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Van: Arts, J.H.E. (Josje)
Verzonden: donderdag 15 maart 2018 12:04
Aan: GR_draftOSH@gr.nl
Onderwerp: Draft document di- and triisocyanates

Hoi Stefan

Hierbij stuur ik een reactie op het OCR 'Di- and triisocyanates' namens AkzoNobel Chemicals.
Hartelijke groet, Josje

Major comments

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'.

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 ug 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 ug 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 already be a sign. The reason why UK is expressing the OEL in ug 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 ug 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?
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).

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 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.

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.

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???

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 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)?

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.

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.

Finally, it is the question whether air monitoring is technically feasible. And if not technically feasible, what value has this proposed HBROEL value?

Minor comments

Page 18. CAS number of HDI trimer isocyanurate is: 3779-63-3.

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?

Section 6 Mechanism of action

- *(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.

- *(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?

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Date:	November 28, 2018	Your ref:	Email, dated March 15th, 2018	E-mail:	sr.vink@gr.nl
Encl:	-	Our ref:	1450319/SV/jh/459-W74	Phone:	+31 6 52781584
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 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).

The fact that only 3 countries are using this metric (UK, Switzerland and Australia) may 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	The corresponding 8h-values for the exposure categories are not specified, as not these values, but the cumulative exposures

concentration levels would have been mentioned (which were stated to have been back calculated from the original publications).	have been used for the analysis.
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	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.

concentration * time concept (a daily 8-h mean which does not exclude peaks). Most probably people get sensitized due to one or 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)?	DECOS notes that correlations exist between 8h-TWA and the occurrence of peak exposures, however the attribution of 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	A positive skin prick test is indicative for an

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?	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,

S.R. Vink, PhD
Scientific Staff Member

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.

May 9, 2018

Discrepancy between the English and Dutch text version
In the English text reference is made to a Health based limit value, while in the Dutch text the recommendation refers to a "reference value", which is truly a risk based value
This is a fundamental difference as the reference value need to be assessed for feasibility in the tri partite committee (the SER).

DECOS Guidance
Health council is conducting their own analyses, utilizing the information that they obtained from the Pronk (2007, 2009). This analysis has not been published in a peer reviewed journal and the report does not provide the necessary detail to fully understand the process that was followed. By utilizing "non peer" reviewed data, the health council likely did not follow their own guidance to limit the information considered to peer reviewed and publicly available information (as is done by other scientific organizations).

Multiple agents
Relying on health effects in car repair shops, where exposure may occur to many agents that affect the health of the workers, may lead to erroneous association with di- and triisocyanates alone.
It might be of interest 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 (e.g. manufacturing isocyanates, production of PU components, application of coatings). The first two sectors will give few rises to confounding exposure to other agents.

General population
The committee states that an exposure limit for di- and triisocyanates exists below which no occupational asthma develops. Although the committee cannot derive this limit based on their in-depth review the committee does not include studies and calculations from Pauluhn (2008/2015) which leads to exposure limit being in line with the German MAK (Maximum Allowed Concentration) values.
The Socio Economic Committee (SER) of the Netherlands wants to strive to ensure that no more than 1% more sensitization is created by a working life with exposure to an allergen than to the general population. This is in line with the SER advice on inhalable allergens. (G&VW/GW/2009/20619).

The sensitization level for the general population in the Pronk study (2007, 2009) is 0% (based on a control group of 50 office workers). An extra 1% for a working life exposure will still be zero. No reference values, neither historical, were given on asthma cases due exposure to di- and triisocyanates of the general population. This illustrates also the weakness of this route of calculation in the Pronk study (2007, 2009) as di- and triisocyanate spray (coating and/or foam) are not used by the general public (This use is not registered for any di-and triisocyanate under REACH, thus it is forbidden: used advised against in REACH dossiers).
Of the most relevant di- and triisocyanates only MDI has few consumer uses, including a restriction under Annex XVII of REACH.
With this draft advice the committee is taking a too negative approach towards di- and triisocyanates. It is known that di- and triisocyanates are sensitisers and can cause occupational asthma by prolonged over-exposure but this doesn't mean that large numbers of workers develop occupational asthma from working with them. An earlier report from TNO (TNO report V9408, 2011) prioritizes diisocyanate exposure as a medium to low problem area. In the Netherland the NCVB (Dutch Center for Occupational Illness) reports already for many years a very low number of asthma cases due to the use of di- and triisocyanates. Between 2002 and 2017 there were eighteen reports of occupational diseases involving isocyanates, 1 – 2 per year. Of these total of 18 reports, three are related to sprayed foam. This concerns reports from 2002, 2004 and 2012. Because no protocol was used at that time, it is impossible to find out what the source of the complaints was. There has been no increase in recent years.

Current limit values
The SER committee states that when the government makes it clear to which allergens it sets limits, the other allergens fall into the private domain. This means that companies must, as required by the Working Conditions Decree, set limits themselves, whether or not based on sectoral action or an occupational health and safety catalog. Industry has derived limits in their REACH dossiers, the so-called DNEL's, these are supported by the Pauluhn data (2008, 2011, 2015) and the German MAK (AGS, German Committee on Hazardous Substances, 2007) data. Globally binding legal limit values for TDI are all in the range from 1 – 10 ppb, other diisocyanates have typically higher limit values (see attached table 1).

There is in the Netherlands no legal binding limit value for TDI but industry follows the averages of the neighboring countries. For di- and triisocyanates the European limit values for various countries are given in table 1(see attachment). They vary from 1 – 10 ppb (8.1 µg/m3 – 81 µg/m3) which is similar the DNEL's in the REACH dossier.
The German Committee on Hazardous Substances (AGS) for example established an OEL of 0.035 mg/m3 (0.005 ppm = 5 ppb) referring to an 8-hour exposure period. The justification of the OELs was based on a TDI evaluation of the German MAK Commission (1999) and published in criteria documents for 2,4- and 2,6-TDI (January 2006) with the following statements:
"Human experience shows clearly that if the exposure concentrations of TDI are kept below 0.01 to 0.02 ppm (20 ppb), generally no new cases of TDI asthma are observed (Porter et al., 1975; Karol 1981; Olsen et al., 1989). The impairment of lung function by long-term exposure to TDI has been investigated in several studies. It can be deduced from these data that with observance of an 8-hour average value at the workplace of 0.005 ppm and limitation of exposure peaks to 0.02 ppm no significant deterioration in lung function is to be expected (DFG (German Research Foundation) 1999). Since the OEL for TDI was based on human data

no additional assessment factors are required. Inter-individual variability was taken into account by a large number of TDI exposed workers."

It is realized that the commission follows a clear scientific path to derive a health-based recommendation on occupational exposure limit but it does not take into account the current situation in Europe and in the Netherlands. Despite the increased use of diisocyanates there is a decrease in health cases, this is also acknowledged by the BAuA in their REACH Annex XV restriction report on diisocyanates, BAuA (2016).

Developments under REACH

There will be a further reduction in number of health cases with the implementation of the REACH restriction on diisocyanates as prepared by BAuA (German Federal Institute for Occupational Safety and Health) in 2016, which was approved by RAC and SEAC of ECHA and is currently under review by the European Commission. This restriction foresees a mandatory training and certification for industrial and professional users (up to 4 million in Europe), covering all sectors, including car repair and the building sector. In parallel to this restriction the IPA (The Institute for Prevention and Occupational Medicine of the German Social Accident Insurance is an institute of the Ruhr-University Bochum), the BAuA and industry are preparing for a longitudinal Cohort Study. The study will start in 2019 (duration: 5 years) and will be organized by IPA experts. The goal of the cohort study, with about 1500 workers, is the verification if skin and respiratory diseases, caused by diisocyanate exposure, can be prevented by proper industrial hygiene conditions. Endpoints related to health effects caused by diisocyanate exposure, e.g. respiratory sensitization, skin effects, will be studied. An establishment of a thorough dose-response curve might not be feasible; however, it might be possible to form diisocyanate groups based on concentration intervals like low, medium and high risk. The relevance of diisocyanate skin contact for the induction of respiratory sensitization in humans will be elucidated.
Results of this study will help to prevent occupational asthma caused by diisocyanates by proper handling, organization and technical measures and personal protection.
The diisocyanate restriction under review clearly states why the BAuA has chosen for the route of restriction.
The final conclusion in the ECHA document (BAuA, 2016) is:
"Despite a large number of available studies, none of the epidemiological studies is eligible for deriving a quantitative value. The cause of this lies in limitations of the studies, but is also inherent in the mechanism of the disease. No study overcomes the problem that sensitive predictive markers for diisocyanate sensitisation are missing and that dermal exposure as well as inhalation peak exposure likely contributes to the induction of sensitisation, but cannot be assessed appropriately to date. The DS concludes that the human data show too many uncertainties to derive a DNEL or DMEL."

Polyurethane foam

In chapter 4.1 of the DECOS document it is mentioned that PU foam contains diisocyanates and refer to Verschoor (2014). Polyurethane end products do not contain diisocyanates, in the Polyurethane production process the diisocyanates react with polyols (polyalcohols) and with other ingredients depending on the recipe. DECOS probably refer to the application of PU spray foam in crawl spaces in the Netherlands, where during the applying of the diisocyanate (Polymeric MDI) and a polyol mixture there is exposure. Within seconds the

Polyurethane foam is formed and the Polymeric MDI is reacted away. Both the TNO (TNO 2013 R10642, TNO 2013 R10642) and the RPS report (RPS February 2014) show that within 30

minutes the Polymeric MDI exposure in the crawl space (extracted during and sealed afterwards) is reduced to very low levels causing a negligible risk. Verschoor (2014) also claims that 30% of the workers handling isocyanates get sensitized, however they don't provided data.
Verschoor (2014) claim there are several hundred health complains from people who had their crawl space insulated with PU spray foam, several series of complaining where medically examined by the GGD (Dutch Public Health Service) but none were found sensitized to diisocyanates. Verschoor categorically refuses to send the complaining for medical examination.

Conclusion
Both BHR and MCC (Methacholine challenge) have expectations for better diagnostic and prognostic outcomes. Neither has been proven, even when including studies in mining – platinum and PG metals, food and soaps – enzymes and chemicals (chlorine, Vanadium and anhydrides). It does complicate the regulators task, instead of merely lowering exposure values it needs a more comprehensive toolkit of activities, as we call it – layers of protection. Risk reduction measures therefore should include the layers of protection approach rather than exposure limit based alone.
As for the sensitization, indeed this cannot be based on exposure levels only, the susceptibility/genetic disposition (not atopy), previous exposure, type of allergen etc. complicates the picture and negates the emphasis of lowering exposures only.
The upcoming REACH restriction on diisocyanates will address the topic of occupational asthma due to diisocyanates and will reduce the respective asthma cases.
BHR is not sufficient to indicate occupational asthma. A reduction of the OEL based on insufficient data is contra productive, especially taken into account the upcoming restriction.

References:

BAuA ANNEX XV Restriction report. Proposal for a restriction, substance name(s): diisocyanates, October 2016. BAuA, Dortmund, Germany

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MAK collection for Occupational Health and Safety (www.mak-collection.com). Hexamethylene diisocyanate (HDI), 2,4- and 2,6- Toluylene diisocyanate (TDI; toluene- 2,4- and 2,6- diisocyanate) [Air Monitoring Methods, 1999/2006].

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Pauluhn J, Poole A. Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): determination of the elicitation threshold concentration of after inhalation sensitization. Toxicology 2011; 281(1-3): 15-24.

Porter, CV; Higgins, RL; and Scheel, LD (1975): A retrospective study of clinical, physiological and immunological changes in workers exposed to toluene diisocyanate. American Industrial Hygiene Association Journal 36 (3), 159-168

Pronk A, Preller L, Raulf-Heimsoth M, Jonkers IC, Lammers JW, Wouters IM, et al. Respiratory symptoms, sensitization, and exposure response relationships in spray painters exposed to isocyanates. Am J Respir Crit Care Med 2007; 176(11): 1090-7.

Pronk A, Preller L, Doekes G, Wouters IM, Rooijackers J, Lammers JW, et al. Different respiratory phenotypes are associated with isocyanate exposure in spray painters. Eur Respir J 2009; 33(3): 494-501.

RPS February 2014, Advies-en ingenieursbureau bv. Sprayed PUR foam emissions from crawl spaces SER-advies inhaleerbare allergenen, September 2009 (G&VW/GW/2009/20619).

TNO-rapport, V9408 final, 22 december 2011, Bijlage 7

TNO-rapport, TNO 2013 R10642, Evaluatie van gezondheidsrisiko's voor bewoners, op basis van resultaten van metingen in woningen waar SPF-vloerisolatie is aangebracht.

TNO-rapport, TNO 2013 R11049, Evaluatie van gezondheidsrisick's voor bewoners op basis van resultaten van metingen in woningen tijdens en direct na aanbrengen van SPF-vloerisolatie

Verschoor L, Verschoor AH. Nonoccupational and occupational exposure to 24 isocyanates. Curr Opin Pulm Med 2014; 20(2): 199-204.

Annex I
Table listing available European national di- and triisocyanate OEL's.

Mr. J. Palmersheim
ISOPA Aisbl
ALIPA Aisbl
Secretary General
Av. Van Nieuwenhuyse laan 6, B - 1160 Brussels

Gezondheidsraad
Health Council of the Netherlands

Date:	November 28, 2018	Your ref:	Email, dated May 10th, 2018	E-mail:	sr.vink@gr.nl
Encl:	-	Our ref:	1450320/SV/jh/459-Y74	Phone:	+31 6 52781584
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.

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"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.

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

[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.

(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.

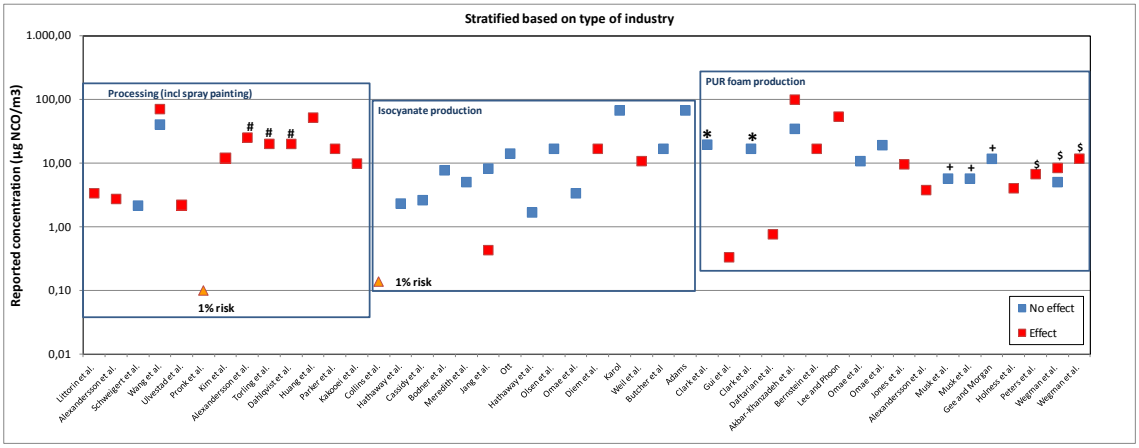
Response of DECOS: Although the Health Council only takes into account publicly available data, the Committee will perform its own analysis if necessary as has been done on a regular basis. The public consultation round serves as a form of peer review. Sufficient details should be available to review 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.

Gezondheidsraad
Health Council of the Netherlands

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,

S.R. Vink, PhD
Scientific Staff Member

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

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March 15, 2018

Health Council of the Netherlands
Attn: Dr. S.R. Vink
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the Netherlands

Dear Dr. Vink:

Thank you for the opportunity to review the draft report on *Di- and triisocyanates* prepared by the Committee of the Health Council of the Netherlands, a committee of the Dutch Expert Committee on Occupational Safety (DECOS). Comments are enclosed that were prepared by Robert Streicher, Research Chemist, NIOSH/Division of Applied Research and Technology and Naomi Hudson, Health Scientist, NIOSH/Education and Information Division, 1090 Tusculum Avenue, Cincinnati, OH 45226; Paul Siegel, Research Scientist and Justin Hettick, Research Chemist, NIOSH/Health Effects Laboratory Division, 1095 Willowdale Road, Morgantown, WV 26506 and Crystal Forester, Research Chemist, NIOSH/National Personal Protective Laboratory, 626 Cochrans Mill Road, Pittsburgh, PA 15236.

If you have any questions regarding the comments, please contact me at 513-533-8260 (telephone) or by Email at tbl7@cdc.gov.

Sincerely yours,

Thomas J. Lentz, Ph.D., M.P.H.
Branch Chief
Document Development Branch
Education and Information Division

2 Enclosures

Comments on DECOS draft document on Di- and Triisocyanates
By: Robert Streicher, Chemist, NIOSH/Division of Applied Research and Technology 1090 Tusculum Avenue, Cincinnati, OH 45226

SECTION & PARAGRAPH	COMMENT
General Comments	My expertise is in chemistry and measurement of isocyanates, so my comments will be almost exclusively limited to those areas of the document.
	The "Solubility" section for the different isocyanates are very different. For TDI, there is a list of appropriate organic solvents. However, for HDI, the only statement is "Hydrolytically unstable." For all of the isocyanates, a list of suitable organic solvents could have been given (many of the same solvents). And it could have been mentioned in each case that the isocyanates are hydrolytically unstable (though some more unstable than others). There should be a consistency in the information provided here.
	HMDI, CAS # 5124-30-1, is a fairly commonly used diisocyanate, and warrants a section in this document. It is mentioned at least one time in the body of the document (Page 36, section 7.1.1, line 5, listed as H12MDI).
Specific Comments	
Page 11, line 16	Annex D is not a list of those commenting on the draft.
Page 12, line 20	One of the synonyms for TDI is incorrect. It should state 4- and **3**-methyl-1,3-phenylene diisocyanate.
Page 13, TDI data, Conversion factor	On page 20, line 11, the authors correctly show the equation that relates ppm and mg/cu m based on a compound's molecular weight and the factor 24.45 (for 25 C and 1 atm). However, in the tables of isocyanate properties, the conversion factor given does not correspond to consistently using the value 24.45. For TDI, the conversion factor should be 1 ppm = 7.1 mg/cu m. Conversion factors need to show the temperature and pressure (which should be standardized at 25 C and 1 atm).
Page 14, HDI vapour pressure	Although there is some variability in literature values, the listed value (0.007 hPa = 0.7 Pa at 20 C) is relatively low. Several references state 7 Pa at 25 C.
Page 14, footnote	One of the MDI isomers is 2,4' (' was missing).
Page 15, MDI use	The first sentence is inaccurate: "Typically, a mixture of MDI and its dimer and trimer is formed (polymeric MDI)." The footnote on the previous page actually defines polymeric MDI (PMDI) more accurately: "...a mixture that contains 25-80% monomeric 4,4' as well as oligomers containing 3-6 rings..."
Page 15, solubility	Providing a solubility in water when MDI is highly reactive with water seems inappropriate.
Page 15, MDI data, conversion factor	MW of 250.252/24.45 = 10.2 at 25 C and 1 atm .
Page 16, NDI data	ILO International Chemical Safety Card has density and flash point data.
Page 17, HDI biuret EC number	Pubchem shows the EC number as 223-718-8
Page 18, HDI biuret use	There is no use shown. The HDI biuret (as well as the HDI isocyanurate) have essentially replaced monomeric HDI in coatings.

Page 18, HDI biuret conversion factor	Because the conversion factor is a calculated value, not a measured value, I recommend standardizing all the compounds at 25 C and 1 atm, calculating this by MW (478.58) divided by 24.45 = 19.57 or 19.6.
Page 18, HDI isocyanurate	The CAS # was input incorrectly. It should be 3779-63-3.
Page 19, HDI isocyanurate use	There is no use shown. The HDI isocyanurate (as well as the HDI biuret) have essentially replaced monomeric HDI in coatings.
Page 19, HDI isocyanurate vapor pressure	The HDI isocyanurate (and the HDI biuret) have extremely low vapor pressures. The vapor pressure given (0.0012 Pa at 20 C) is much higher than is possible for this compound. It is possible that the actual commercial product, which may contain other compounds such as residual HDI monomer, gives a vapor pressure this high. However, it is not from the HDI isocyanurate molecule.
Page 19, Melting point	This should simply say "No melting point could be observed down to -150 °C."
Page 19, Conversion factor	This calculates to 20.64 at 25 C and 1 atm.
Page 21, Section 2.3, line 16	Here and elsewhere (e.g. Page 22, line 6), "derivation" should be "derivatization."
Page 21, Section 2.3, lines 27-28	"Impregnated glass fiber filters are efficient to collect particles of widely varying sizes and vapors" Add: "However, fast-reacting isocyanate aerosols, such as MDI-based spray foam insulation, should not be collected with an impregnated filter because the necessary derivatisation reaction is inefficient and the measurement of isocyanate will be underestimated."
Page 21, lines 29-31	"The fiber filters impregnated with 1-(9-anthracenylmethyl)piperazine (MAP) can be used to sample vapors, aliphatic isocyanate aerosols, aromatic isocyanate aerosols with particle diameter < 2 µm." It should be stated that this holds for any fast-reacting derivatising reagent, 1-2MP, 1-2PP, etc., not just MAP. The authors may want to replace "1-(9-anthracenylmethyl)piperazine (MAP)" here with "a derivatising reagent." Also, I suggest modifying the descriptions of aliphatic and aromatic somewhat. Here is my overall recommendation for this section: "The fiber filters impregnated with a derivatising reagent can be used to sample vapors, slow-reacting aerosols (typically aliphatic isocyanate systems), and isocyanate aerosols with particle diameter < 2 µm."
Page 22, line 7	"After collection, isocyanates are derivatized to stabilize the compounds…" This is strictly true, but it gives the impression to the reader that the derivatisation is a separate step carried out by the user after the isocyanate has been collected. In reality, this is happening as soon as the isocyanate is collected in the reagent-containing sampler; this can be clarified by saying instead "*Upon* collection, isocyanates are derivatized…"
Page 22, line 11	"After derivatisation, the samples collected using a filter need to be extracted from the filter." I suggest two changes here. Since derivatisation is not actually a step the user carries out, it should say "After sampling…". Also, the extraction from the filter should occur in the field if the filter was collecting isocyanate aerosols that require immediate extraction for full derivatisation. So I suggest the following: "After sampling, filter samples need to be extracted. If the filter was collecting isocyanate aerosol, the extraction should take place in the field immediately after sampling. If the filter was collecting isocyanate vapors only, the extraction can take place at the laboratory performing the analysis."

Page 22, lines13-14	I suggest the following: "Pure analytical standards are available for monomers but not for the vast majority of oligomeric isocyanate species, and qualitative..."
Page 22, line 18 (Table), column 4, row 4	"HPLC/UV *and* fluorescence."
Page 23, continuation of Table from Page 22, column 2	Replace "...immediately after measurement with 1,2-mpp" with "immediately after sampling" (do not need to say "...with 1,2-mpp)."
Page 23, line 1 (Table), column 2, row 1	All of these OSHA methods use the derivatising reagent 1-(2-pyridyl)piperazine (1-2PP), *not* 1,2-mpp.
Page 23, line 1 (Table), column 2, row 3	Should say "tryptamine in DMSO."
Page 24, line 1 (Table), column 2, row 4	OSHA method 18 uses the nitro reagent (which is also the reagent in the row below).
Page 26, section 4.1, line 6	"insulating", not "isolating."
Page 28, lines 30-34	"For TDI, fractions of 74-98% and 99.7% of the absorbed radioactivity were found in the blood...highest concentrations have been found in stomach and small intestine ...respiratory tract..." Is this a contradiction because it states that most of the radioactivity is in the blood, but then later that most was in these various organs?
Page 29, section 5.3, line 15	"Hexamethylene diisocyanate ethylene diamine" should simply be "Hexamethylene diamine."
Page 30, section 5.5, line 21 (Table)	"methylenediamine" should be "methylene dianiline" (which is MDA).
Page 36, section 7.1.1, lines 23-29	It appears that exposure data is repeated here, either intentionally or not. But there appears to be an error in the repetition, the earlier saying "4-66,464" and the later saying "15.4-66,464."
Page 48, line 29	The authors refer to Figure B, but mean to refer to Figure C.
Page 50, line 24	"in vivo, as considered..." The name of the isocyanate was left out.
Page 53, section 8.2, USA OSHA data	There are no exposure limits listed for OSHA, but OSHA has PELs for MDI and 2,4-TDI.

Comments on DECOS draft document on Di- and Triisocyanates

By: Paul Siegel, Research Scientist, and Justin Hettick, Research Scientist, NIOSH/Health Effects Laboratory Division, 1095 Willowdale Road, Morgantown, WV 26505; Crystal Forester, Research Chemist, NIOSH/National Personal Protective Laboratory, 626 Cochrans Mill Road, Pittsburgh, PA 15236 and Naomi Hudson, Health Scientist, NIOSH/Education and Information Division, 1090 Tusculum Avenue, Cincinnati, OH 45226

SECTION & PARAGRAPH	COMMENT
General Comments	
	The Committee's findings are appropriate based on data from previous epidemiological studies. This document is well written with applicable statistics and conclusions by the authors. The citations are appropriate.
	The section on the epidemiological studies of cancer is based on the 1999 IARC evaluation. All three cohorts have been updated since the IARC evaluation, and this section needs to be revised to reflect these updates listed below: Sorahan T, Nichols L [2002]. Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958-98. Occup Environ Med 59:751-758. Pinkerton LE, Yiin JH, Daniels RD, Fent KW [2016]. Mortality among workers exposed to toluene diisocyanate in the US polyurethane foam industry: update and exposure-response analyses. Am J Ind Med 59:630-643. Mikoczy Z, Welinder H, Tinnerberg H, Hagmar L [2004]. Cancer incidence and mortality of isocyanate exposed workers from the Swedish polyurethane foam industry: updated findings 1959-98. Occup Environ Med 61: 432-437.
Specific Comments	
Page 22, lines 6 & 11	Derivatization is the correct term for the chemical process, not derivation.
Page 30, line 23	The statement that "sensitization can be determined by the skin prick test" may not be accurate for isocyanates since the traditional antigen used to detect isocyanate specific IgE is an isocyanate conjugated human albumin. Also, it may not be clinically acceptable from a safety standpoint especially with the *in vitro* measures available.
Page 30, line 26	Discussion of half-life, isocyanate specific IgE testing: Reference 16 reported serum half-lives of isocyanate-specific IgE from 4-7 months. This is much longer than the plasma diisocyanate protein adduct half-lives. Suggest deleting or revising the statement that isocyanate-specific IgE testing is "therefore primarily limited to workers who are regularly exposed." The referenced manuscript did recommend measuring specific IgE within 1 month of the last exposure (although using modern

	immunoassay techniques, it probably would be detectable, depending on initial titers, for potentially > a year).
Page 32, line 23	The sentence is hard to understand and the reference is a secondary source (in French). TDI immune mediated/allergic asthma has been reported following inhalation challenge studies with asthma responses at challenge levels as low as 0.005 ppm TDI (Butcher et al, JACI 58(1):89-100, 1976).
Page 34, line 6	Direct pharmacological mechanisms: There are older studies using high dose TDI (high ppb to ppm *in vivo*, µM for *in vitro*). It is questionable that these mechanisms play even a minor role in immune mediated TDI asthma since these effects are observed at much higher exposure concentrations that TDI occupational asthma elicitation.
Page 45, line 13	Add "The" before Committee at the beginning of the sentence.

Gezondheidsraad
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Subject:	Comments on draft report 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,

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February 2018

Comments on Draft Di- and Triisocyanates

„Absorption via the skin"

Draft page page 28 line 8+9 — page 9 line 8+9 — page 29 line 5 — page 34 line 17, etc:

Commonly, the term „**absorption via the skin**" means that the substance passes the skin barrier and is distributed systemically in the organism.

"Dermal (percutaneous, skin) **absorption** is a global term that describes the transport of chemicals from the outer surface of the skin **to the systemic circulation** (OECD, Guidance document for the conduct of skin absorption studies, 2004). This is often divided into:

- penetration, which is the entry of a substance into a particular layer or structure, such as the entrance of a compound into the stratum corneum;
- permeation, which is the penetration through one layer into a second layer that is both functionally and structurally different from the first layer; and
- resorption, which is the uptake of a substance into the skin lymph and local vascular system and in most cases will lead to entry into the systemic circulation (systemic absorption)."

(WHO, Environmental Health Criteria 235: Dermal Absorption, 2006, p. 8)

It is generally accepted that (di)isocyanates are <u>not</u> absorbed through the skin in the sense of dermal / percutaneous / skin absorption. After penetration into the outer skin layer (di)isocyanates are transformed into conjugates or metabolites, probably deposited in the skin (and most of them possibly being relevant for sensitisation mechanisms). This also is expressed in draft chapter 5.3, line 3.

To avoid misunderstandings, all text passages referring to dermal absorption etc. should be rephrased to dermal <u>contact</u> / skin contact.

Skin contact and respiratory sensitization

Since skin contact with products containing isocyanates may occur easily at work **we suggest to include some more information about the possible induction of asthma caused by skin contact** to diisocyanate.

There is growing evidence suggesting that skin contact with diisocyanate can induce respiratory sensitization even in humans.

However, knowledge on isocyanate sensitization of airways by skin contact is not new. Asthmatic reactions were already mentioned in the textbook Konietzko, Handbuch der Arbeitsmedizin (Vol. IV Chapter 5.4) in 1991: Miners who experienced at least one massive dermal contact with MDI (while all airborne exposures were fairly below OEL) started suffering from asthma. The textbook concluded that isocyanate asthma appears to be induced rather by skin contact than by inhalation.

Already in 1992 (when attention was still focussed on inhalation toxicity of isocyanates) the German MAK Value Documentation on MDI noted that sensitisation of airways can be induced by skin exposure. The 2008 MAK Documentation Update emphasised the crucial role of skin contact, summarising several studies concerning this effect. This update highlighted the relevance of skin contact for the induction of asthma in respect of the work environment. (To alert against skin contact hazard, MDI was actually marked with 'skin notation'. It should be noted that in contrast to the real meaning of 'skin notation' diisocyanate does not show any systemic effect due to resorption through the skin.)

Remarkably, in 2007 the MAK-Commission of the DFG extended the definition of the "skin notation" used in the list of MAK values. To point out the crucial role of skin contact, in particular to diisocyanates, the MAK-Commission broadened the criteria for skin notation for designating substances with "H". The underscored amendment of the criteria had been added:

> Substances are designated with an "H" if through dermal exposure the observance of the MAK value on its own no longer guarantees the prevention of important adverse effects on health which were considered for establishment of the threshold value. In addition to systemic effects these can also include the sensitization of the respiratory tract if it has been demonstrated to be induced by skin contact. Substances are not designated with an "H" if toxic effects are not to be expected under workplace con-

This has been done on account of the serious diisocyanate effects due to the skin contact to (not resorption of!) diisocyanates. This is quite remarkable.

> (Side note: Nevertheless, we do not support a "skin notation" in these cases, leading to misunderstand able double-labelling of substances, because in workplace practice clear messages to workers, their representatives and employers are needed – 'skin notation' should assign to systemic availability of a substance due to its dermal resorption, and should not mixed up with 'sens notation'.)

Research findings (in particular by J. Pauluhn) in animal models which show immunological properties similar to those in humans, support the assumption that human respiratory sensitization likely is induced by skin contact.

Throughout the previous decades, scientific and medical attention focussed on adverse sensitization by inhalation (and on sensitization of the skin, which is rather rarely). Technical measures succeeded in reducing the airborne workplace exposure. But, small attention was (and is) still given to the induction of sensitization by skin contact.

Even though the mechanisms of induction through the skin pathway yet are not completely clear, today there seems to be sufficient evidence that skin contact to diisocyanate represents a severe respiratory sensitization hazard for humans.
At least, the induction of human respiratory sensitization hazard must be anticipated in respect of the precautionary principle.

Avoiding any skin contact with isocyanates must be a top priority — besides observing the OEL and lowering the air concentrations as far as possible.

Chapter 5.5 Biological monitoring:

It should be mentioned in the paper that the **relevance of biological monitoring of isocyanate-derived amines is questionable**.

To date biomonitoring methods are not capable of providing trustworthy and well-to-interpret results. Some research findings:

One day after controlled exposure (dermal, inhalation) of rats to MDI the respective biomarkers in urine and in blood were analysed. After inhalation, only 0.3% of administered MDI was found (in its metabolised form MDA) in the collected urine. After dermal application, even only 0.001–0.01% of administered MDI was found in urine. Over a period of 3 days, the collected urine showed a time-proportionally increasing recovery rate in the case of dermal application. The (slow, even long lasting) renal elimination of MDA is to be interpreted by the time-dependent bioavailability of MDI-conjugated proteins released from depots in the former exposed skin. On the other hand, in this study also MDA was administered. MDA showed recovery rates 10 to 100 times higher than for MDI in both exposure routes. (Pauluhn 2013, Tiermodell zur Bestimmung der Asthma-Auslöseschwelle von Diisocyanaten und seine Relevanz für die Ableitung von Arbeitsplatzgrenzwerten [Animal model for the determination of the elicitation threshold of diisocyanate asthma and its relevance for the derivation of occupational exposure levels]. Arbeitsmedizin Sozialmedizin Umweltmedizin 48 (3), 120-129; etc)

Therefore, biomonitoring of workers exposed to MDA (e.g. touching surfaces contaminated with MDA originating from hydrolysed MDI or from other MDA uses) may pretend an isocyanate exposure.

It is believed that the gross amount of dermally administered diisocyanate forms MDI-protein/-peptid conjugates in the upper layer of the exposed skin; inhalative intake results in haemoglobin-adducts respectively. The MDI deposited as protein conjugates in the skin layers is subject to a (very) slow clearance followed by renal elimination. Renal elimination of MDI-haemoglobin-adducts takes place after the decease of the erythrocyte (average life span of erythrocytes is 120 days).

Both elimination mechanisms are able to explain why urine biomarkers do not properly reflect the current isocyanate exposure.

The experimental findings are supportive of a conceptual pathway of which the formation of 4,4'-MDA-related biomarkers depends on the GSH-adduct rather than isocyanate derived amines. The percentage of urinary 4,4'-MDA as a proxy of the exposure to pMDI ranged from 0.03 to 0.5% which supports the conclusion that back calculations to potential external exposures are subject to significant errors. … There remains a need for further validations and rationalizations about the relationship between the airborne concentrations of diisocyanates and biomarkers of exposure before establishing general methods for biological monitoring. (Pauluhn etal. 2006, Analysis of biomarkers in rats and dogs exposed to polymeric methylenediphenyl diisocyanate (pMDI) and its glutathione adduct, Toxicology 222 (2006) 202–212)

Already the factor 17 (0.03% vs. 0.5%) demonstrates a high degree of uncertainty in biomonitoring results. It seems to be evident that for workplace risk assessment more precise and reliable data are needed.

Against this background, it is not surprising that inconsistent results and inaccurate correlation are often seen in workplace field investigations using biomonitoring.

The biological limit of the German MAK-Commission for MDA is a biological indicator (BLW), but not a biological tolerance value (BAT). This is due to the poor and inadequate data underlying this indicator. No biological limit for MDA is given in the official Technical Rule for Hazardous Substances (TRGS) 903 for this reason. The German biological tolerance value of HDA as well is based on a weak

data basis (consisting of 19 male workers) and the Value Documentation states that it was not possible to establish a dose-effect-relation.

Referring to the assessment of potential sensitizing exposures, *"biomonitoring does not provide a prognostic nor specific patho-diagnostic significance because time-variable local exposure patterns cannot be reflected adequately by systemic and integrating exposure markers"*. (Pauluhn 2013, translated)

However, biomonitoring of amines may be useable for selected specially designed scientific research projects (e.g. pre-shift vs. post-shift designs) but not for determination of skin contact or for routine health surveillance relying on absolute limit values.

Routine invasive biomonitoring using blood samples would not be appropriate in respect of human rights (right to physical integrity, right to self-determination, etc.). Besides that, biomonitoring in blood is not scientifically developed to date.

Since the scientific basis of biological levels of isocyanate-derived diamines is questionable, **no recommendation should be given in the paper**.

For a thorough scientific discussion, it is recommended to personally consult Prof. Pauluhn (who is also active in the German MAK-commission).

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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,

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