Vink, S.R. (Stefan)

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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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:

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Karol, MH (1981): Survey of industrial workers for antibodies to toluene diisocyanate. Journal of Occupational Medicine 23 (11), 741-747.

MAK collection for Occupational Health and Safety (www.mak-collection.com) 4,4'-Methylene diphenyl diisocyanate, (MDI) and "polymeric" MDI (PMDI), 2000

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. Brown Norway rat asthma model of diphenylmethane-4,4'-diisocyanate (MDI): analysis of the elicitation dose-response relationship. Toxicol Sci 2008; 104(2): 320-31.

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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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Centers for Disease Control and Prevention
National Institute for Occupational
Safety and Health
1090 Tusculum Avenue
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March 15, 2018

Health Council of the Netherlands
Attn: Dr. S.R. Vink
PO Box 16052
2500 BB, The Hague
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

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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.

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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).