section on international OELs, as you suggested.

The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public. In the accompanying email you will find a link to a copy of the final report.

3 Reactie op commentaar Dr. Johns (NIOSH)

Response to comments Dr. Johns (NIOSH)

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Dr. Johns (NIOSH) op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).
On September 3rd 2024 the Health Council sent a letter to Dr. Johns (NIOSH) in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Dr. Johns,

Thank you for accepting the invitation to comment on the draft report 'carbon monoxide', which was published for public review by the Health Council in December 2023. The Dutch Expert Committee on Occupational Safety (DECOS) appreciates the thorough review of the report.

You recommend to include the EPA Integrated Science Assessment (ISA) explicitly as a source of scientific data. The Committee notes that the EPA science assessment for carbon monoxide contains a comprehensive overview of the literature, up to 2010. Due to the amount of data and scientific assessments available, not all assessment reports could be included. The Committee has based its review on a selection of reports of other organisations, with a focus on reports specifically addressing worker exposure and aiming to derive a limit value for workers. The Committee has taken note of the EPA ISA report, and has concluded that it does not contain information that contradicts the Committee's conclusions on the critical health effects. Therefore, the Committee has decided not to include EPA afterwards.

The Committee agrees with the EPA conclusion that limited data are available on adverse health effects due long-term low-level exposure (EPA ISA, page 2-6). That is one of the reasons that the Committee selected a meta-analysis and systematic review on cardiovascular disease and relatively short exposures to carbon monoxide (up to 7 days).

You further recommended to include people with cardiovascular disease and obstructive lung disease as a group at extra risk. The committee agrees that these groups of people are more sensitive to carbon monoxide. However, as described in the DECOS guidance document, the committee advises on health-based recommended occupational exposure limits to a healthy workers population. Therefore, people with underlying disease are not included as a group at extra risk.

Finally, as you suggested, the text "and the Environmental Protection Agency (EPA)" was deleted from a sentence on page 32 of the report.

The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public. In the accompanying email you will find a link to a copy of the final report.

4 Reactie op commentaar Dr. Thompson (NIOSH)

Response to comments Dr. Thompson (NIOSH)

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Dr. Thompson (NIOSH) op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 3rd 2024 the Health Council sent a letter to Dr. Thompson (NIOSH) in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Dr. Thompson,

Thank you for accepting the invitation to comment on the draft report 'carbon monoxide', which was published for public review by the Health Council in December 2023. The Dutch Expert Committee on Occupational Safety (DECOS) appreciates the thorough review of the report.

In your commentary, you note that you support the OEL recommended by the Committee. Further, you suggest to correct some grammatical, editorial and punctuation errors. Corrections have been made where appropriate.

The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public. In the accompanying email you will find a link to a copy of the final report.

5 Reactie op commentaar Mr. Hardt (NIOSH)

Response to comments Mr. Hardt (NIOSH)

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Mr. Hardt (NIOSH) op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 3rd 2024 the Health Council sent a letter to Mr. Hardt (NIOSH) in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Mr. Hardt,

Thank you for accepting the invitation to comment on the draft report 'Carbon monoxide' (CO), which was published for public review by the Health Council in December 2023. The Dutch Expert Committee on Occupational Safety (DECOS) appreciates the thorough review of the report.

In your response you focus on the fact that studies on environmental carbon monoxide exposures are used to derive an occupational exposure limit. You note that more discussion about the role of potential confounders in the reported associations with environmental exposures is warranted.

The committee understands your concern and agrees that more explanation is warranted regarding the role of potential confounders. The committee is of the opinion that this role is expected to be limited due to the design of the study by Lee et al. The considerations of the committee have been added to the advisory report (paragraph 8.3).

The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public. In the accompanying email you will find a link to a copy of the final report.

6 Reactie op commentaar Caesar Consult namens Koninklijke Metaalunie en Vereniging FME

Response to comments Caesar Consult on behalf of Koninklijke Metaalunie and Vereniging FME

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Koninklijke Metaalunie en Vereniging FME op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 3rd 2024 the Health Council sent a letter to Koninklijke Metaalunie and Vereniging FME in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Mr.. Halm,

Thank you for accepting the invitation to comment on the draft report *Carbon monoxide*, which was published for public review in December 2023 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. The DECOS highly appreciates the comments made by Caesar Consult on behalf of Koninklijke Metaalunie and Vereniging FME, which enabled the committees to modify and improve its advisory report. On behalf of the President of the Health Council, I send you this reply.

Generally, Caesar Consult is of the opinion that for its draft report, the DECOS does not adhere to its own working methods, as documented in its guideline in 2021. Caesar notes, and finds it undesirable, that the DECOS evaluation has been based on reports of other organisations. I would like to point out that the DECOS guideline allows the use of evaluations by other organisations as a starting point for its evaluation. The DECOS performs systematic reviews when it can not rely on good systematic reviews by others. DECOS always strives for a systematic and transparent approach to reviews.
Depending on the data available, the DECOS selects the most appropriate data and evaluates the scientific basis. In case of carbon monoxide, the DECOS outlined its choice for a WHO report on air quality guidelines that uses a study by Lee et al. The DECOS strongly disagrees with the statement made by Caesar that reports of other organisations have been disqualified as these reports were not used as single primary source. The DECOS has evaluated these reports thoroughly and has taken them into account for its recommendations.
Caesar also notes the difference in approach for carbon monoxide and respirable crystalline silica, which is drafted in collaboration with the NEG. This difference is not related to the collaboration with the NEG but to the differences in types of adverse effects, modes of action and available data. Most notably, the physiological role for endogenous carbon monoxide and

lack of reliable occupational epidemiological studies have made the DECOS decide to take a more pragmatic approach for carbon monoxide.

For a response on specific comments made by Caesar related to the content of the draft report, I refer to the Annex of this letter. The final advisory report *Carbon monoxide* will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public.

LOCATION (CHAPTER, PAGE, LINE)	COMMENTS REVIEWER	REPLY COMMITTEE
Page 9, line 8-8	DECOS is kindly requested to include the letter from the Minister of SZW with the formal request for advice on carbon monoxide in the appendix of the report.	The formal request concerns a general request for advice that is not specific to CO. This information is added to the report.
Sources. Page 14, line 27-30	DECOS is kindly requested to explain what is meant by troposphere.	An explanation of the term troposphere is added.
Kinetics. Page 21, line 8 – 14	DECOS is kindly requested to provide the elimination half-live (t1/2) of COHb under standard conditions among adults: about 4 – 5 hours.	DECOS notes that a value of almost 5 h is already specified in the text.
Mechanism of toxicity. Page 21, line20 until page 23, 1 - 2	DECOS is kindly requested to consider the proposed text adjustments in this chapter 7. Mechanisms of toxicity.	The proposed adjustments have been made in the final report.
Effects. Page 24, line 1	DECOS is kindly requested to consider the proposed adjustment of the title of chapter 8.	The proposed adjustments have been made in the final report.
Effects. Page 40, line 15-16	DECOS is kindly requested to consider an extra paragraph '§ 8.1.8 Summary of evaluations by other expert groups' and to add a table that summarizes the identified critical effects and recommended limit values.	A table summarising the OELs and underlying critical effects has been added.
Effects. Page 40, line 16 until page 49, line 10	DECOS is kindly requested to report whether recently published literature provide new insights regarding the critical health effects of carbon monoxide, and whether there are any studies recently published that can/should be regarded as new key studies (revision of § 8.2 and § 8.3).	A conclusion on the critical health effects and key studies regarding recent literature has been added.
Effects. Page 47, line 31 – page 49, line 11	DECOS has chosen to put aside findings from other expert groups and to put aside studies using COHb as exposure measure,	A well-known volunteer study was published by Allred et al was commissioned by the US EPA from the Health Effects Institute (HEI) in 1983 to

	occupational exposure studies and even volunteer studies!? DECOS does not seem to realize that the uncertainties associated with epidemiological studies of the effects of an air pollutant such as carbon monoxide in the general population, are much greater. This concerns uncertainties that arise from, among other things, the relatively low level and low variation in exposure, the exposure characterization of the general population and possible contribution of other (confounding) air pollutants such as nitrogen dioxide.	provide a scientific basis for the CO National Ambient Air Quality Standards. Since Allred et al only studied 50- to 70-minute exposures that ranged from 42 to 357 ppm, their results should not be cited as evidence that any lower level of exposure is safe over 8 hours. Such volunteer and occupational studies cannot be extrapolated with any clinical or statistical confidence to much lower and/or longer CO exposures. The diagnostic procedures will not change substantially (or at all) between high CO days and the reference days as they are reasonably close in time. This is a benefit of such short term evaluations over chronic studies making potential confounding by factors that do not change day-today (such as smoking and lifestyle factors) of less concern. Other time-varying air pollutants can still be potential confounders due to correlation with carbon monoxide, which is the reason why Lee et al. concluded the evidence to be of moderate certainty. This is clarified in the advisory document (paragraph 8.3).
Page 51, line 15 – 21	DECOS is kindly requested to adjust and correct the calculation of the HBR-OEL.	The calculation is done according to the guidelines. The mentioned correction factors of difference in exposure weeks per year and difference in years of exposure are only used for (cancer) risk values and not for deviating HB-OELs. The noted level of protection by limit values (99% for general public; 95% for workers) is not taken into account conform the DECOS guidance.

7 Reactie op commentaar Mr. Donnay

Response to comments Mr. Donnay

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Mr. Donnay op het concept van het advies Koolmonoxide. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 3rd 2024 the Health Council sent a letter to Mr. Donnay in response to the comments on the draft report on Carbon monoxide. The response is cited below.

Dear Mr. Donnay,

Thank you for accepting the invitation to comment on the draft report Carbon monoxide, which was published for public review in December 2023 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. The DECOS highly appreciates the comments by Donnay Detoxicology LLC, which enabled the committee to modify and improve its report. On behalf of the President of the Health Council, I give you a reply.

In a large part of your comments, you address the publications and scientific data used by the DECOS. You justly note that the scientific literature used was not adequate according to the issues specified in the covering letter accompanying the public consultation, namely (1) “the publications and scientific data used (is the report comprehensive and exhaustive?”, (2) “the interpretation of the scientific data”, and (3) “errors and inconsistencies”. For the evaluation of carbon monoxide, the committee decided to deviate from its general approach for recommending classifications and health-based occupational exposure limits (HBR-OEL). The committee has decided to, rather than aiming to be comprehensive and exhaustive, use assessment reports previously published by other scientific organisations as a starting point and only address underlying literature when considered necessary. The general covering letter for the public consultation round was not adapted appropriately to the working method applied for the advice on carbon monoxide. Furthermore, for the additional literature search, only literature was used involving low carbon monoxide exposures and addressing only the critical endpoints. For the subsequent selection of the literature, criteria were used as specified in the advisory report.

For a response on the specific comments I refer to the Annex of this letter. The final advisory report Carbon monoxide will be published on the website of the Health Council on September 3rd 2024, including your comments and this letter by the committee. All comments and replies are available to the public.

Comment	COMMENTS REVIEWER	REPLY COMMITTEE
Comment 1.3	In the description of the search criteria used to find studies about “carbon monoxide” and “occupational exposure”, the authors say they searched for articles published “from 2012 until March 2023.” But on page 10 at line 14 they wrote “up to April 2023.” This is inconsistent. […] I recommend the authors relax some of their exclusion criteria and reevaluate the results so their review may be	The inconsistency was deleted. . … For the purpose of deriving a HBR-OEL, quantification of exposure is essential. Therefore the DECOS is of the opinion that searching for ‘carbon monoxide’ and ‘occupational exposure’ and subsequent selection based on abstract is acceptable. Furthermore, no key literature is identified

	informed by at least some studies of occupational CO exposures published after 2012.	in the literature provided in your commentary.
Comment 1.4	In Appendix A starting on page 61, the authors present short descriptions and results from what they consider the most relevant results from 18 prenatal and perinatal animal studies of CO. But Appendix A does not give references for any of these studies, so there is no way to easily identify them in the literature list starting on page 54. There is no reason to include results of animal studies in this review of human occupational exposures, so I recommend not including them in the literature list. If they are removed, I recommend that Appendix A be replaced with a similar appendix giving details of much more relevant studies of CO exposure in humans. Whatever types of studies are included in Appendix A, the source of each should be identified and linked by either a number or the last name of the first author and year of publication (name, year) so the reader can look up the full references in the literature list.	The references in the draft report were specified by number in the last column of the table (under 'remarks'). In the final report, the references have been specified more clearly. The DECOS notes that these developmental studies were not part of the occupational literature, but were separately addressed for the purpose of deriving a HBR-OEL since developmental toxicity has been identified as critical endpoint for carbon monoxide. Although epidemiological data are preferred, animal data should also be considered and evaluated. In Chapter 9, the DECOS explains why these data were not used.
Comment 1.5	Unlike with the animal studies discussed in comment 1.4 above, the report does not contain any appendix with the results of human CO studies. Instead, several tables are given in the report that contain short unreferenced descriptions of what the authors consider the most important human CO studies and results that other governments and scientific organizations have cited in their self-published reports about CO health effects and exposure limits. I recommend that all studies from which any results are presented in any section or table of the final report be linked to a full reference in the literature list that starts on page 54. I am not making any accusations here, but according to the Committee on Publication Ethics (COPE), republishing the results of other previously peer-reviewed and published studies without including a reference to the original work or any other acknowledgment of the actual authors is considered a form of plagiarism that warrants correction (as shown in this flowchart: https://publicationethics.org/resources/flowcharts/plagiarism-published-article).	The DECOS notes that also the most recent information on human cardiovascular effects of carbon monoxide were individually summarised in the draft report. The DECOS agrees with your critical comments on including tables of unreferenced literature. These tables have been deleted from the final report.
Comment 1.6	Among the unreferenced human CO studies mentioned in comment 1.5 is one that is described slightly differently in each of the tables in which it is described, as shown below […]. This is inconsistent. I recommend that this and any other study summarized in more than one table should be described in exactly the same way, as well as referenced	See reply to comment 1.5.

	the same way, so this is not hidden from readers.	
Comment 2.1	The authors derive an occupational limit for CO of 7.5 mg/m3 average over 8 hours by applying various correction factors to the WHO's 24-hour average CO guideline of 4 mg/m3. Critically, the report does not cite any studies of any kind that tested 8-hour CO exposures up to an average of 7.5 mg/3 to see what effects they produce in working adults. So the authors cannot credibly say this level will be safe workers of all ages and genders. The WHO 2021 review made the same mistake, recommending a CO limit of 4mg/m3 as protective even though all the epidemiology studies its contractor reviewed found significantly increased risks of cardiovascular disease and death at lower levels of 24-hour exposure. I recommend that the authors acknowledge this shortcoming and propose a lower occupational limit for 8 hours based on a broader review of the epidemiology literature (see comment 2.3 below).	Studies related to 8-hour CO exposures up to an average of 7.5mg/m3 were not available. Also specific data on ages and gender are not available. Therefore, the DECOS applies default assessment factor to account for intra-and interindividual differences, as specified in its guidance (Guidance for recommending classifications and health based occupational exposure limits | Other | The Health Council of the Netherlands).
Comment 2.2	The authors say there is not enough evidence to set a 15-minute short-term exposure limit (STEL, and at line 16, they say the same about a Ceiling limit for immediate evacuation. I oppose the decisions to not recommend STEL or ceiling limits as they are not based on an exhaustive and comprehensive review of the available literature on occupational CO poisonings, as discussed in Comment 1.2. These limits are needed to protect workers who might otherwise be legally exposed to much higher levels over shorter times, such as over 120 mg/m3 for 30 minutes. The current limits are better than nothing and should be retained if the authors cannot find any evidence to warrant lowering them. Given that employers and workers have become accustomed to working with their limits, they should not be discarded without some replacement. I recommend that the authors recommend a one-hour average CO limit that is no more than quadruple their 8-hour limit, and a STEL limit that is no more than double their 1-hour limit.	The DECOS notes that a STEL is only recommended when scientifically substantiated. No literature was available to the DECOS to derive a limit value for 15 min exposures.
Comment 2.3	I welcome the inclusion of 6 air pollution epidemiology studies that all found statistically significantly increased rates of hospitalization or death for mostly cardiac-related disorders correlated with small increases in ambient CO of just 1 or less above low background levels, below 3ppm. But I disagree with the authors' decision to limit their review to these studies. There are	The selection and use of literature was outlined previously in this letter. With respect to the air pollution epidemiology studies, the DECOS considered address the meta-analysis by Lee et al. most relevant for deriving a HBR-OEL, as has been outlined in Chapter 9.

	more than 720 other air pollution epidemiology studies published between 2012 and March 2023 that indicate workers would be at much greater risk for adverse outcomes if they were exposed to CO up to 7.5 mg/m3 average over 8 hours compared to if their average CO exposure was kept below 1 ppm. I recommend that the authors acknowledge that all the epidemiology studies of CO ambient exposures published from 2012 through March 2023 that found statistically significant risks of adverse outcomes associated with increases in CO exposure found these risks in environments where CO never exceeded 5 ppm and the 8-hour and 24-hour means remained below 2 ppm.	
Comment 2.4	On page 12 starting at line 15: The authors incorrectly describe pulse oximeters that can measure CO, which they should describe as "pulse CO oximeters that use a fingertip clip or skin patch to give an estimate of arterial COHb." I recommend the authors also mention these pulse CO oximeters display a trademark measure that Masimo, the US-based developer, calls SpCo™ -- which is closer to arterial COHb than venous (just as SpO2 measured with traditional pulse oximeters is closer to arterial O2Hb). Whether or not SpCO overestimates arterial COHb is not clear since most published studies compared it only to venous COHb, under the mistaken belief that they would not be significantly different.	The suggested correction of the described pulse oximeter was made in the final report. With respect to the additional information on oximeters, the DECOS is of the opinion that this level of detail is out of the scope of the report.
Comment 2.5	On page 52 starting at line 1: in the discussion of Groups at Extra Risk, I recommend the authors also list occupations that require working in confined microenvironments with limited ventilation in which lower acceptable levels of chemical exposure levels and/or shorter exposure times are recommended or required to protect against higher risks of poisoning and death, such as in mines, tunnels, storage tanks and silos, vehicles, enclosed garages, submarines, tanks, aircraft, and below deck on ships.	The DECOS notes that groups of extra risk are identified irrespective of the anticipated exposure levels. The groups you specify have extra risk of exposure, however, exposure exceeding the recommended OEL should not occur.
Comment 2.6	On page 18 at line 12: Authors correctly note that "Carbon monoxide is not classified for carcinogenic properties." But this concise wording is not the whole truth and conceals more than it discloses. I assume the authors verified this claim by looking up carbon monoxide in at least one database of carcinogens that have been classified by organizations such as the IARC and not finding it. But the fact that CO has not yet been evaluated by any cancer organizations does not mean CO has no carcinogenic	See the DECOS' general response on the search and use of literature.

	properties. It also does not excuse the authors from considering the peer-reviewed literature on this vital topic, at least that published from 2012 until April 2023, to be consistent with the method they used to review all the other potential adverse health effects of occupational CO exposures.	
Comment 3.1	Authors acknowledge they deviated from the standard DECOS guidance for recommending health-based occupational exposure limits: "Given the complex toxicity profile of carbon monoxide (i.e. several potential health effects that **might occur at a similar (low) exposure levels)** and the large amount of available data, the Committee has decided to use assessment reports previously published by other scientific organisations as a starting point, and only address underlying literature when needed. These reports were assessed for the quality of systematic approaches and considered for evidence that could support an 8h time-weighted average (TWA) exposure limit, a 15-min STEL, or a ceiling value." (emphasis added) I recommend the bold phrase be changed to "that may occur at low exposure levels"	This was adapted in the final report.
Comment 3.2	the authors include 5 papers published from 2000 to 2017 (#24, 25, 27, 28, and 30), that discuss the clinical management of acute non-occupational CO poisonings caused by high exposures, which should have been excluded according to the search criteria on page 74. This is inconsistent. I recommend the authors either delete these references and all discussion of them in the text, or change their report's exclusion criteria on page 74 to allow reports of acute non-occupational CO poisoning.	These references apply to the descriptive chapters on toxicokinetics and modes of action, which are largely based on data on acute exposures. Data on CO poisoning was not included in the Chapter on the recent literature and was not used for deriving an 8h-HBR-OEL.
Comment 3.3	The authors do not mention any studies of CO exposure that reported both arterial and venous COHb levels. As shown in the scatterplots below, arterial and venous CO are rarely the same and not consistently correlated. Arterial COHb is usually but not always greater than venous and differences up to 46% have been reported. Full references for these studies are given below the figure along with abstract and doi where available. These studies cast doubt on how to interpret results of the majority of CO exposure studies, including all the ones cited in the report, that only reported arterial or venous CO without identifying which was greater. For this reason, I recommend that the authors add these references in the literature list starting on page 54.	Chapter 2.2.2 indeed discusses the lack in correlation between COHb as a general biomarker for carbon monoxide exposure and the occurrence of adverse effects, and is therefore not considered further in the report. The DECOS considers the recommended literature on COHb of to much detail for the scope of this report.
Comment 3.4	the authors include 5 studies (#24, 25, 27, 28, 30) that describe the management of acute poisoning cases caused by high CO	See reply to comment 3.2

	exposures, which the methodology section of the report says were excluded. This is not consistent. I recommend the authors either delete these references and all discussion of them in the text, or change the methodology section to acknowledge that reports of acute CO poisoning were considered.	
Comment 3.5	Table of Contents is missing a line for the (cited) Literature section, which starts in text on page 54 at line 1 and runs the end of page 58. This section should be identified as number 10 in both the table of contents on page 3 and in the text on page 54.	This has been adapted.
Comment 3.6	ACHIH should be ACGIH, and Biological Exposure Indice should be Index (or Indices if plural).	This has been adapted..
Comment 3.7	The last line in this table for US OSHA does not show any STEL for CO. This is an error. OSHA has long had a regulation requiring the evacuation of workers when CO is over 100ppm. Unfortunately, this only applies to workers in marine terminals, but I still recommend including it because there are many marine terminals in the Netherlands.	DECOS recommends limit values applicable to the general working population and not recommend for specific occupations. Therefore, the DECOS has decided not to add the specific limit for marine terminal workers to the report.
Comment 3.8	the same range of expected COHb (1-5%) is given for exposure to 10 ppm (which can at most raise COHb to 2%, given approximately 5ppm per 1% COHb) and exposure to 20 ppm (which can raise COHb to 4%). This is an error. I recommend authors correct this by deleting all discussion of this study since it is from a 1958 study that is no longer available and cannot be checked.	This concerns a summary of the WHO indoor air quality report and is meant to be descriptive. The DECOS' evaluation of previous reports and recent literature (section 8.3) did not consider this specific reference from 1958 to be relevant for HBR-OEL derivation.
Comment 3.9	A report is cited as NRC 2010. But NRC does not appear in the literature list that starts on page 54. This is an error. I recommend the authors correct this by adding the full reference below to the literature list US National Research Council Committee on Acute Exposure Guideline Levels. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 8. Washington (DC): National Academies Press; 2010.	This has been adapted.
Comment 3.10	the authors refer to "existing criteria documents (NEG, WHO, EU, NIOSH, DECOS)." But there are no references for any documents by the EU, NIOSH or DECOS in the literature list that starts on page 54. This is an error. I recommend the authors correct this by adding full references in the literature list. I am unable to provide them here because I do not know what "criteria documents" the authors are writing about.	See reply to comment 3.9.
Comment 3.11	"WHO report indoor air quality", the authors review a WHO report published in 2010, for which the reference given in the literature list	The reference was adapted. However ,the statement that the 2010 report is outdated is incorrect as the 2010 report concerns

	on page 54 is “WHO. World Health Organization. WHO guidelines for indoor air quality: selected pollutants. 2010; ISBN 978 92 890 0213 4.” This is incorrect. This is actually a report of the WHO Regional Office for Europe (as shown on the cover and repeated on the title page at https://iris.who.int/bitstream/handle/10665/260127/9789289002134-eng.pdf?sequence=1). I recommend the authors correct this in the literature list. … More importantly, the 2010 report is outdated by a 2021 report from WHO entitled Global Air Quality Guidelines: particulate matter (PM2.5 and PM10), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide, which is already in the literature list (#9) and online here https://iris.who.int/bitstream/handle/10665/345329/9789240034228-eng.pdf The 2021 report is discussed later in section 8.1.7, starting on page 28 at line 2, which (confusingly!) has the exact same title as section 8.1.3 (“WHO report indoor air quality”). This is inconsistent since the reports reviewed in 8.1.3 and 8.1.7 do not have the same title, publisher, or scope: the 2010 is focused exclusively on indoor exposures while the 2021 applies explicitly to both indoor and outdoor non-occupational exposures. I recommend the authors merge section 8.1.3 and 8.1.7 into a new section entitled “WHO air quality guidelines.” The most recent global guidelines from 2021 should be discussed first in this section (what is now 8.1.7), followed by the now superseded guidelines for Europe from 2021 (what is now 8.1.3), which the authors should note allowed 75% more CO over a 24-hour average (7 mg/m3 instead of the current 4). In this way, the report can still include the authors’ reviews of the 4 occupational studies (starting on page 31 at line 2)that were included in the 2010 guidelines but not the 2021. The authors also should note that, although the global WHO guidelines from 2021 cite the same 1-hour and 8-hour average CO exposure limits as WHO Regional Office for Europe published in 2010, the 1-hour limit of 35 mg/m3 is 17% higher than 30 mg/m3 the WHO recommended in 2000, in the second edition of its Guidelines for Air Quality (see Table 2 on page 32 at https://iris.who.int/bitstream/handle/10665/107	indoor air quality and the 2021 report concerns outdoor air quality.

	335/9789289013581-eng.pdf). The WHO has never published any explanation of this change, so it is not publicly known whether this was done inadvertently or because of new studies showing people can tolerate a higher level of CO exposure for one hour than previously thought. If the authors make these changes, they will also need to change the following phrase that appears on page 34 starting at line 18, in reference to the Sari study of indoor barbecue workers. I recommend changing from: “which is summarised in section on the WHO indoor air report (2010) (see Section 8.1.3 ‘WHO report outdoor air quality’).” to: “which is summarised in a report by the WHO Regional Office for Europe on guidelines for indoor air quality (2010).”	

8 Reactie op commentaar Prof. Lindhout

Response to comments Prof. Lindhout

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Prof. Lindhout op het concept van het advies Koolmonoxide. De reactie staat hieronder.

On September 3rd 2024 the Health Council sent a letter to Prof. Lindhout in response to the comments on the draft report on Carbon monoxide. The response is cited below, in the same language as the original comments (Dutch).

Geachte Prof. Lindhout,

Dank voor uw interesse in het conceptadvies over koolmonoxide. In een email d.d. 10 januari 2024 wijst u op de mogelijke late effecten van koolmonoxide-blootstelling, en de mogelijke relevantie voor de werkplek (zoals bij accidentele blootstelling).

De commissie GBBS adviseert over het veilig werken met stoffen, indien mogelijk leidt de commissie gezondheidskundige advieswaarden af voor een hele werkdag (de 8-uurswaarde) en een waarde om te beschermen tegen piekblootstellingen (de 15-min STEL). Uitgangspunt voor het afleiden van de 8-uurswaarde zijn gegevens over schadelijke effecten die als eerste optreden na langdurige blootstelling. Dit betreft concentraties die niet tot acute vergiftiging leiden. Voor de 15-min STEL worden wel gegevens over acute vergiftiging gebruikt, echter, vaak ontbreekt er betrouwbare informatie over de exacte concentratie en tijd van blootstelling om een 15-min STEL af te leiden. Bovenstaande is ook van toepassing op de literatuur die u aandraagt over neurologische effecten die beschreven zijn na relatief hoge koolmonoxide blootstelling.

Het advies over *Koolmonoxide* zal worden gepubliceerd op de website van de Gezondheidsraad op 3 september 2024 inclusief uw commentaar en deze brief. Alle commentaarbrieven en reacties daarop zijn publiekelijk beschikbaar.

9 Reactie op commentaar Mr. Van Slooten

Response to comments Mr. Van Slooten

Op 3 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Mr.. Van Slooten op het concept van het advies Koolmonoxide. De reactie staat hieronder.

On September 3rd 2024 the Health Council sent a letter to Mr.. Van Slooten in response to the comments on the draft report on Carbon monoxide. The response is cited below, in the same language as the original comments (Dutch).

Geachte heer Van Slooten,

Dank voor uw interesse in het conceptadvies over koolmonoxide. In uw commentaar, ontvangen per email op 6 april 2024 deelt u uw eigen ervaring over nadelige gezondheidseffecten door blootstelling aan koolmonoxide en de rol van endogeen koolmonoxide. Daarbij wijst u op een gebrek aan bewustzijn over de gezondheidsrisico's en een gebrek aan doeltreffende maatregelen.

De commissie GBBS adviseert op basis van de stand van de wetenschap over het veilig werken met stoffen, indien mogelijk leidt de commissie algemene gezondheidskundige advieswaarden af. De commissie begrijpt de punten die u aandraagt over risico's van koolmonoxide in specifieke situaties en de beperking ervan, maar wijst er op dat deze buiten de strekking van het advies vallen.

Het definitieve advies over koolmonoxide zal worden gepubliceerd op de website van de Gezondheidsraad op 3 september 2024, inclusief uw commentaar en deze brief. Al het commentaar en reacties daarop zijn publiekelijk beschikbaar.