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Subject: Comments on draft report on di-and triisocyanates

Dear mrs Arts,

Thank you for your interest in the draft report *Di- and triisocyanates*, which was made public in November, 2017 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. The Committee appreciates your comments, and has taken them into consideration when finalising the report. On behalf of the President of the Health Council, I herewith send you the Committee's reply on your commentary letters. Your comments and the response of the Committee on each comment can be found in the table below.

Major comments	Response of DECOS
First of all the names of the substances concerned are a bit misleading. Diisocyanates are monomers (consisting of 2 NCO groups) whereas the 'triisocyanates' are trimers (consisting of 3 connected monomers resulting in 3 NCO groups with a larger distance between the NCO groups). Using the terminology 'diisocyanates/triisocyanates' suggests a much closer relationship compared to 'monomers/trimers'.	The Committee is aware of the chemical differences between di- and triisocyanates, which has been addressed in the report. Given the exposures in practice (not only to monomers/trimer-forms) and the use of [NCO]-weight in the exposure metric, the Committee is of the opinion that this title is most appropriate.
Section 2.1 The argument to express concentration measurements in µg NCO/m3 - because 'this would be most relevant from a toxicological point of view and allows a direct comparison between different isocyanates' -is not correct because: (1) Measurement in µg NCO/m3 is only a more easy way to determine total NCO and does not allow discrimination between different diisocyanates (monomeric) and triisocyanates (trimeric), or even polymeric isocyanates. (2) This means that potent, less potent or even no sensitizers will be included in total NCO; in addition, it is the question whether oligomeric (e.g. trimeric) isocyanates have respiratory allergenic potency, if at all. Because of differences in potency, the metric µg NCO/m3 therefore, will not allow a direct comparison between different isocyanates. The fact that only 3 countries are using this metric (UK, Switzerland and Australia) may	The Committee considers the NCO-group toxicologically the most relevant group, as it is the reactive and most critical group for the endpoint in question (sensitisation). As the NCO-group defines all di- and triisocyanates, the Committee considers it the most practical metric for regulatory purposes. The Committee agrees with you that di- and triisocyanates do not (necessarily) have a similar sensitisation potency. DECOS notes however, that no reliable data on sensitisation potency differences are available which can be used for establishing advisory values (see the Committee's response on this matter below).

already be a sign. The reason why UK is expressing the OEL in µg NCO/m3 may relate to the fact that in the 1980s-1990s, no TDI was used in the UK but only MDI, for which it was most easiest to measure in µg NCO/m3.	
Section 7 Effects In the study by Pronk et al. (Page 36, lines 18-36) it has been indicated that statistically significant exposure-related decreases in FEV1, FEV1/FVC and flow-volume parameters were found independent of BHR. Yet BHR was used to set the HBROEL. But how can BHR20 - which is aspecific - be used as an indicator for occupational asthma specifically due to diisocyanates?	Although BHR is an aspecific parameter for occupational asthma, there is a clear relationship. As outlined in the report, the Committee considers BHR most predictive parameter available. The Committee notes that endpoints used for derivation of advisory values are generally not very specific (with the exception of specific IgE-levels). Critical is this regard that a statistically significant exposure response-relationship is obtained and confounders have been taken into account. You note that exposure-response relationship of BHR was independent of other lung function parameters. The Committee attributes this to the fact that these are independent effects with different modes of action
On page 36, it has been indicated that workers were exposed to isocyanate oligomers, whereas on Page 73 (Annex D) it was stated that workers were mainly exposed to isocyanate oligomers. Because concentrations were measured as NCO, it is not clear what the contribution of monomers was versus that of oligomers, also in view of the much lower respiratory allergenic potency of oligomers, if at all. F.i. HDI trimer isocyanurate (CAS no. 3779-63-3) has been REACH registered and has not been classified for respiratory sensitisation based on in vivo studies with the structural analogue HDI oligomers, isocyanurate type (CAS no. 28182-81-2; UVCB). HDI biuret (CAS no. 4035-89-6) has not been REACH registered but could be expected to behave the same. In addition, trimeric IPDI was negative in the respiratory LLNA in contrast to the monomers IPDI, TDI and HDI (Arts et al. (2008); Tox Sci 106(2): 423- 434).	The DECOS acknowledges that the attribution of monomers in the Pronk study is unclear. However, also in practice workers can be exposed to different isocyanate forms (monomers and oligomers). The fact is that a statistically significant exposure response-relationship was found when exposure was expressed as µg NCO, and was therefore used by DECOS as starting point for the risk calculation. DECOS notes that limited data on potency of different isocyanates are available. Further, these are obtained in non-validated animal models which DECOS considers these data not suitable for deriving an advisory value.
Section 9 and Annex D First of all it would have been more helpful to understand this Annex when the daily concentration levels would have been mentioned (which were stated to have been	The corresponding 8h-values for the exposure categories are not specified, as not these values, but the cumulative exposures have been used for the analysis.

back calculated from the original publications).	
Based on the above, a possible lack of respiratory sensitization potential for oligomeric isocyanates, it is remarkable to note that the report of the Health Council includes di- and triisocyanates, and that by indicating one HBROEL value they consider these to be of the same potency. However, in fact the triisocyanates would then even be of higher potency because to obtain 0.1 ug NCO/m3, there would be (much) less trimeric molecules than monomeric molecules.	As mentioned above, reliable data on potency that can be used for deriving advisory values are not available. Considering that the NCO-group are the functional groups, DECOS considers an advisory value based on this group most appropriate.
On page 37, in the footnote, it has been indicated that an increase of 1% of sensitized individuals above background values is used in NL as benchmark for establishing OELs of allergens for which no safe exposure level can be derived. In the present case this 1% has been linked to BHR and asthma (BHR and wheeze) whereas increases in BHR and wheeze are not necessarily related to respiratory allergy (see also comment above). In the present study, there were 2 controls with asthma (BHR20 and wheeze) and 3 controls with BHR20 (if the same persons, one without wheeze?) indicating that also in individuals work-aggravated asthma could have existed.	The Committee agrees that cases of work-aggravated asthma could have been present in the studied population, however has no indication that affected the risk estimation.
Using approach no. 2 it is very remarkable that at 0.10 ug NCO/m3 workers would have an additional risk of 1% of developing 'BHR20' compared to the background risk in the general population. Thus compared to a value of 6.3% in controls, this would be 7.3%? In addition, at 0.19 ug NCO/m3 this would be 2% extra, at 0.37 ug/m3 3% extra, and at 1.39 ug/m3 5% extra. However, for 'asthma (BHR20 and wheeze) these levels would be respectively: 0.13, 0.36, 0.97 and 7.09 ug/m3???	This is the result of non-linearity of the different exposure-response relationships.
As the Health Council noted: short-time exposure to peak levels of isocyanates might result in relatively high risks for the development of isocyanate-induced occupational asthma. Therefore, it is remarkable that the HBROEL has been set as an 8-h TWA as if allergy is based on a concentration * time concept (a daily 8-h mean which does not exclude peaks). Most probably people get sensitized due to one or	The task of DECOS is to recommend 8h-TWA advisory values and, if possible, a short-term value (STEL). It is assumed that sensitisation risk is high with exposures to peak exposure, however there are insufficient data to derive a short-term exposure level. DECOS notes that correlations exist between 8h-TWA and the occurrence of peak exposures, however the attribution of

more exposures at high(er) levels (e.g. due to spills which might result in inhalation as well as dermal exposure), and then a lower air concentration may be sufficient to induce allergic reactions. So what is the purpose of setting an 8-h HBROEL? Is this to prevent sensitization? Or to prevent elicitation reactions in those people already sensitized? And how will an 8-h TWA HBROEL average help to prevent peak exposure(s)?	peak exposures cannot be quantified. In the Pronk study, statistically significant exposure-response relationships have been reported for cumulative exposures. With assumptions, e.g. on the concentration*time concept, 8h-TWA values can be derived. Applying an 8h value however, will also indirectly limit, and therefore protect against, peak exposures as these are discounted in this value. This value is (primarily) based on data on BHR, and therefore aims to prevent cases of BHR (as a surrogate parameter for asthma).
The current OEL value for diisocyanates in most countries (5 ppb) has shown that the number of occupational asthma cases has decreased over time but is not zero. However, most probably the number of cases not being zero is not due to the value as such but due to (accidental) occurrence of peak values or spills.	The evaluation of the prevalence and incidence of occupational asthma cases due to isocyanate exposure has not been a focus of the report. However, in this context it is important to note that the diagnosis and registration of occupational asthma cases have severe limitations.
Also, if the HBROEL will be expressed in ug NCO/m3, it will create difference in concentration levels as the effect of these chemicals should not be expressed in mass (dose = mg/m3 * exposure duration) but in moles (number of molecules; thus ppm/ppb): The general OEL for TDI is (currently): 5 ppb which equals ~35 ug/m3 The general OEL for IPDI is (currently): 5 ppb which equals ~45 ug/m3 So 0.1 ug NCO/m3 would result in a different value for every diisocyanate (and also for oligomers). For TDI this would be: 0.1 ug NCO/m3 = 0.2 ug TDI/m3 = 0.028 ppb = ~180 times lower. For IPDI: 0.1 ug NCO/m3 = 0.2 ug IPDI/m3 = 0.022 ppb = ~230 times lower.	The Committee agrees with this conclusion. However, it is important to note that DECOS has derived a risk-based value (i.e. an exposure level corresponding an extra risk of 1%) based on epidemiological data. This is a fundamentally different value that the value of 5 ppb applied in other countries, which is a presumed threshold value based on animal data. Therefore, these values cannot be directly compared.
Finally, it is the question whether air monitoring is technically feasible. And if not technically feasible, what value has this proposed HBROEL value?	The Committee's recommendations are solely health-based. It is the task of the OEL subcommittee of the Social and Economic Council to take into account consideration on technical feasibility.

Minor comments	Response of DECOS
Page 18. CAS number of HDI trimer isocyanurate is: 3779-63-3.	This has been adapted in the final report.
Section 2.1 Section 5 Biological monitoring It has been indicated that skin prick tests resulting in a wheal diameter of at least 3 mm larger than the negative control after 15 min are usually considered positive for sensitization. Sensitization for what: Dermal? Inhalation? Both?	A positive skin prick test is indicative for an immune response against isocyanates, and does not necessarily provide information on the route of sensitisation.
(Page 32, lines 10-12). TDI is one of the main agents responsible for occupational asthma (5 to 15% of occupational chemical asthma).This clearly needs a reference.	The percentage range mentioned was deleted, as no reliable data source was found to substantiate this.
(Page 33, lines 11-14). Improper diagnosis of TDI sensitization was also discussed: on 75 subjects positively diagnosed by questionnaire, less than half responded to the challenge with high molecular weight allergens. Why would subjects positively diagnosed by questionnaire be challenged with high molecular weight allergens?	The purpose of this text was to note that improper diagnosis of allergen-induced asthma is also a cause of the inability to measure specific IgE. The text has been clarified.

The accompanying e-mail contains a link to the final report on di- and triisocyanates.

Best regards,

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Subject: Comments on draft report on di-and triisocyanates

Dear mr Palmersheim,

Thank you for your interest in the draft report di- and triisocyanates, which was made public in November, 2017 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council. The Committee appreciates the thorough review by Gradient, and has taken your comments into consideration when finalising the report. The accompanying e-mail contains a link to the final report on di- and triisocyanates. On behalf of the President of the Health Council, I herewith send you the Committee's reply on your commentary letters.

First, the Committee responds on your commentary letter 'Comments on the Dutch Expert Committee on Occupational Safety (DECOS) Draft Health-based Recommendation on Occupational Exposure Limits (OELs) for Di- and Triisocyanates' dated May 3rd. Thereafter, your commentary letter 'Regulatory and other comments on the Dutch Expert Committee on Occupational Safety (DECOS) Draft Health-based Recommendation on Occupational Exposure Limits (OELs) for Di- and Triisocyanates', dated May 9th, is addressed. The Committee's response is in order of the different sections specified in these letters.

Response of DECOS on commentary letter drafted by Gradient

"Di- and triisocyanates do not all pose the same risk of occupational asthma"

In your commentary letter it is stated that di- and triisocyanates do not all have the same irritant or acute toxicity potential, referring to a publication by Pauluhn (2004). Subsequently, you argue that one advisory value for all di- and triisocyanates (expressed as ug NCO) is not appropriate, as it would be overly conservative for isocyanate types which would be less potent than TDI.

Response of DECOS: The Committee acknowledges that different isocyanates are likely to have different toxic potencies. For irritation and acute toxicity this has been clearly shown. However, for respiratory sensitisation, limited data on potency are available, based on non-validated animal models. Furthermore, animal data are related to exposure to monomers, whereas in practice, exposure occurs to mixtures of monomers, oligomers and reaction products. The epidemiological data, although these also have limitations, do not indicate obvious potency differences for different diisocyanates. In this context, the Committee notes that a risk calculation based on a recent publication by Collins et al. (2017) on TDI exposure and TDI-induced asthma results in an advisory value comparable with an advisory value calculated based on BHR in spray painters exposed to HDI oligomer mixtures (Pronk et al.

2007, 2009). Overall, the Committee considers a group approach appropriate. The considerations of the committee have been clarified in the final version of the advisory report.

"It is our opinion that the studies by Pronk et al. (2007, 2009) should not be the sole basis for an OEL for isocyanates"

In your commentary letter, several potential limitations and/or confounders have been outlined, including uncertainty related to the use of a composite exposure metric and the use of BHR as effect parameter. ALIPA further commented that BHR was only measured at one point in time, and many factors (i.e. presence of other diseases and conditions associated with BHR, exposure to other irritants, and residual and unmeasured confounding) that could have impacted BHR were not sufficiently controlled for. It is concluded by ALIPA that the study by Pronk et al. (2007) is not suitable as starting point for a risk calculation.

Response of the DECOS: The Committee acknowledges that inherent to epidemiological studies, in particular of studies on allergens, Pronk et al. has limitations. Several were noted in the draft manuscript. With respect to the use of NCO as exposure metric and the subsequent introduction of uncertainty, the Committee notes that this uncertainty is manifested in the exposure-response relationship that has been established based on the Pronk et al. study. The Committee notes that this relationship was statistically significant.

The Committee is aware that exposure to other irritants may occur. Some exposure measurements focused on solvents were performed in the Pronk et al. study. Authors concluded that 'exposure levels were all well below existing occupational exposure limits' (Pronk et al. 2009). Highest exposure levels were found for nonspray-painting tasks, and solvent exposure did not correlate with isocyanate exposure. Therefore, the Committee considers it unlikely that solvents are responsible for the exposure-response relationships found in the Pronk et al. study. Other exposures with possibly irritating properties, such as welding fumes and sanding dust were experienced mainly by auto body workers, which were included in the 'other workers' category, and cannot explain the higher risks found for spray painters.

With respect to residual confounding, Gradient notes that Pronk et al. corrected for current smoking (instead of history of smoking, i.e. using additional corrections for pack-years) and no correction was applied for respiratory diseases. The Committee notes that the relationship between BHR and smoking is relatively weak and considers a correction based on current smoking sufficient. Even for a strong relationship such as smoking and lung cancer, 'current/ever smoking' alone is the most important predictor and although 'pack years' and other intensity indicators further improve goodness-of-fit, this effect is relatively minor and may introduce multicollinearity if age is included as well (Leffondré et al. (2002)[a]). Furthermore, according to Blair et al. (2007)[b] tobacco use is rarely a confounder for lung cancer risks in occupational studies. It is therefore even less likely that residual confounding by smoking, a much more modest risk factor for BHR, would have a substantial effect on the exposure-response relationship with isocyanate exposure.

[a] Leffondré K, Abrahamowicz M, Siemiatycki J, Rachet B. Modeling smoking history: a comparison of different approaches. Am J Epidemiol. 2002;156(9):813-23.
[b] Blair A, Stewart P, Lubin JH, Forastiere F. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. Am J Ind Med. 2007;50(3):199-207.

With respect to other diseases and conditions associated with BHR, the Committee notes that misclassification of COPD is likely to occur in the relatively young study population of Pronk et al. COPD symptoms may overlap with asthma symptoms, and COPD was based on FEV1/FVC<0.70 which is well-known to overestimate COPD. Finally, a bronchodilator test (reversibility) was not used to assess fixed or reversible obstruction. Excluding or adjusting for subjects with 'COPD' would change both the background risk and the exposure-response slope, while there are no suggestions in published literature that isocyanates would cause fixed airflow obstruction. With respect to the use of medication: as part of the spirometry protocol, participants are asked to stop using medication before the test so it will not influence the test results.

Overall, the DECOS is of the opinion that the factors noted above are not likely to have substantially impacted the results of the risk calculation.

Your comment on the suitability of BHR as critical effect will be addressed below.

"BHR alone is not a reliable basis for derivation of an OEL for isocyanates"

ALIPA states that BHR as a parameter for occupational asthma has several limitations which have not been addressed in the concept report. ALIPA is of the opinion that "BHR is not appropriate to use as the sole endpoint for the critical effect of OA. At the very least, the implications of BHR as a common response among individuals with non-occupational asthma or other lung diseases (e.g., COPD), smokers, and other non-atopic individuals should be discussed if this endpoint is selected as the basis for an OEL."

Response of DECOS: The Committee agrees with ALIPA that BHR has limitations as an effect parameter for occupational asthma. ALIPA notes in this regard in particular the limited specificity of BHR. In absence of a more specific parameter (e.g. IgE), the Committee considers BHR the most suitable surrogate parameter, as was outlined in the draft report. Given that BHR is considered a hallmark of occupational asthma, and a statistically significant exposure-response relationship has been derived for isocyanate exposure and BHR, the Committee considers it acceptable to derive an advisory value based on BHR. The Committee notes that a recent study of Collins et al. (2017) was added to the final report, who studied exposure to TDI and the incidence of TDI-induced asthma. Although this study too has its limitations, a quantitative analysis suggests a similar risk estimate, in this case of TDI-induced asthma, as the Pronk et al. study. This quantitative analysis has been added to the Annex of the report. Also, additional considerations on the use of BHR as effect parameter have been added.

A combination of respiratory endpoints is the most reliable basis for an OEL for isocyanates

ALIPA outlines in its commentary the difficulty of an accurate diagnosis of occupational asthma and concludes 'It is our opinion that studies with exposure-response data for a combination of respiratory endpoints are the most appropriate basis for deriving an OEL for isocyanates.'

Response of DECOS: The Committee agrees with ALIPA that diagnosis of OA is preferably based on several parameters. However, studies that describe exposure-response relationships for multiple parameters are not available (with the exception of Pronk et al.; see below). In absence of studies with multiple parameters, the Committee is of the opinion that BHR is the

most relevant effect parameter in this case, and that an exposure-response relationship between isocyanate exposure and BHR is an acceptable basis for deriving an advisory value. The Committee notes that the Pronk et al. studies have also taken into account respiratory complaints, i.e. wheeze combined with BHR. For this combined parameter, a similar 1% risk-exposure level is derived as for BHR alone (0.13 and 0.10 µg NCO/m3, respectively).

It is our opinion that the methodology used for the exposure-response analyses should acknowledge uncertainties and consider a threshold

In this section of its commentary, ALIPA argues that the exposure-response analysis performed by the Committee has limitations, and was not peer reviewed. Furthermore, ALIPA is of the opinion that there is evidence suggesting a threshold below which new asthma cases are not expected and therefore a threshold model should be applied. Finally, ALIPA suggests that the reference group used in the Pronk et al. study was inappropriate, as this consisted of office workers who 'were more likely to be females and former smokers, to have worked in airplane paint shops, and to have worked for fewer years than spray painters and other workers'.

Response of DECOS: The Committee notes that the Health Council applies a public consultation round, in which the concept report can be reviewed. The details of the risk calculation are provided in an Annex. The Committee acknowledges that evidence is available that there is a threshold for respiratory effects of isocyanate exposure. However, these data primarily relate to irritation effects, which are primarily derived in animal models. For respiratory sensitisation, there is currently no validated animal model available. The Committee also notes that there is currently no clear evidence in humans that sensitisation cannot occur below the irritation threshold. Therefore, it has based its advisory value on epidemiological data, which were derived by applying a regression model to fit the data of the Pronk et al. study. A similar approach was chosen by Collins et al. (2017). The Committee is not aware of a model that can reliably estimate a possible threshold for the applied dataset.

In the final report, the Committee has clarified the composition of the reference group. With respect to the reference group in the Pronk et al. study, the Committee is of the opinion that it is acceptable that this group is used to derive an exposure-response relationship with isocyanate exposure for several reasons. The control group consists of workers in the same companies, which minimizes the possibility that systematic differences occur between the reference and exposed groups, and extensive exposure assessment measurements were done across all job tasks. Differences in job history are not expected to have influenced the exposure-response relationship unless a substantial 'healthy worker effect' has led to a higher prevalence of BHR in the control group, resulting in underestimation of the exposure-response relationship. The regression models adjusted for differences in personal characteristics, such as gender and smoking status, as discussed above.

Alternative epidemiology data can be considered for exposure-response analyses in the derivation of an OEL for isocyanates

ALIPA addresses in its commentary the limitations of cross-sectional studies on lung function, and concludes that long-term studies on respiratory symptoms and measurements should be preferred. ALIPA also points to additional epidemiological literature as an alternative source for deriving an advisory value.

Response of DECOS: The Committee does not agree with the conclusion that longitudinal data should be preferred over short-term studies. The Committee considers short-term (over a working day) better suited to determine the temporary, reversible nature of effects related to occupational asthma. This was outlined by the Committee in the report when evaluating the epidemiological data. The Committee appreciates ALIPA for drawing attention to the recent studies of Cassidy et al. (2017), Collins et al. (2017), and Middendorf et al. (2017) (the studies of Ott et al. (2000) and Bodner et al. (2001) were already included in the report). The study of Cassidy et al. (2017) does not contain information on exposure levels. The Committee has included Collins et al. (2017) and Middendorf et al. (2017) in the report and has also taken them into consideration for the hazard assessment. The Committee has performed a risk calculation based on Collins et al. and has included this additional calculation in the An annex. Interestingly, a similar advisory value (e.g. an exposure level corresponding with an additional risk of 1%) is obtained.

Response of DECOS on letter containing Regulatory and other comments

Discrepancy between the English and Dutch text version

In your commentary, Alipa refers to a discrepancy in the report: in the English text the term health-based limit value is used, while in the Dutch text the term ‘reference value’ is used. Alipa states that these are fundamentally different values with different implications in practice.

Response of DECOS: The Committee agrees with Alipa that the draft report is not consistent in the term used for DECOS’ advisory value. The Committee notes that the term ‘reference value’ has not been adopted in the Dutch OEL system, and could be confused with (non-health based) reference values used in other frameworks (for instance reference values proposed for nanomaterials). The Committee notes that for the risk-based values for allergens, a feasibility assessment is not necessarily performed. In the final report, the term ‘reference value’ is replaced with the term ‘advisory value’, consisted with the task of the Committee. In several sections of the document, it is noted that the recommendation is risk-based, to emphasize the difference with a recommendation based on the assumption of a threshold below which adverse effects are not anticipated.

DECOS Guidance

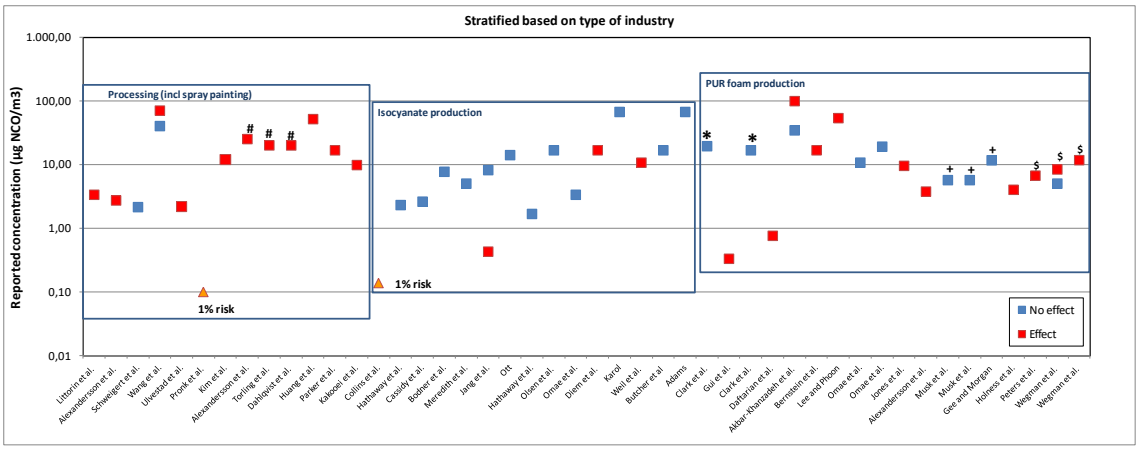
Alipa notes that the report contains an analysis of data obtained by Pronk et al., which was not peer reviewed. Furthermore, Alipa is of the opinion that not the necessary details are provided and also questions whether the Health Council followed its own guidance with this analysis.

Response of DECOS: Although the Health Council only takes into account publicly available data, the Committee will perform its own analysis if necessary as has been done on a regular basis. The public consultation round serves as a form of peer review. Sufficient details should be available to review the analysis. The Committee is of the opinion that this was the case for this draft report. Some details on the analysis (in particular on the control group) have been added in the final report.

Multiple agents

Alipa reasons that exposure to multiple agents in car repair shops could have led to an erroneous association with di- and triisocyanates alone. Therefore, Alipa suggested to develop an extra figure in the DECOS document (in addition to A, B and C) where studies are separated based on the industry from which they were derived.

Response of DECOS: The Committee acknowledges the possibility of co-exposure, however as noted above, considers the likelihood that a co-exposure accounts for (a significant part) of the exposure-response relationship observed between exposure to isocyanates and BHR, low. Nonetheless, the Committee agrees with Alipa that a separation of studies based on types of industry is informative. This analysis is shown in the following figure:



This figure suggests that positive findings are more likely to be observed in studies on spray painting and PUR foam production than in studies on isocyanate production. The Committee notes however, that conclusions cannot be drawn as this association could also be caused by differences in study design (i.e. between shift and longitudinal). As this figure does not change the conclusions of the Committee, it is not included in the final report.

General population

In this paragraph, Alipa addresses several issues. First, Alipa argues that studies and calculations by Pauluhn should be included. Second, Alipa questions whether a reference value of 1% risk can be calculated, as the sensitisation level for the general population is zero. Third, Alipa is of the opinion that the reference value calculated for di- and triisocyanates is a too conservative approach, the number of workers developing asthma due to exposure is limited and notes that consumer use of di-and triisocyanates is limited or even forbidden under REACH.

Response of DECOS: Regarding the studies of Pauluhn, the Committee is of the opinion that animal data do not provide a suitable starting point for deriving an advisory value (in particular in case of available epidemiological data). Limited animal data are available, derived with non-validated models with exposures that are not representative for the worker situation (i.e. monomeric single isocyanate exposures). Although the epidemiological data also have

limitations, as is outlined in the report, the Committee considers that these provide a more relevant starting point for deriving an advisory value.

With respect to the calculation of the advisory value, the Committee notes that the corresponding 1% risk relates to an extra 1% compared to the general population and is therefore independent from the background risk.

The Committee acknowledges that one general reference value for all di- and triisocyanates could be a conservative approach for some types of isocyanates. However, there are no reliable data available to quantify differences in sensitisation potential which can subsequently be used for deriving reference values for different types of di-and triisocyanates. Therefore, the Committee considers a group approach appropriate. For its evaluation, the Committee did not take into account the number of cases of occupational asthma due to exposure to isocyanates in practice. The Committee, however, notes that the diagnosis and registration of these cases have severe limitations and could therefore lead to an underestimation of the health effects.

Current limit values

Alipa refers to the DNELs and the occupational exposure limits set by the German MAK Kommission derived for different isocyanates, and the statement by the MAK Kommission that new cases of TDI-asthma are not observed at exposures below 0.01 to 0.02 ppm. Alipa also refers to a selection of the literature to support this statement. Alipa concludes that currently a decrease is observed in health cases.

Response of DECOS: The Committee has applied a different approach than what was applied by the MAK Kommission. As outlined above, the Committee has applied a risk-based approach, based on epidemiological data. This approach has been explained in the report. As noted above, the Committee did not address the number of cases of occupational asthma due to exposure to isocyanates being reported currently in practice.

Developments under REACH

Alipa summarises developments under REACH, which include both the introduction of protection measures as the generation of new data. An anticipated study is noted with the aim of verification if skin and respiratory diseases, caused by diisocyanate exposure, can be prevented by proper industrial hygiene conditions. Alipa argues that these will reduce the number of health cases in the future. Further, Alipa cites a conclusion in the ECHA restriction proposal that no quantitative value can be derived from the epidemiological data.

Response of DECOS: The task of the Committee is to derive an advisory value in the air, based on the currently available evidence. The Committee welcomes the developments under REACH, which DECOS considers of additional value to its derived advisory value. The conclusion made in the ECHA restriction proposal on the use of epidemiological data is not supported by the Committee. The considerations of the Committee on deriving an advisory value based on epidemiological data have been outlined in the report.

Polyurethane foam

Alipa indicates that in the draft report (Chapter 4.1), the Committee states that PU foam contains diisocyanates. Alipa notes that this not applies to the endproduct as isocyanates are only present in a short time after PUR is being formed, and that there is uncertainty about PUR-related health complaints.

Response of DECOS: The Committee has rephrased the potential ioscyanate exposure of the general population after use of PUR for isolation purposes.

Thank you again for your interest in our advisory report on di- and triisocyanates. The accompanying e-mail contains a link to the final report.

Best regards,

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Date:	November 28, 2018	Your ref:	Email, dated March 16th, 2018	E-mail:	sr.vink @gr.nl
Encl:	-	Our ref:	1450324/SV/jh/459-Z74	Phone:	+31 6 52781584

Subject: Comments on draft report on di-and triisocyanates

Dear Dr. Lentz,

Thank you for accepting the invitation to comment on the draft report 'di- and triisocyanates', which was made public in November, 2017 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council. DECOS appreciates the review of mr. Streicher, mr Siegel and mr. Hettick, and has taken your comments into consideration when finalising the report.

Mr. Streicher has made various suggestions on the chemistry and measurement sections of the report. These suggestions led to significant improvements.

DECOS is pleased that mr Siegel and mr. Hettick are of the opinion that the report is well written and support the conclusions. They also made some valuable comments, including textual suggestions and reference to updated literature on carcinogenicity.

The accompanying e-mail contains a link to the final report on di- and triisocyanates.

Best regards,

Stefan Vink
Scientific staff member

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Joe Pueringer
Austrian Workers' Compensation Board
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Gezondheidsraad
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Date:	November 28, 2018	Your ref:	Email, dated Febr. 22th, 2018	E-mail:	sr.vink @gr.nl
Encl:	-	Our ref:	1450318/SV/jh/459-X74	Phone:	+31 6 52781584

Subject: Comments on draft report on di-and triisocyanates

Dear mr Pueringer,

Thank you for your interest in the draft report di- and triisocyanates, which was made public in November, 2017 by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands. DECOS appreciates your thorough review, and has taken your comments into consideration when finalising the report. On behalf of the President of the Health Council, I herewith send you the Committee's reply on your commentary letter.

In your letter, you pointed out several issues regarding skin exposure to isocyanates. First, you noted that isocyanates penetrate the skin and are conjugated or metabolised, rather than that isocyanates are absorbed (which implies systemic availability). Second, you noted that a skin notation has been applied by the MAK Kommission, although the sensitisation results from dermal contact rather dermal absorption. The Committee has clarified sections of the report referring to dermal absorption. In addition, in view of the dermal hazard in relation to respiratory allergenic effects, the Committee decided to recommend a skin notation. In the section on a skin notation (section 9.4), it is emphasized that in the case of isocyanates, a skin notation is not related to the amount absorbed through the skin but rather to the contribution of dermal contact to the development of systemic effects.

Furthermore, you are of the opinion that it should be mentioned in the paper that the relevance of biological monitoring of isocyanate-derived amines is questionable, and provided supporting evidence for this view. DECOS agrees with you on the limitation of biological monitoring of isocyanates, and has added a subsequent paragraph in this section of the report.

The accompanying e-mail contains a link to the final report on di- and triisocyanates.

Best regards,

Stefan Vink
Scientific staff member

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