Gezondheidsraad

Reactie Gezondheidsraad op commentaar conceptadvies Respirabel kristallijn silica

Response Health Council to comments draft report Respirable crystalline silica

Inhoud

1 Reactie op commentaar NIOSH
Response to comments NIOSH

Op 10 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van het NIOSH op het concept van het advies Respirable crystalline silica. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).
On September 10, 2024, the Health Council sent a letter to the NIOSH in response to the comments on the draft report on Respirable crystalline silica. The response is cited below.

Dear Mr. Esswein, Mr. Sussel, Mr. Joseph, Mr. Wang and Ms. Rice,

Thank you for accepting the invitation to comment on the draft report *Respirable crystalline silica*, 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 and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The DECOS and NEG highly appreciate the comments made by NIOSH, which enabled the committees to modify and improve its final advisory report. On behalf of the President of the Dutch Health Council, I give you a reply.

Concerning procedures following a recommendation by DECOS
For RCS the committees have recommended a prohibition (or high) risk level and a target (or low) risk level. After publication of this report, the economic and technical feasibility of the recommended cancer risk values will be investigated by an advisory body in which employers, employees and independent experts work together. The Dutch Minister of Social Affairs and Employment will then decide on the concentration level of a legal occupational exposure limit for RCS in the air for the Dutch working population. The committees only make health-based recommendations for occupational exposure limits. The feasibility of such a recommendation does not fall under the scope of the advisory reports of DECOS and NEG.

Editorial comments
All relevant editorial comments have been adapted in the final advisory report.

Information on analytical methods
The information on analytical methods presented in Tables 3 and 4 have been updated.

Figure 1
Figure 1 has been developed by a graphic designer working for the Dutch Health Council. It is based on other figures derived from literature and edited according to the insights of the committees.

Research needs
The committees agree on including the development of highly sensitive and practical methods to improve early and accurate detection of RCS-related pulmonary diseases. The chapter on research needs in the final advisory report has been adapted accordingly.

References
The entire reference list has been checked and adapted for the final advisory report.

Abbreviations in Annex B (now Annex II)
The committees have extended the list with missing abbreviations. However, the committees assumed it unnecessary to add units of measure to the list of abbreviations.

The final advisory report *Respirable crystalline silica* has been published on the website of the Health Council on September 10, 2024, including your comments and this letter by the committees. All comments and replies are available for the public.

Kind regards,

Daisy Boers, PhD
Scientific secretary
Health Council

2 Reactie op commentaar Eurosil
Response to comments Eurosil

Op 10 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Eurosil op het concept van het advies *Respirable crystalline silica*. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).
On September 10, 2024, the Health Council sent a letter to Eurosil in response to the comments on the draft report on Respirable crystalline silica. The response is cited below.

Dear Ms. Lumen,

Thank you for accepting the invitation to comment on the draft report *Respirable crystalline silica*, 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 and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The DECOS and NEG highly appreciate the comments made by Mr. Mundt, Mr. Thompson, and Mr. Birk on behalf of EUROSIL, which enabled the committees to modify and improve its advisory report. On behalf of the President of the Dutch Health Council, I give you a reply.

Considering the procedures following a recommendation by the committees
DECOS and NEG evaluate the toxic properties and health effects of occupational exposures to hazardous substances to help protect workers against the potentially harmful effects of these hazardous substances. In that course the committees recommend health-based occupational exposure limits. In the case of HBC-OCRVs the committees recommend a prohibition (or high) risk level as well as a target (or low) risk level. After publication of this report, another advisory body will investigate the economic and technical feasibility of the recommended cancer risk values. The Dutch Minister of Social Affairs and Employment will then decide on the concentration level of a legal occupational exposure limit for RCS in the air for the Dutch working population. The committees only make health-based recommendations for occupational exposure limits. The feasibility of such a recommendation does not fall under the scope of the advisory reports of DECOS and NEG.

Validity of historical occupational exposures
The reviewers expressed their concern about the amount of variance in the modelled RCS exposures that could not be explained. The variance in the modelled RCS exposures, is indeed not all explained, as is described in Peters et al. (2011). However, this publication also indicates the sources of this variability. Furthermore, the presented ORs in the study by Ge et al (2020) are not expected to be affected by the unexplained variance. The robustness of the SYNERGY data is also demonstrated by Ohlander et al. (2024), who investigated the effect of differences in dimensions (e.g., job-specific, region-specific, prior expert ratings) in SYN-JEM on occupational RCS exposure estimates and associated risk of lung cancer. The results showed little difference between versions of SYN-JEM. The original SYN-JEM, as applied by Ge et al

(2020), provided the best model fit. The final advisory report has been adapted at this point and updated with the reference of Ohlander et al. (2024)
Furthermore, the reviewers are concerned about the possibility of bias in the exposure assessment because it relied on recalled and self-reported occupational histories and exposures. The occupational histories were self-reported, which are typically well-recalled by subjects. The occupational exposures, however, are explicitly *not* self-reported because that might have incorporated recall bias in the data. The historical occupational exposures were assigned based on modelled personal measurement data.

No clear association between RCS exposure and lung cancer
The committees are of the opinion that there is ample epidemiological evidence for a causal relationship between occupational RCS exposure and lung cancer. Also, IARC and others have classified RCS as a human carcinogen. IARC has already done so in 1997, the classification was reinforced with new evidence in an update in 2012.
Furthermore, the committees believe that the results from table 2 in the publication by Ge et al. (2020) clearly demonstrate an association between respirable quartz exposure and lung cancer, also at lower cumulative respirable quartz concentrations.

Smoking remains the strongest common cause of lung cancer
Smoking is a well-known risk factor for lung cancer. However, in the publication by Ge et al. (2020) significant exposure-response relationships were reported even after adjustments for smoking habits (including information on pack-years and time since quitting). The stratified analyses by smoking status show the same pattern across the strata compared to the analysis in Table 2. The group of never smokers in the stratified analysis (Table 5) is, however, relatively small and therefore not all categories show statistically significant effects. The test for trend is on a continuous scale and significant as is for the other strata in the stratified analysis for smoking. The committees have stated this more clearly in the final advisory report.

Incorrect statement in draft report stating the 'the stratified analyses showed that regardless of smoking status, increasing cumulative silica exposure was associated with increasing risk of lung cancer'.
The committees are of the opinion that Table 5 shows that among the higher cumulative exposure category (≥2.4 mg/m^3-years) ORs among never, former and current smokers show a rather similar effect (ORs are 1.40, 1.47, and 1.39 for never, former, and current smokers respectively) indicating an effect of cumulative respirable quarts exposure on lung cancer regardless of smoking status. In addition, the lower cumulative exposure category shows a similar but smaller increased risk of lung cancer due to occupational exposure to RCS among never, former and current smokers. The committees have made some edits to the text of the final advisory report to clarify their statement.

The final advisory report *Respirable crystalline silica* has been published on the website of the Health Council on September 10, 2024, including your comments and this letter by the committees. All comments and replies are available for the public.

Kind regards,

Daisy Boers, PhD
Scientific secretary
Health Council

3 Reactie op commentaar Koninklijke metaalunie en vereniging FME

Response to comments *Koninklijke metaalunie en vereniging FME*

Op 10 september 2024 heeft de Gezondheidsraad per brief gereageerd op het commentaar van Koninklijke Metaalunie en Vereniging FME op het concept van het advies *Respirable crystalline silica*. De reactie staat hieronder, in dezelfde taal als het oorspronkelijke commentaar (Engels).

On September 10, 2024, the Health Council sent a letter to Koninklijke Metaalunie en Vereniging FME *in response to the comments on the draft report on Respirable crystalline silica. The response is cited below.*

Dear Mr. Halm,

Thank you for accepting the invitation to comment on the draft report *Respirable crystalline silica*, 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 and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The DECOS and NEG highly appreciate 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 give you a reply.

Concerning procedures and possible consequences following a recommendation by DECOS
DECOS and NEG evaluate the toxic properties and health effects of occupational exposures to hazardous substances to help protect workers against the potentially harmful effects of these hazardous substances. In that course the committees recommend health-based occupational exposure limits. In the case of HBC-OCRVs the committees recommend a prohibition (or high) risk level as well as a target (or low) risk level. After publication of this report, another advosiry body will be asked to evaluate the social-economic and technical feasibility of the recommended cancer risk values. The Dutch Minister of Social Affairs and Employment will then decide on the concentration level of a legal occupational exposure limit for RCS in the air for the Dutch working population.

Working method not according to guidelines
The committees are of the opinion that the working method, as applied to respirable crystalline silica, was according to guidelines. The committees could use several good, thorough and some even recent evaluation reports as a basis for the overview on toxicity. An additional literature search was carried out, specifically for epidemiological studies with quantitative exposure response data, for more information on health effects in relation to RCS exposure. The availability of quantitative exposure-response data (in humans) is crucial to establish a possible causal relation as well as to derive a health-based occupational exposure limit. The committees clearly report in the guidelines that for the derivation of an occupational exposure limit, the

committees prefer to use epidemiological studies in occupational settings if available, because these data reflect actual exposures in workers in working conditions.

No thorough evaluation of toxicological studies
The committees focussed on thorough evaluations by other organisations and epidemiological studies with quantitative exposure-response data, but that does not mean that other types of studies were neglected. The DECOS subcommittee for instance used predominantly toxicological studies for their evaluation on the carcinogenic mechanism of RCS.

Re-assess the critical health effect
The committees are of the opinion that they have made a thorough evaluation on the possible health effects that could serve as a critical health effect. There is sufficient evidence from the available literature to conclude that there is a causal relation between occupational exposure to RCS and silicosis as well as lung cancer. There is also evidence that both health effects may occur at low exposure levels. Considering the possible underreporting of silicosis and the better diagnostics and reporting of lung cancer, the committees decided on lung cancer for the critical health effect in the assumption that the resulting cancer risk level also protects against other health effects. The committees have addressed this point more clearly in the final advisory report.

Re-assess the mode of action
The committees will not re-assess the mode of action (MoA). The committees admit and report clearly in the advisory report that the carcinogenic mechanism primarily results from indirect genotoxic mechanisms. The committees also acknowledge that thus far there is no evidence that RCS can enter the nucleus, however based on a limited number of studies. Apart from that, the committees also note that RCS can form ROS directly at the particle surface. Of ROS we know, in general, that these can enter the nucleus. In the Guideline for the Classification of Carcinogenic Substances it is noted that substances that generate ROS are considered as direct genotoxic substances as well. A direct genotoxic mechanism is not very likely, but considering the limited number of studies and that RCS can directly generate ROS at their surface, the possibility of a direct genotoxic mechanism cannot be excluded. In addition, if a direct genotoxic mechanism cannot be excluded or when the genotoxic mechanism is not clear than it is common practice (according to DECOS guidelines as well as ECHA, NFA and NEG) to take a precautionary approach and assume a non-threshold or risk-based approach.

The wrong approach (risk-based instead of threshold-based)
The MoA is not entirely clear. Based on the currently available data, the possibility of a direct genotoxic mechanism cannot be excluded. The committees, therefore decided (out of precaution), on a non-threshold (or risk-based) approach.
In addition, the available exposure-response data gave no indication of a threshold concentration. The theoretical threshold is probably so low it cannot be detected and in that situation the committees also prefer to use a risk-based approach (see also page 36 of Guidance for recommending classifications and health-based occupational exposure limits). Other international organisations have either used a non-threshold (or risk-based) approach as

well in their evaluations of RCS (NFA, OSHA), or were unable to establish an (occupational) exposure limit because a threshold could not be determined (SCOEL, ATSDR). In conclusion, the committees are of the opinion that a risk-based or non-threshold approach is currently the best approach for occupational exposures to RCS.

The final advisory report *Respirable crystalline silica* has been published on the website of the Health Council on September 10, 2024, including your comments and this letter by the committees. All comments and replies are available for the public.

Kind regards,

Daisy Boers, PhD
Scientific secretary
Health Council