Committee for Risk Assessment

RAC

Opinion on scientific evaluation of occupational exposure limits for

Diisocyanates

ECHA/RAC/A77-O-0000006826-64-01/F

11 June 2020

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OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON THE EVALUATION OF THE OCCUPATIONAL EXPOSURE LIMITS (OELs) FOR DIISOCYANATES

Commission request

The Commission, in view of the preparation of the proposals for its amendment of Directive 98/24/EC on the protection of the health and safety of workers from the risks related to chemical agents at work (CAD), and in line with the 2017 Commission Communication '*Safer and Healthier Work for All*' - *Modernisation of the EU Occupational Safety and Health Legislation and Policy*[1], asked the advice of RAC to assess the scientific relevance of occupational exposure limits for some chemical agents.

Therefore, the Commission made a request on 26 March 2019 to ECHA in accordance with the Service Level Agreement (SLA) (Ares(2019)18725), to evaluate, in accordance with the Directive (98/24/EC), the following chemical agents: **diisocyanates**.

I PROCESS FOR ADOPTION OF THE OPINION

Following the above request from the European Commission RAC is requested to draw up an opinion on the evaluation of the scientific relevance of occupational exposure limits (OELs) for diisocyanates with a deadline of 26 September 2020.

Chemical name(s): Diisocyanates

In support of the Commission's request, ECHA prepared a scientific report concerning occupational limit values for diisocyanates at the workplace. In the preparatory phase of making this report, a call for evidence was started on 17 April 2019 to invite interested parties to submit comments and evidence on the subject by 30 June 2019.

This scientific report was made publically available on **17 October 2019** and interested parties were invited to submit comments by **16 December 2019**[2].

RAC developed its opinion on the basis of the scientific report submitted by ECHA. During the preparation of the opinion, the scientific report was further developed as an Annex 1 to the RAC opinion to ensure alignment.

The RAC opinion includes a recommendation to the Advisory Committee on Safety and Health at Work (ACSH) in line with the relevant Occupational Safety and Health legislative procedures.

II ADOPTION OF THE OPINION OF THE RAC

Rapporteurs, appointed by RAC: **Veda Varnai** and **Dick Heederik**

The opinion was adopted by consensus on **11 June 2020.**

[1] http://ec.europa.eu/social/main.jsp?langId=en&catId=148&newsId=2709&furtherNews=yes

[2] https://echa.europa.eu/oels-pc-on-oel-recommendation

RAC Opinion of the assessment of the scientific relevance of OELs for diisocyanates

RECOMMENDATION

The opinion of RAC on the assessment of the scientific relevance of Occupational Exposure Limits (OELs) for diisocyanates is set out in the table below and in the following summary of the evaluation, supported by Annex 1.

SUMMARY TABLE

The table presents the outcome of the RAC evaluation to derive limit values for diisocyanates.

Derived Limit Values

<table>
<tr><td>OEL as 8-hour time weighted average (TWA) exposure:</td><td>A threshold for bronchial hyper-responsiveness or for the development of asthma, could not be observed.

However, an OEL defined as an 8-hour time weighted average (TWA) exposure based on the ‘NCO group’ can be obtained from the exposure - excess risk relationships for hyperresponsiveness or diisocyanate asthma as derived below.
<table><tr><th>Excess risk over a working life period</th><th>Exposure - response relations derived from Pronk et al. (2009), and Collins et al. (2017), in µg/m^3 NCO in air</th></tr><tr><td>0.1%</td><td><0.025</td></tr><tr><td>0.5%</td><td>0.027-0.040</td></tr><tr><td>1%</td><td>0.055-0.070</td></tr><tr><td>2%</td><td>0.12-0.19</td></tr><tr><td>3%</td><td>0.22-0.33</td></tr><tr><td>4%</td><td>0.40-0.48</td></tr><tr><td>5%</td><td>>0.67</td></tr></table></td></tr>
<tr><td>STEL:</td><td>A 15-minutes Short Term Exposure Limit (STEL) value which is maximally a factor 2 higher than a derived OEL based on the exposure - excess risk relation. This STEL value should not exceed 6 µg/m^3 NCO.</td></tr>
<tr><td>BLV:</td><td>No BLV</td></tr>
<tr><td>BGV:</td><td>Set at the limits of quantification (LOQs) for relevant diisocyanate metabolites (diamines) in urine</td></tr>
</table>

Notations

Notations:	skin sensitisation, respiratory sensitisation, ‘skin’

RAC OPINION

Background

This opinion concerns **diisocyanates** (See section 1 of Annex 1 for a definition).

This evaluation, makes use of the literature as described in Annex 1 as well as previous reviews, in particular:

- Recent international evaluations:
  - the Dutch Expert Committee on Occupational Safety report recommending a health-based occupational exposure limit for di- and triisocyanates (DECOS, 2018);
  - the draft French Agency for Food, Environmental and Occupational Health & Safety report recommending occupational limits for TDI (ANSES, 2019);
  - the Agency for Toxic Substances and Disease Registry documents - toxicological profile for toluene diisocyanate and methylenediphenyl diisocyanate (ATSDR, 2018);
  - earlier evaluations described in Annex 1;
- the opinion of RAC and SEAC recommending restriction of diisocyanates at the workplace (ECHA, 2018);
- relevant REACH registration dossiers;
- A literature search of published peer review papers from the last ten years (and some older articles regarding chemical agent identification and physico-chemical properties).

Key conclusions of the evaluation

- Respiratory health effects (occupational asthma, isocyanate sensitisation and bronchial hyperresponsiveness) are the critical endpoints related to diisocyanate exposure.
- Because (IgE) sensitisation is only present in a fraction of occupational diisocyanate asthma patients and mechanisms other than IgE sensitisation play a role, any risk assessment of diisocyanates should focus on (occupational) asthma as an endpoint or generally accepted proxies of these endpoints (bronchial hyper-responsiveness and/or work related asthma symptoms). Endpoints considered in surveillance studies such as cross-shift lung function changes and accelerated lung function decline are not considered to be sufficiently sensitive and accurate proxies for indicating occupational isocyanate asthma.
- Both inhalation and dermal exposure are likely and relevant routes for occupational exposure to diisocyanates. Both routes are relevant for induction of respiratory sensitisation. The contribution of dermal exposure to respiratory sensitisation cannot be quantified at present.
- A NCO group (R-N=C=O) approach for all diisocyanates is proposed, since diisocyanates share a common mechanism of inducing hypersensitivity reactions and there is not enough data to assess differences in potency for different diisocyanates.
- RAC derived exposure - risk relations from two independent studies that showed exposure-response relations for bronchial hyperresponsiveness and occupational asthma. The two exposure response relations are very similar. The estimates from these two studies are generally in line with other studies that report asthma cases at low exposure levels.

- A threshold for bronchial hyper-responsiveness or for the development of asthma could not, however, be observed, although theoretically sensitisation and elicitation are threshold phenomena. The threshold for developing sensitisation and asthma probably occurs at very low levels for which few observations exist.
- It was therefore considered appropriate to use the exposure-response curves for bronchial hyper-responsiveness and the development of asthma for deriving an exposure-excess risk relation.
- RAC adjusted the exposure risk relations obtained from the two studies to a working life-long exposure by multiplying the risks calculated from the two studies by a factor of 2.
- Point estimates from these exposure response relations contain some uncertainties resulting from: unmeasured dermal exposure in addition to air exposure, selection bias (healthy worker effect) and the observed high risk after short term exposure in some of the studies. These uncertainties act in different directions and cannot be quantified.
- Any Occupational Exposure Limit, for occupational diisocyanate exposure, derived from the exposure-excess risk relation, will be associated with a residual excess risk for developing occupational asthma. The lower the exposure the lower the risk for developing asthma.
- The exposure associated with different excess risk levels can form the basis for deriving an Occupational Exposure Limit. RAC notes that Article 3 of Directive 98/24/EC - when setting the procedures to be followed and factors to be considered in establishing indicative or binding occupational exposure limit values at Community level - does not define a level of residual excess risk to be considered in case a safe threshold cannot be identified. Therefore, a table has been derived with different risk levels and point estimates of associated exposure levels in µg/m^3 NCO in air for possible use by the Commission in following the procedures of Article 3 of Directive 98/24/EC.

Table 1: Excess risk levels and point estimates of associated exposure levels in µg/m^3 NCO in air

Excess risk over a working life period	Estimated 8-hour time weighted average exposure, based on exposure response relations derived from Pronk et al. (2009), and Collins et al. (2017), in µg/m^3 NCO in air
0.1%	<0.025
0.5%	0.027-0.040
1%	0.055-0.070
2%	0.12-0.19
3%	0.22-0.33
4%	0.40-0.48
5%	>0.67

- RAC advises a 15-minutes Short Term Exposure Limit (STEL) value which is maximally a factor 2 higher than a derived 8-hour time weighted average OEL based on the exposure excess risk relation. This STEL value should not exceed 6 µg/m^3 NCO.
- An OEL defined as an 8-hour TWA, obtained from the exposure-risk relation as derived by RAC and taking other potential factors into account than scientific assessment, should never exceed the proposed STEL value.

- No Biological Limit Value (BLV) can be established.
- A Biological Guidance Value (BGV) is proposed, and set at the limits of quantification (LOQs) for relevant diisocyanate metabolites (diamines) in urine.
- Since all diisocyanates considered in this evaluation have a harmonised classification under CLP, either as skin sensitisers, respiratory sensitisers or both, “skin sensitisation” and “respiratory sensitisation” notations are warranted.
- A ‘skin’ notation is proposed in order to ensure prevention of systemic immunological effects (i.e. respiratory sensitisation) from dermal contact with diisocyanates.
- A specific health surveillance is appropriate, in line with Articles 6.3 and 10 of the Chemicals Agents Directive (Council Directive 98/24/EC), and the Member States are recommended to introduce appropriate arrangements (in accordance with national laws and/or practice, and in line with the principles and practices of occupational medicine) aiming to identify early signs and symptoms of respiratory sensitisation.

Mode of action considerations (see section 7 of Annex 1 for full discussion)

The predominant health effects of occupational exposure to diisocyanates are irritation and sensitisation of the respiratory tract and skin, occurring both after acute and long-term exposure. In animals, in addition to respiratory and skin sensitisation, inflammatory effects in the upper and lower respiratory tract were observed following acute and repeated exposure.

Other toxic effects reported to be potentially related to diisocyanate exposure include neurotoxicity, genotoxicity and carcinogenicity.

Neurotoxicity (central and peripheral nerve system) has been suggested following heavy inhalation exposure in workers (Axford et al., 1976, Le Quesne et al. 1976, Singer and Scott, 1987) (for more details see section 7.3 of Annex 1). Nevertheless, available human data are inadequate to establish a causal association and no plausible mechanisms of toxicity were identified (Hughes et al., 2014). Also, no indication of neurotoxicity was observed in animal studies.

Genotoxicity was indicated by some animal data and limited human data exists. The data are, however, inconclusive and equivocal (for full discussion see section 7.6 of Annex 1). Presently, no diisocyanate has a harmonised classification as a mutagen.

Several diisocyanates (e.g. TDI, MDI) are classified for carcinogenicity. IARC (1999) classified TDI as possibly carcinogenic to humans (Group 2B), since there is inadequate evidence of its carcinogenicity in humans, but sufficient evidence in animals (increased incidences of tumours in rodents exposed to TDI by oral gavage in NTP studies). MDI has been designated by IARC (1999) as not classifiable, due to inadequate evidence in humans and limited evidence in animals. Because the IARC report was published in 1999, More recent literature was reviewed, including critical review papers prepared by Prueitt et al. (2013, 2017), but did not identify any new information that would affect the present classification.

No epidemiological studies are available that explore reproductive effects from diisocyanate exposure. Animal data does not indicate that reproductive or developmental toxic effects occur resulting from exposure to diisocyanates.

Respiratory effects (see section 7 of Annex 1 for full discussion)

The available evidence from human studies (epidemiological observational studies and challenge studies) shows that diisocyanate exposure leads to respiratory effects including specific sensitisation, asthma, as well as accelerated lung function decline.

Respiratory effects, in particular occupational asthma and sensitization are the critical endpoints in case of diisocyanate exposure. These are the relevant endpoints that should be used as a point of departure for risk assessment for diisocyanates.

There are a few important issues with regard to these endpoints. Occupational asthma is a disease characterised by variable airflow limitation and/or hyperresponsiveness associated with inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Different types of occupational asthma are distinguished. Diisocyanate exposure can lead to immunoglobulin (Ig)E-mediated asthma after a latency period, but short high exposure episodes can also lead to irritant asthma with or without a latency period. Diisocyanate exposure also leads to forms of asthma with unknown pathological mechanisms, also with a latency period. A positive diisocyanate specific IgE test (sIgE) has a high specificity when compared to an occupational asthma diagnosis, but a low sensitivity. Thus, those with a positive sIgE test are likely to have occupational asthma, but many individuals with occupational asthma have no diisocyanate sIgE. As a result, diisocyanate sIgE testing has a high false negative test rate. Alternative mechanisms, other than sIgE sensitisation have been suggested (see for a review on the role of IgE (Wisnewsky & Jones, 2010)). Others have suggested that adaptive immune responses or oxidative stress might play a role.

The diagnosis of occupational asthma is usually done by tests that separate asthma cases from normality or other lung diseases, tests that identify the workplace as the cause of the respiratory symptoms, and tests that identify the agent causing the occupational asthma; procedures are extensively discussed in an European Respiratory Society working group report (Baur et al., 2012). Workers with confirmed sensitisation-induced occupational asthma may not fulfil the criteria for compensation in a particular country. Criteria for legal compensation vary between different administrations (Baur et al., 2012). It should be realised that the diagnostic criteria are less rigid for epidemiological studies than in case of individual compensation. In epidemiological studies, a complete clinical workup is often not feasible and because of the complex etiology of diisocyanate asthma, as well as the different phenotypes of asthma, proxies of occupational diisocyanate asthma are often being used for practical reasons such as combinations of (work related) asthma symptoms and bronchial hyperresponsiveness (assessed by metacholine challenge), and/or peak expiratory flow records over longer periods of time.

These issues should be considered when data from monitoring or surveillance programs or etiologic epidemiological studies are being interpreted or used in risk assessment. In particular early studies conducted on TDI health effects, in particular those conducted between the 1960-ies and 1980-ies measured cross-shift lung function changes or accelerated lung function decline over several years. Both of these measures are sub-optimal proxies for assessing (work-related) asthma and not sufficiently sensitive and specific to define (occupational) asthma.

It should be noted that respiratory sensitisation to diisocyanates can be induced not only via the inhalation route, but also via dermal exposure (Bello et al., 2007, North et al., 2016, Pauluhn, 2014, Tsui et al., 2020). Human and animal data indicate that a chemical may induce respiratory disease after sensitisation via dermal exposure even when the air levels are too low to cause sensitisation via the respiratory tract (Tsui et al., 2020).

Consideration of threshold for respiratory sensitisation to diisocyanates

Development of an occupational allergic respiratory disease due to exposure to low-molecular weight chemicals (including diisocyanates), could be described as a two-step process (Sullivan et al., 2017, Cochrane et al., 2015). The first step involves induction of respiratory sensitisation, which may result either following inhalation or dermal exposure (Bello et al., 2007). The second step occurs when a sensitised person is subsequently exposed to the same substance via inhalation (elicitation phase), which may result in inflammation in the respiratory tract and clinical symptoms, such as rhinitis or asthma.

Although mechanistic *in vitro* studies and studies in animals suggest that a threshold for these effects probably exists (e.g. Arts et al., 2006, Enoch et al., 2009, Schupp and Collins, 2012, Pauluhn and Poole, 2011, Pauluhn 2014, Sullivan et al., 2017), RAC considers that presently available data do not allow to define a threshold level, at least not for humans. As described in Annex 1, pathophysiological mechanisms involved in the development of diisocyanate-induced asthma are not sufficiently understood, the quantitative relationships between key events involved in the induction of dermal and respiratory sensitisation are not known (Sullivan et al., 2017)[3], and there are no reliable markers of (respiratory) sensitisation to diisocyanates that could be used to identify either a threshold or a dose-response relationship for induction of sensitisation.

Regarding the second step, it was observed that very low levels of diisocyanates can induce an adverse respiratory response in workers with pre-existing diisocyanate-related asthma. For example, in specific inhalation challenge tests, sensitised workers had a positive response to 1 ppb of MDI, TDI or HDI (Lemière et al., 2002, Burge, 1982), or even to 0.05 ppb (0.51 µg/m^3) of MDI (Suojalehto et al., 2011). Exposure levels required to develop asthma are not known.

Based on animal experiments (e.g. Schupp and Collins, 2012; several experiments done by Pauluhn et al.), it has been proposed that inhalation exposure to irritant doses of diisocyanates is required for development of an allergic response in the respiratory tract, that thresholds for irritation are lower than those for specific, immunologically mediated airway reactions, so that irritation thresholds should be also protective for respiratory sensitisation. While it is well recognised that irritative substances can trigger an asthmatic response in sensitised individuals and aggravate allergic asthmatic disease (Vincent et al., 2017, Sastre et al., 2003, Jenkins et al., 1999, Devalia et al., 1998), there is only sparse data that indicates that irritation can promote the initiation of respiratory sensitisation to allergens in humans (e.g. Diaz-Sanchez et al., 1999, Devalia et al., 1998). Data on thresholds for respiratory irritation following diisocyanate exposure in humans are limited, and, as mentioned above, respiratory sensitisation thresholds for these substances cannot be defined for humans. It is, therefore, considered that the available human data are too limited to provide evidence that sensitisation to diisocyanates (or any other allergen) cannot occur below the irritation threshold.

It is considered that the animal evidence is insufficient to determine a specific threshold value applicable to human risk assessment for respiratory sensitisation induced by diisocyanates (Lynch et al., 2018). Presently, there is no standardised and validated animal model for respiratory allergy and asthma, and limitations of reported animal models are numerous (please see Annex 1, section 7.5.2 for further details). The main reasons include the absence of a clear consensus about the mechanisms through which chemicals cause sensitisation of the respiratory tract (Kimber et al., 2011, Pauluhn, 2014), and a lack of data on potential differences between modes of action in humans and animals (DECOS, 2018). Therefore, RAC is of the opinion that a translation of threshold values for respiratory sensitisation from animals to humans is unreliable for diisocyanates, and that OELs for this hazard endpoint cannot be based on animal data.

[3] For example, the level at which intercellular ‘‘danger signals’’ approach a threshold beyond which an activation of antigen-presenting cells is certain is not known (Sullivan et al., 2017).

Occupational asthma risk assessment and exposure limit values (see section 8 of Annex 1 for full discussion, as well as Table 36 in Appendix 3 of Annex 1)

In various EU Member States as well as outside the EU, OEL's for diisocyanates, either as individual substances or as a group, are established at a national level. Two Member States have recently evaluated diisocyanates but the proposed Occupational Exposure Limits have not yet been decided upon. Other exposure limits result from reviews that took place more than a decade ago.

In the EU Member States and in the USA, 8-hour TWAs range from 0.02 – 0.1 mg/m^3 for 4,4'-MDI, 0.001 – 0.08 mg/m^3 for 2,4 TDI, 0.02 – 1 mg/m^3 for HDI, and approximately from 0.007 – 0.02 mg/m^3 for diisocyanates as a group (expressed in NCO group).

For short-term exposure, values range from 0.05 – 0.2 mg/m^3 for 4,4'-MDI, 0.006 – 0.15 mg/m^3 for 2,4 TDI, 0.03 – 0.15 mg/m^3 for HDI, and approximately from 0.02 – 0.07 mg/m^3 for diisocyanates as a group (expressed in NCO group).

Some Member States have also published biological limit values (Table 9 in Annex 1).

Below is a summary of a rationale behind different relevant national occupational reference values, mainly those presented in Annex 1.

ANSES, 2019 (draft opinion). The French OEL Committee considered that:

- A dose-response relationship cannot be established on the basis of available human data, due to studies' limitations (non- quantifiable dermal and peak exposures; real exposure is difficult to establish due to e.g. use of personal protective equipment, previous exposures, dermal exposure and co-exposure with other chemicals; limited size of the test populations; lack of more objective outcome measurements).
- The available animal studies indicate that both respiratory irritation and sensitisation may be interdependent, and that both irritation and sensitisation by TDI is a threshold phenomenon (e.g. Schupp and Collins, 2012, Pauluhn, 2014).

Based on these data, pulmonary irritation was selected as the critical end point to derive an OEL for TDI, which will be protective against irritation and induction of sensitisation, but not against elicitation reaction (i.e. allergic reactions in sensitised individuals).

A STEL value of 1.3 ppb (as a 15-min short-term limit value for respiratory irritation) was derived from the Vandenplas et al. (1999) study in human volunteers (for more details on the study please see section *Short term limit value (STEL)* in this Opinion), applying assessment factors of 3 for LOAEC to the NOAEC extrapolation, and 5 for intra-species variability, in order to take into account higher variability in sensitivity among workers and to prevent chronic ffect (i.e. in asthmatics TDI induced severe pulmonary response already at 10 ppb during 1-hour exposure).

A pragmatic 8-hour TWA value of 0.04 ppb of TDI (0.1 µg/m^3 of NCO) was derived by dividing STEL value by 32[4] (a direct extrapolation from the STEL, based on a difference in exposure duration).

DECOS, 2018. The Dutch Expert Committee on Occupational Exposure Standards of the Health Council of the Netherlands evaluated human data, and proposed a limit value of 0.10 µg/m^3 as NCO (for di- and triisocyanates), based on an estimated 1% excess risk in prevalence of BHR_{20} (bronchial hyperresponsiveness using a fall in forced expiratory volume in one second (FEV_1) of 20% as a cut-off level) and incidence of occupational asthma (based on Pronk et al., 2009 and Collins et al., 2017, respectively) (for more

[4] In order to minimise the risk of exceeding the 15 min-STEL over the duration of an 8-hour workshift (i.e. 32 times 15 minutes) the atmospheric concentration of TDI should not exceed the 15 min STEL / 32 on a working day of 8 hours.

details please see section *Use of the exposure response relations to calculate risk* of this Opinion, as well as section 8.1.2 and Table 36 of Annex 1). In the Netherlands, a 1% risk increase has been defined by the Minister of Social Affairs and Employment and is considered the "maximal acceptable lifetime risk" for sensitisation or occupational asthma incidence in case of allergen exposure. A health-based short-term exposure limit was not derived by the Committee, due to lack of quantitative data on relationship between short-time exposure to peak levels of isocyanates and the development of isocyanate-induced occupational asthma.

In Germany, in the DFG MAK Value Documentation for MDI, a MAK[5] value of 0.05 mg/m^3 is considered to neither cause bronchial hypersensitivity and its associated symptoms nor the formation of specific antibodies (a non-significant increase in respiratory symptoms was reported in workers exposed up to 0.1 mg/m^3 of 4,4′-MDI, while concentrations of 0.05 mg/m^3 had no effect) (DFG, 2000, 2008). To protect from increased peak exposure, 8-h TWA and short-term exposure limit value for 15 minutes have been set at the same level (0.05 mg/m^3), and a ceiling exposure limit has been set to 0.1 mg/m^3. In the weight of evidence approach, animal data were also considered, and it was concluded that a NOAEC of 0.2 mg/m^3 for local lung effects, observed in long-term inhalation studies in rats, indicates no need to adjust the MAK value.

8-hour TWA of 5 ppb (0.035 mg/m^3) for TDI are based on gradual deterioration in lung function observed in several occupational epidemiological studies (AGS, 2006, DFG, 2003). STEL was set to the same limit as 8-hour TWA. Concerning respiratory sensitisation it was concluded from three epidemiological studies, that under a TDI concentration below 10 to 20 ppb "generally no new cases of TDI asthma are observed". The ceiling limit value for TDI was set to 20 ppb (0.14 mg/m^3).

A MAK value is not available for TDI, since it has been included in the "substances that cause cancer in humans or animals or that are considered to be carcinogenic for humans for which the criteria for classification in Category 4 or 5 are in principle fulfilled" and for which the database "is insufficient for the establishment of a MAK or BAT value" (DFG List of MAK and BAT values 2017).

For HDI, OEL (and MAK) values were set to 5 ppb (0.035 mg/m^3) for 8-hour TWA and STEL, and 10 ppb (0.07 mg/m^3) for ceiling limit value (DFG, 2013).

The available human data were not considered suitable for the derivation of a MAK value (exposures to a mixture of substances with HDI prepolymers, other diisocyanates and solvents; and the real exposure levels have, for the most part, not been recorded quantitatively). Therefore, MAK value was based on animal data, i.e. on dose levels at which irritant effects were no longer observed [NOEC of 5 ppb (0.035 mg/m^3) in a subacute inhalation studies in rats, and NOAEC of 5 ppb for the long-term inhalation study in rats; Mobay Chemical, 1984]. No assessment factor was applied, since it was considered that irritant effects are no longer to be expected at this concentration in human population as well. However, it was pointed out that this limit value may not be protective for persons with non-specific bronchial hyperreactivity or HDI hypersensitivity.

In Sweden an 8-hour TWA is set to 2 ppb (3.4 µg/m^3), and a STEL, as a 5-minute average value, to 5 ppb (8.6 µg/m^3), expressed as NCO (with the equivalent values expressed in mg/m^3 for the various substances).

In Montelius (2001), which is the scientific basis for the Swedish occupational standards, it is stated that isocyanate asthma has been observed in persons occupationally exposed

[5] The MAK value is the maximum permissible concentration of a substance as a gas, vapour or aerosol in the air at the workplace which, according to current knowledge, does not normally affect worker health or cause unreasonable nuisance even with repeated and long-term exposure, usually 8 hours a day, but assuming an average weekly working time of 40 hours.

to TDI at workplaces where air concentrations ranged from 1 to 25 ppb, with 5 ppb as a median value. Asthma symptoms have been observed in individuals hypersensitive to isocyanates at TDI levels of 5 ppb and estimated TDI levels of 1 ppb.

ACGIH, 2016. The American Conference of Governmental Industrial Hygienists (ACGIH, a non-governmental, non-profitable organisation that assesses industrial hygiene health and safety issues and provides scientific guidance for government, academia and corporate facilities), established a Threshold Limit Values (TLVs)[6]. In 2016, 8-hour TWA was set to 1 ppb, and STEL to 5 ppb (correspond to 3.4 and 17 µg NCO/m^3, respectively), based on evaluation of human and animal data.

Although TLVs are based solely on health factors (not taking into account economical or technical feasibility), they are not intended to represent safe limits, but the level of exposure that the typical worker can experience without adverse health effects. In the case of TDI, ACGIH, so, acknowledged that 8-hour TWA of 1 ppb will not prevent all new cases of TDI-induced occupational asthma, and that workers who have already been sensitised to TDI may not be protected.

Nevertheless, as discussed in Annex 1 (section 8.1.1), in the absence of a reliable marker for induction of respiratory sensitisation it is not possible to quantitatively assess a possible threshold or dose-response for induction of sensitisation to TDI. Also, a decline in FEV1, which was used as one of the endpoint in ACGIH assessment, is not considered a sensitive predictive marker of asthma.

Exposure-response studies

Several exposure response studies have been published over the years and several reviews are available that describe these exposure response relations (Ott et al., 2002, Daniels, 2018, Ott et al., 2003). Ott et al. (2002), describe 9 cross-sectional studies and 8 longitudinal studies on occupational asthma occurrence (prevalence or incidence). Because of the relatively small sizes of the population samples considered in these cross-sectional studies (in most cases <100 individuals), these studies are not useful for risk assessment. Very few studies involve quantitative exposure response studies on diisocyanate exposure. Moreover, no internal (i.e. within-study) exposure response analyses were presented. In a separate review by Ott et al., it was concluded that the reviewed studies provided sufficient evidence that the annual incidence of occupational asthma caused by TDI was below 1% and accelerated FEV_1 decline was not observed at exposure levels < 5 ppb (8-hour TWA) and < 20 ppb for peak exposures,[7] but this was debated by others (Hogberg et al., 2005). It should be noted that an annual incidence around or below 1% can still lead to a considerable risk over a working life period.

Daniels (2018) specifically reviewed the literature for studies suitable for exposure-response analyses and identified 8 studies which could potentially be used for secondary exposure-response analyses.

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[6] Threshold Limit Value (**TLV**) is a reserved term from the American Conference of Governmental Industrial Hygienists. Unless a state or the federal movement adopts a hazardous chemical TLV, it is not a regulatory requirement but a recommended guideline. The permissible exposure limit (**PEL**), established by OSHA, is a legal limit in the United States for exposure of an employee to a chemical substance or physical agent. Recommended Exposure Limit (**REL**) is a reserved term from National Institute for Occupational Safety and Health (NIOSH). REL is not a regulatory requirement, but a recommended guideline for upper exposure limits to hazardous substances. NIOSH recommends to OSHA to adopt into regulation the recommended REL as the "new" permissible exposure limit that will subtract, add or update an existing PEL (https://oecscomply.com/difference-pel-tlv-rel/). RELs are based on the most sensitive and relevant health effects reported in the medical and toxicological literature.

[7] The conclusion was based on authors' observation that downward trends in occupational asthma incidence rates over time coincided with a decrease in average TDI exposures during the same time period, and that higher incidence rates were observed in persons experiencing acute overexposures.

RAC concluded that this study cannot be used because of some key methodological issues (see Annex 1). RAC therefore evaluated whether the studies included in the review by Daniels (2018) could supply individual exposure-responses which could be of use in an alternative exposure-response analysis.

Three cross-sectional studies were included in the review (Daftarian et al., 2000, Belin et al., 1983, Omae, 1984). Only one of the three cross-sectional studies included in the review did perform an internal exposure response type of analysis (Daftarian et al., 2000). This study involved 114 workers (participation rate 39%) (numbers differ for different variables) who underwent a medical evaluation (symptoms, serology, serial peak flow measurements). In addition, an extensive exposure survey was completed to characterise exposure to diisocyanates. Because of the relatively small size of the study, a meaningful epidemiological analysis was not possible. Generally, more symptoms and serological responses and a higher peak flow variability were seen among the high exposed (>0,43 µg/m^3 TDI (or ~1ppb)) although differences were generally not statistically significant because of the limited power of the study. The low response rate might have introduced selection bias.

The longitudinal studies included in the Daniels study had an estimated asthma incidence between 0.48 and 1.07 cases per 100 person years of observation at estimated average TDI exposure between 2.0 and 4.2 ppm over eight hours TWA.

Review of the studies included by Daniels (2018), showed that no studies were included that allowed evaluation of an (internal) quantitative exposure response relation to be used in further analyses (see Annex 1).

Two studies that were excluded by Daniels (2018), are of interest because they give information about isocyanate related respiratory effects at low exposure levels. Both studies presented results in such a way that incidence rates of asthma could not be calculated as required by the Daniels (2018), evaluation.

Meredith et al. (2000) compared 27 cases mainly attributed to toluene diisocyanate (TDI) to 51 work area, start and duration of employment, sex, and age matched referents. Time weighted average (TWA) exposures at the time of onset of asthma were higher for cases. The mean TWA exposure for cases was 1.5 ppb (95% c.i.; 1.2 to 1.8). The authors concluded that asthma can occur at low concentrations of isocyanates and even at these low concentrations, risk increases with higher exposure.

Gui et al. (2014), describe a study among forty-nine newly hired workers from a modern TDI polyurethane foam factory in an Eastern European country. These workers were evaluated during a pre-employment medical, and 6- and 12-months post-employment through questionnaire, spirometry, and TDI-specific serology. Airborne TDI levels were monitored by fixed-point air sampling and limited personal sampling. Swipe samples were taken to evaluate potential dermal exposure. Airborne TDI levels overall were low; over 90% of fixed-point air measurements were below the limit of detection (0.1 ppb), no measurements were observed above 5 ppb. Over the first year of employment, 12 of the 49 original workers (24.5%) were lost to follow-up, no additional workers were enrolled, and seven of the 49 original workers (14.2%) developed either new asthma symptoms (n=3), TDI-specific IgG (n=1), new airflow obstruction (n=1) and/or a decline in FEV1 15% (n=3), findings that could indicate TDI-related health effects. The prevalence of current asthma symptoms was significantly higher in the workers lost to follow-up compared to those who completed the 12-month follow-up (25% vs. 2.7%; P=0.04). The findings suggest possible early TDI-related health effects in a modern polyurethane production plant among workers with low TDI exposure.

Two other studies have been published that describe exposure response relations and which were not included by the review by Daniels (2018). The first, by Pronk et al. (2006a, 2006b, 2007, 2009), included workers exposed to predominantly HDI and therefore did not fit the criteria of the Daniels (2018) review. The study by Collins et al. (2017), appeared after the search period covered by the Daniels (2018), study.

Pronk et al., (2007) reported relations for respiratory symptoms and sensitisation in a large population of 581 Dutch spray painters and other workers occupationally exposed to isocyanate oligomers during car and industrial spray painting. The participants were involved in spray painting in various industries ranging from car spray painting, spray painting of air planes, ships and other objects. Exposure to diisocyanates has been studied in great detail using LC-MS for isocyanate monomers, oligomers and products of thermal degradation (Pronk et al., 2006a, 2006b). The sampling strategy was based on short term measurements on task level, which were integrated into a personal exposure estimate for each study participant over a period of a month, based on average time activity patterns.

Statistically significant associations were found between exposure and asthmatic symptoms, COPD-like symptoms, work-related chest tightness, and work-related conjunctivitis. In a second study, nested within the first one,[8] 229 of 581 spray painters underwent a more detailed medical survey (Pronk et al., 2009). Workers with higher isocyanate exposure were more often hyperresponsive. A statistically significant exposure-related decreased FEV1, FEV1/FVC and flow-volume parameters independent of BHR were found. Pronk et al. (2007, 2009) studied the association of HDI exposure and BHR, but also combined BHR with the occurrence of wheezing (operational definition of asthma). The statistically significant exposure response relations for BHR and BHR and asthma symptoms, as obtained through a smoothing spline are shown below.[9]

[8] All workers from companies with at least one worker with detectable specific di-isocyanate IgE or IgG antibodies were invited to participate in the nested study.

[9] To explore the shape of the associations, nonparametric regression modelling (smoothing), using generalised additive models, was applied. In nonparametric regression no assumption about the shape of the exposure response relation. It is a flexible technique to explore deviations from linearity or other models.

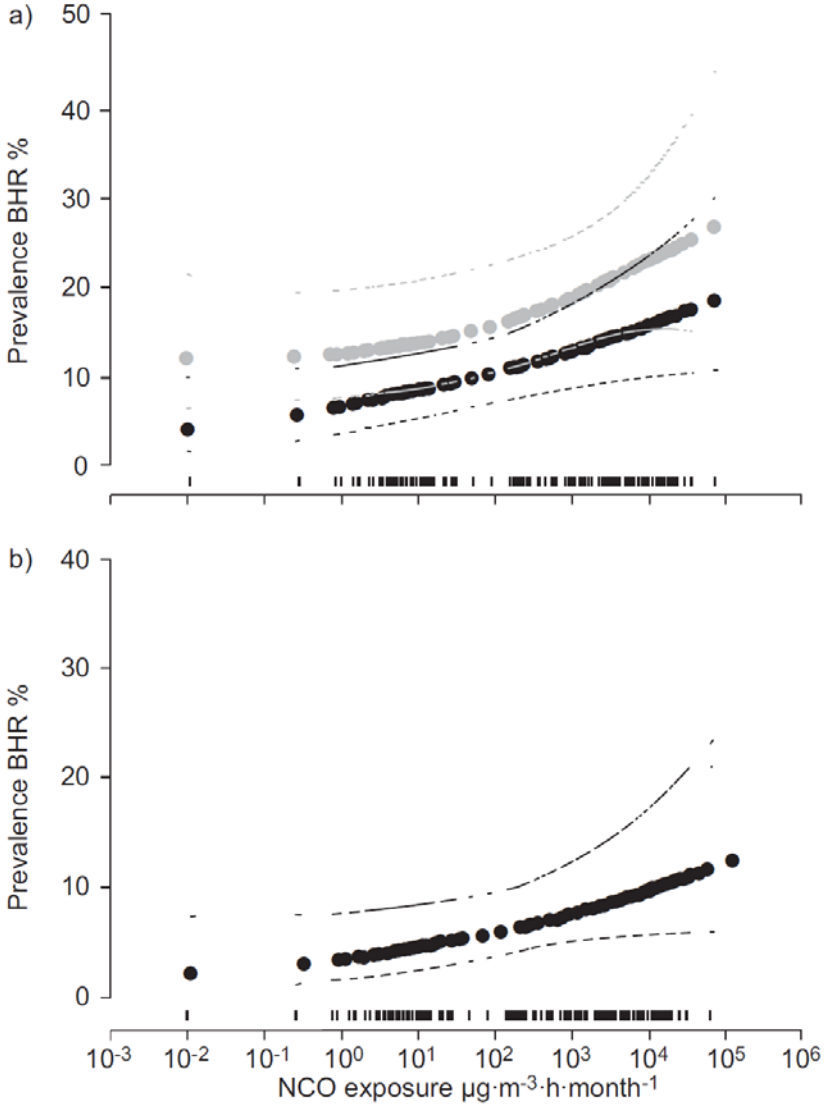

Figure 1: Association between log(exposure to isocyanates) (expressed as NCO) and health endpoints. Penalised smoothed spline plots with 95% confidence interval. a) Bronchial hyperresponsiveness (BHR20 black dots) and BHR15 (grey dots) and b) asthma (BHR20 and wheezing). BHR20, BHR15: bronchial hyperresponsiveness characterized by a respective 20% or 15% reduction in FEV1 as a cut-off level.

These splines did not differ statistically significantly from (parametric) logistic regression results using BHR and BHR and asthma symptoms as endpoints and adjusting for smoking, atopic status and gender. The association between BHR20 and exposure had the highest fit and was used for further analysis. The regression coefficient from the logistic regression models for log NCO exposure was 0.0775 for BHR (p=0.019). Although an exposure threshold is theoretically expected, it cannot be obtained from the available data.

Dermal exposure and biomonitoring of diisocyanate metabolites were considered in a sample of this study, but not included in the epidemiological analysis Pronk et al. (2006b).

Collins et al. (2017) reported results from a study using surveillance data collected over several years in a cohort from three US plants (from BASF Corporation plant in Geismar, Louisiana, a Covestro LLC (formerly Bayer Material Science LLC) plant in Baytown, Texas, and a Dow Chemical Company plant in Freeport, Texas). For this cohort, the exposure

assessment was described by Middendorf et al. (2017). In this study, 197 workers in facilities producing TDI were monitored from 2007-2012 accumulating approximately 750 person-years at risk. New asthma cases were identified from the medical monitoring programme by application of standardised annual medical assessment, including spirometry and questionnaires on symptoms and exposure. Workers could also report symptoms consistent with asthma at any time during follow-up. TDI air concentrations and questionnaires were used to estimate exposure for different exposure groups. Seven cases were identified as consistent with TDI-induced asthma (incidence rate 0.9 per 100 person-years), which falls within the bandwidth suggested by the review made by Daniels (2018). Two cases were considered consistent with asthma but indeterminate regarding work-relatedness (total asthma incidence rate of 1.2 per 100 person-years). Increased risk of cases consistent with TDI asthma was observed for cumulative exposure (OR = 2.08, CI 1.07-4.05, per unit increase in log ppb-years) as well as with peak TDI exposures (OR = 1.18, 95% CI 1.06-1.32, per unit increase in parts per billion). Collins et al. (2017) provide data on an exposure-response relationship which can be used for a risk calculation.

Collins et al. (2017) report an exposure response relation on the basis of a cohort analysis of surveillance data. A total of 197 workers were monitored from 2007 to 2012. The incidence rate of TDI-induced asthma was between 0.9-1.2 per 100 person-years, dependent on the definition of cases. It should be noted that the incidence rate was higher in a small group of workers followed less than 1 year (4 out of 32 individuals) >12.5 cases per 100 person-years. The data were analysed using logistic regression analysis for the association between TDI-induced asthma and cumulative TDI exposure (criteria for diagnosis are described in Cassidy et al. (2017), and exposure assessment was reported by Middendorf et al. (2017)). In the Collins et al. (2017) study, the association between peak exposures (based on 95th percentile) and occupational asthma and other respiratory parameters was also studied but peak exposures were not measured but indirectly estimated from the variability in exposure over a work shift. The paper lacks a clear and explicit visual representation of the data.

Table 2 from Collins et al., presents predicted probabilities from a logistic regression analysis for a range of exposure scenario's in a population with on average 11.8 work years and selected cumulative exposure variables.(24)

TABLE 3. Predicted Probability for Being a Case for Median Age of 42 and Some Selected Levels of Cumulative Exposure

Model 1	5 ppb-years	10 ppb-years	15 ppb-years	20 ppb-years
TDI-induced asthma (seven cases)				
Cumulative exposure	0.053	0.085	0.111	0.134
TDI-induced asthma or indeterminate asthma (nine cases)				
Cumulative exposure	0.061	0.081	0.096	0.107
FEV_1 decline (19 cases)				
Cumulative exposure	0.147	0.177	0.198	0.213
Symptoms of asthma (23 cases)				
Cumulative exposure	0.143	0.160	0.170	0.178

FEV_1, forced expiratory volume in one second; ppb, parts per billion.

Use of the exposure response relations to calculate risk

Pronk et al., performed a logistic regression analysis to associate exposure to bronchial hyperresponsiveness (BHR20) and BHR20 in combination with various respiratory symptoms. The regression coefficient for the association between bronchial hyperresponsiveness and log NCO exposure was 0.0775(p=0.019). RAC used this regression coefficient to estimate the risk of having BHR20 in relation to exposure. The baseline prevalence of BHR20 and asthma (BHR20 and wheeze) were 6.25 and 4.17% respectively. Using the prevalence information, the exposure can be calculated at which the prevalence is 0.1, 0.5, 1%, etc., higher by using the regression coefficient and the equation OR=exp(ß.exposure) with the exposure as given in the paper by Pronk et al. (in

log µg/m^3 NCO over a month). These units were converted to µg/m^3 NCO over a working day (8-hour TWA).[10]

Collins et al. performed a logistic regression analysis with data on cumulative exposure to TDI and the number of cases "consistent with TDI-induced asthma" (Collins et al., 2017). RAC used the exposure-response relationship reported by Collins et al. (2017), to calculate the exposure level corresponding to a range of excess risk values for being a case "consistent with TDI-induced asthma" and used the same approach as described by DECOS, but over a wider range of exposure levels. In short, the table by Collins et al. (2017) presents probabilities of disease for different exposure scenarios. The probability of disease can be used to calculate the so called disease odds (=probability of disease/probability of no-disease=p/(1-p)). The log(odds) is linearly associated with the log(cumulative exposure). Based on the table, this linear relation can be reconstructed and subsequently be used to calculate the exposures for any assumed risk level. RAC made the exposure-risk calculations at a range of disease risk levels; 0.05%, 0.1%, 1% to 5% with a 1% increment. Log(cumulative exposure) had to be recalculated to 8-hour Time Weighted Average (TWA) exposure and ppm was converted to microgram/m3 (factor 2.4). For calculation of TWA exposure, the cumulative exposure had to be recalculated into 8-hour TWA exposure levels by dividing the cumulative exposure by the average duration of exposure. Duration of exposure was estimated in a suboptimal way and this may have introduced some bias, which cannot be estimated on the basis of the available information. On the other hand, this study has other limitations that may contribute to uncertainty in the estimates, such as the high incidence of disease in the short term exposed workers. The calculations lead to estimated exposure levels at different risk levels as presented in the table below.

Table 3 Excess risk for having BHR or developing clinically defined occupational asthma using exposure response relations as published by two studies (Pronk et al., 2009, Collins et al., 2017)

	Estimated exposure based on exposure response relations	
Excess risk	by Pronk et al. (2009), for BHR20 in µg/m^3	Collins et al. (2017), in µg/m^3 (as originally published in ppb)
0.1%	0.05	0.006 (0.0017)
0.5%	0.08	0.054 (0.016)
1%	0.11	0.14 (0.04)
2%	0.23	0.38 (0.11)
3%	0.44	0.65 (0.19)
4%	0.79	0.96 (0.28)
5%	1.33	1.34 (0.39)

The estimates for exposure at different excess risk levels differ less than a factor 2 from excess risk levels of 0.5% and higher. Similar analyses have been conducted for the Pronk study for BHR20 or BHR15 (15% FEV1 change after metacholine challenge) and asthma

[10] The 8-hours TWA exposure was obtained from log µg/m^3 NCO over a month by taking the antilog and multiplying by 8/161 from Pronk et al., 2007, 2009).

like symptoms (BHR20 or BHR15 and wheezing). These analyses resulted generally in similar risk estimates; between 1 and 3% excess risk range.

These two studies lead to higher risk estimates when compared to the risk estimates across the different longitudinal studies used by Daniels (2018). The estimates from these two studies are generally in line with the studies that report asthma cases at low exposure levels although a detailed quantitative comparison cannot be made because of the limitations of these studies (Meredith et al., 2000, Gui et al., 2014).

It should be realised that these exposure risk combinations occur for the Pronk et al. (2009) study after an average working life as a spray painter of 14.9 years at an average age of approximately 40. For the Collins et al.(2017) study, risks were estimated at the median age of the cohort of 42 years and selected levels of cumulative exposure.

Specific considerations in the interpretation of the available evidence

Potency issues

The human studies do not allow evaluation of differences in potency between different diisocyanates. Studies on the same diisocyanate do show considerable differences in risk estimates which may be explained by differences in exposure but also study methodology, choice of health endpoints evaluated and exposure assessment strategy.

With regard to animal data; there are only very few studies that assessed exposure to several different diisocyanates; there are not many comparable study reports using similar/comparable study protocols. For the critical endpoint of interest (respiratory sensitisation) no internationally validated standard test protocols exist. Animal data, therefore, cannot provide adequate information for potency comparisons between different diisocyanates.

Personal protective equipment

Generally, human studies do not take into account respirator use and generally measure external (personal) exposure. The use of personal protective equipment will have lowered true exposure. This leads to overestimation of exposure when exposure assessment is based on external measurements (measurements in the work environment or personal measurements at the body of a worker). For the outcomes of a risk assessment process this means that health effects may occur at lower levels than assumed on the basis of the exposure information. Thus health risk occurring at a certain air level of exposure are underestimated. It should be realised that in most situations workers only make use of this type of equipment part of the time.

Dermal exposure and inhalation exposure

Associations between diisocyanate air concentrations and asthma incidence in workers contain the uncertainty that the incidence was not solely caused by the measured air concentration, but may have been caused to some extent by dermal exposure. Indeed, exposure response relations described above have been built on real-life situations (i.e. epidemiological studies in workers' populations) in which dermal exposure to diisocyanates is likely to have occurred in conjunction to air exposure. Since available data do not allow to quantitatively differentiate the contributions of these two types of exposures RAC considers that any limit value intended to protect workers from diisocyanate-related asthma should be based on data that inherently take into account both routes of exposure. Occupational dermal exposure to diisocyanates is not only a problem of the past. Also in a modern, state-of-art industries it has been recognised as a potential route of exposure (e.g. Gui et al., 2014, Tsui et al., 2020). When dermal exposure is omitted in studies, the risk associated with a certain air level of exposure is overestimated.

Exposure peaks

Another uncertainty relates to the contribution of peak exposures to calculated excess asthma risk. There are indications that peak exposures are important and drive the

sensitisation process (e.g. Ott et al., 2003). However, measuring peaks in human epidemiological studies is not practically possible because of measurement difficulties. The few available studies in which peak exposures have been assessed show that these are correlated highly with average exposure (Ott et al., 2000, Meijster et al., 2007). This means that work shift exposure can be explained by the number of peaks. Also, in the Pronk et al. (2007) study, sampling was based on a task based strategy and then integrated into a longer term average exposure levels; implying that tasks with regular exposure peaks, which contribute to longer term average exposure, have certainly been considered and accounted for in the estimate for longer term exposure.

Inter-individual differences in risk

From epidemiological studies it is generally concluded that exposure is the major risk factor for developing occupational diisocyanate asthma. Atopy is not considered a risk factor for diisocyanate sensitisation and asthma, as, in contrast, it is known to be for high molecular weight sensitising agents. Smoking also does not modify the risk for developing diisocyanate sensitisation and asthma (see Annex 1).

NCO group approach

RAC proposes to use a NCO group (R-N=C=O) approach for all diisocyanates (see Annex 1). The main arguments are that diisocyanates share a common mechanism of inducing hypersensitivity reactions and that there is not enough data to assess differences in potency for different diisocyanates.

The NCO group is considered to be responsible for the sensitising properties of isocyanates, since this group is responsible for binding to proteins, which is considered to be the “molecular initiating event” of sensitisation induced by low molecular weight substances. Additionally, for most of the cases of respiratory sensitisation the specific (di)isocyanate (or oligomer) is not known; workers may be exposed to more than one diisocyanate in their workplace because mixtures of isocyanates are being used or as a result of the reactivity of diisocyanates; and cross-reactivity between different diisocyanates has been demonstrated (summarised in ECHA, 2018a).

Estimated exposure based on exposure response relation

RAC calculated excess risks associated with different exposure 8-hr TWA levels on the basis of two specific studies assuming exposure over a working life period. RAC adjusted the exposure risk relations obtained from the two studies to a working life long exposure by multiplying the risks calculated from the two studies by a factor 2 (see Table 1).

The exposure estimates are within a narrow range between excess risks of 0.5-5%.

Because no “no observed (adverse) effect level” can be derived from these exposure-response relations, the exposure level chosen as a level for any OEL is still associated with a residual risk for developing occupational isocyanate asthma. ECHA notes furthermore that while Article 3 of Directive 98/24/EC sets the procedures to be followed and factors to be considered when establishing indicative or binding occupational exposure limit values at Community level, it does not define a level of residual excess risk to be considered in case a safe threshold cannot be identified. An OEL defined as 8-hour TWA, obtained from the exposure-risk relation as derived by RAC should never exceed the Short Term Exposure Limit value. In practice, an OEL defined as 8-hour TWA is usually a factor 2-5 lower than a STEL value defined over a 15-minute period.

Short term limit value (STEL)

A limited number of studies evaluated the effects of short term exposures to diisocyanates. Cross-shift changes in lung function have been observed in epidemiological surveys. A few challenge studies have been published in which naïve subjects inhaled diisocyanates and the respiratory and inflammatory response has been studied. Vandenplas et al. (1999), evaluated the effect of a single exposure in 17 healthy volunteers without respiratory

symptoms indicative of asthma or COPD and without occupational exposure to diisocyanates. The subjects were randomly exposed to ambient air and to TDI levels of 5 ppb for 6 hours, followed by 20 ppb for 20 minutes, in a single blind crossover design. At least 4 weeks separated the two exposure events. None of the subjects experienced significant respiratory symptoms in response to the exposures. A modest increase in specific airway conductance was seen and well as a small change in the Maximum Expiratory Flow at 25% of the Forced Vital Capacity (FVC) compared to exposure to ambient air. A small but statistically significant increase in albumin in lavage fluid was seen. This means that single low level exposure to TDI is associated to a reduction in airflow and increase in airway permeability.

RAC considers the study by Vandenplas et al. (1999) not sufficiently informative in particular resulting from the small size and the fact that volunteers were challenged at two exposure concentrations, both above a No Observed Effect level, to derive a value for a health based short term exposure limit (STEL). RAC therefore proposes to use a 15-minute Short Term Exposure Limit (STEL) value which is maximally a factor 2 higher than a derived 8-hour time weighted average OEL based on the exposure excess risk relation given in the previous section.

The study shows that local irritative respiratory effects are observed at a Lowest Observed (Adverse) Effect Level of 20 ppb TDI in the air in humans over an exposure period of 20 minutes. Applying an assessment factor of 3 for extrapolating to a NO(A)EL from a LO(A)EL and a factor 5, as a standard intraspecies assessment factor for workers a NO(A)EL of 20 / (3 * 5) = 1.33 ppb TDI or 4.58 µg/m^3 NCO per m^3). Adjusting the 20 minutes exposure period from the experimental challenge study to a 15-minute to a level 6.1 µg/m^3 NCO per m^3 or a rounded off value of 6 µg NCO per m^3. RAC considers that the STEL value, obtained from the exposure-excess risk relation based on an 8-hour TWA exposure, should not exceed 6 µg/m^3 NCO over a 15 minute period.

Animal data and OELs

Animal data have been used to derive an occupational reference values as a part of weight-of-evidence approach (ACGIH, 2016, MAK value for MDI; DFG), for a mechanistic explanation for choosing a relevant hazard endpoint (ANSES, 2019), and as a basis for setting an occupational reference value (e.g. MAK values for HDI; DFG, 2013) (details are given in section Occupational asthma risk assessment and exposure limit values in this Opinion and in Annex 1). Also, based on dose-response curves for elicitation of respiratory response (primarily assessed as a percentage of neutrophilic granulocytes in bronchoalveolar lavage (BAL)) in rats sensitised to diisocyanates, Pauluhn (2015) estimated 8-hour human workplace equivalent concentrations (HEC), with limit values of 0.006 ppm (0.04 mg/m^3, corresponding to 0.021 mg/m^3 NCO) for TDI and HDI, and 0.001 ppm for MDI (0.0126 mg/m^3 corresponding to 0.004 mg/m^3 NCO) (details are given in section 8.1.1 in Annex 1).

Nevertheless, as explained previously, RAC is of the opinion that OELs for respiratory effects of diisocyanates cannot be based on threshold values observed in animal studies. Animal studies providing a dose-response relationship on diisocyanate-induced irritative respiratory response in non-sensitised animals are rather limited. Diisocyanate-induced sensory irritation of the upper respiratory tract in animal models (i.e. rodents), quantified as a reflex reduction in the respiratory rate, is not considered relevant for irritation threshold derivation in humans. Regarding other effects of respiratory irritation (i.e. “tissue irritation” endpoints; reviewed in DFG 2013), it is hard to put animal data into human perspective due to species differences in toxicokinetics of inhaled diisocyanates,[11]

different exposure patterns, as well as limitations in experiments methodology or reporting (for further information please see Annex 1, section 7.4.2).

RAC considers, therefore, that uncertainties caused by extrapolation from animal to human data for diisocyanate-related respiratory sensitisation and irritation endpoints can not be quantified at present and this limits the use of animal data even as supportive evidence when deciding on a reference value for the human population.

(Bio) monitoring of exposure (see section 6 of Annex 1 for full discussion)

Air monitoring

There are standard methods for monitoring diisocyanates in workplace air (mainly according to the criteria set out in the standard EN 482 “Workplace exposure. General requirements for the performance of procedures for the measurement of chemical agents”), although some shortcomings in validation data may exist (explained in Annex 1). The methods are listed in Table 15 of Annex 1.

In general, sampling is based on reagent-impregnated filters and/or impingers, ensuring derivatisation already during sampling, which is necessary due to high reactivity of diisocyanates. Analyses are performed with liquid chromatography connected to UV/DAD, fluorimetric, electrochemical nitrogen or mass detection.

The lowest limit of detection (LOD) for 15 L sample is 0.6 ng/m^3 for HDI and 0.02 ng/m^3 for TDI (LC-MS method). Normally limit of quantification (LOQ) is around 0.3 - 0.7 µg NCO/m^3 for 15 L sample, but LOQ can be reduced by increasing the volume of the sample. For instance, for 120 L sample, the LOQ would be 0.03 µg/m^3. The results are expressed in µg diisocyanate/m^3 or µg NCO/m^3, depending on the method.

Expanded uncertainties vary for different methods. For example, for ISO 16702:2007 expanded uncertainty is 54% and for ISO 17735:2019 it is 36%.

There are also direct reading devices available for the most common diisocyanates (e.g. TDI, MDI, HDI), aimed to warn about excessive or peak exposures. Their sensitivity is markedly lower than of the methods mentioned above. Namely, LOD of direct reading devices is typically around 1 ppb (i.e. around 3.4 µg NCO/m^3), with the lowest LOD around 0.5 ppb (i.e. around 1.7 µg NCO/m^3) and a resolution of 1 ppb.

As described in the Restriction Dossier Background Document, accurate measurement of airborne diisocyanates is a complex task, since these substances are highly reactive, and therefore unstable. Also, spray foam aerosols are fast curing droplets of highly reactive mixtures of isocyanates with polyols, which makes sampling demanding. Compared to monomers, quantification of polyisocyanates (oligomers/prepolymers) is much more complex and often not as accurate (for justification please see Annex I, section 6.1.1).

In conclusion, standard, sensitive methods for air monitoring of diisocyanate monomers exist, and they are applicable for personal monitoring. Nevertheless, air monitoring of isocyanates (especially polyisocyanates) is technically challenging and it is considered that the collection and analysis of air samples requires considerable expertise (Creely et al., 2006).

Monitoring of dermal exposure

A reliable quantitative measurement of dermal exposure to isocyanates is not feasible at the workplace. There are inexpensive and easy to use semi-quantitative methods available, such as direct reading indicators in the form of wipes (e.g. colorimetric SWYPE™ indicators) or visual scoring system for dermal exposure assessment (WHO 2014). Different quantitative techniques have been applied in workers occupationally exposed to isocyanates (e.g. skin surface wipe sampling, skin tape stripping, sampling of inner gloves and pads under PPE) (Heederik et al., 2012), but these methods are not standardised, have undergone limited validation, and could be technically challenging (Bello et al., 2007).

Biomonitoring

Biological monitoring of diisocyanates is usually based on the determination of corresponding diamines in urine. They are markers of a short-term exposure, due to short half-lives of diisocyanates in an organism (usually only few hours), although there are differences in excretion kinetics between diisocyanates (Budnik et al., 2011). Experiments in volunteers indicate notable inter-individual variability,[12] suggested to be mainly due to metabolic differences between workers (Brorson et al., 1990), and maybe also due to differences in respiration rate, diisocyanate uptake and absorption, and corresponding diamine clearance rate (Liu et al., 2004).

The analysis of diisocyanate-adducts with haemoglobin (Hb) or albumin in the blood reflects long-term exposure (albumin has a half-life of 19 days and Hb has a lifespan of 120 days), and they are specific markers of exposure. However, there is significantly less literature data on diisocyanate-adducts compared to diamine levels in urine or plasma, and there is no much data for background levels for these biomarkers.

More specific biomarkers, such as U-TAHI for HDI-isocyanurate, ABP-Val-Hyd for MDI, and MDI-lysine for MDI, are also being developed, but they are not commercially available yet (there are potential issues with standards), and they are not yet to be used widely (Scholten et al., 2020).

Among most abundantly used diisocyanates (MDI, TDI and HDI), the highest correlations between urinary or plasma diamines and diisocyanates air levels were observed for a volatile TDI ($r > 0.8$), except where respiratory protective equipment (RPE) use or skin contact was significant (Scholten et al., 2020). For HDI and MDI correlations between airborne levels and urinary and plasma metabolites were found as well, but they were markedly weaker compared to those observed for TDI (Scholten et al., 2020). It is hypothesised that the different excretion kinetics of different diisocyanates, use of RPE, inter-individual differences in toxicokinetics and the contribution of dermal uptake of diisocyanates, make it difficult to find a correlation between air monitoring data and biomarker concentration (Annex I, section 6.2.2). For other diisocyanates, literature data are very poor. Also, there are only few data correlating diisocyanate adducts to airborne levels (Scholten et al., 2020).

Both types of biomarkers (diamines in urine or plasma and diisocyanate-adducts) reflect not only inhalation exposure to diisocyanates, but also dermal uptake (e.g. Bello et al., 2007, Flack et al., 2010, Scholten et al., 2020), and inhalation or dermal uptake of the corresponding diamines.[13] The extent of systemic availability of diisocyanates following dermal absorption in humans is not yet adequately explored. Although according to limited data in humans (Hamada et al., 2018) and animals (e.g. Hoffman et al., 2010), diisocyanates' absorption via the skin seems to be very low (<1%),[14] several human

[12] For example, in a test chamber study with HDI (2-hour respiratory exposure to HDI biuret aerosol, at TWA of 53.8, 98.7, and 58.2 µg/m3 for monomer, oligomers and NCO, respectively) in 23 auto body shop workers, Liu et al. (2004) described 200-fold variation (0.4 to 101 µg/g creatinine) in net post-exposure increase in urinary HDA. It should be noted that the workers were exposed to HDI recently before the start of the experiment, which is a limitation of the study. Nevertheless, there was marked variation in post-exposure net increase in urinary HDA also in the subjects with low urinary HDA baseline values (at or below 0.7 µg/g creatinine).

[13] For example, diisocyanates could be externally (e.g. on contaminated hands, clothes or surfaces) hydrolysed to diamines, which are readily absorbed through human skin.

[14] Hamada et al. (2018) dermally exposed four volunteers to 10, 25, 49 or 50 mg 4,4'-MDI (as 2.0% MDI in petrolatum) for 8 hours. Based on sum of plasma and urine MDA, systemic absorption of applied MDI dose ranged from <0.01% to 0.2%. The authors concluded that 4,4'-MDI absorbed by the skin probably remained bound in the upper layers of the skin. Hoffman et al. (2010) observed in male rats that less than <1% of dermally applied radiolabelled MDI and TDI was systemically available, and considerable amounts of applied radioactivity was found bound at the application site.

studies indicate that the dermal exposure could be a significant predictor of urinary biomarker levels (Scholten et al., 2020). Regarding co-exposure to corresponding diamines, limited survey of different uses of diisocyanates (Jones et al., 2017) indicates that monomeric diisocyanates are the predominant source of resulting diamine levels in diisocyanate-exposed workers.

There is no information available about how the different diisocyanates are metabolised when the atmosphere contains a mixture of several isocyanates (such as, for example, during thermal degradation of polyurethanes) (Budnik et al., 2011).

Isocyanate-specific IgG is another biomarker of exposure, since it is not normally found in human serum, but could be present with a relatively high prevalence among exposed workers (Wisnewski et al., 2012). Nevertheless, it also reflects dermal exposure, and the potential influence of other factors, such as genetics or environmental co-exposures, are not adequately explored at the present moment (Wisnewski et al., 2012).

For any of the above mentioned biomarkers, the level at which adverse health effects (respiratory sensitisation to diisocyanates or diisocyanate-related occupational asthma) are observed cannot be identified.

Biological guidance and limit values (see sections 8.2.3, 8.2.4 and 6.2 of Annex 1)

Biological Limit Value (BLV)

RAC does not propose a BLV since an OEL value has not been proposed by RAC, and there is no reliable correlation between diisocyanate biomarkers and diisocyanate airborne levels, especially at low exposure levels (Scholten et al., 2020; please also see section above and section 6.2 in Annex 1).

Biological Guidance Value (BGV)

RAC advises to set a BGV, at the LOQs for relevant diisocyanate metabolites (diamines) in urine, in order to improve workers' safety. Since diamines' levels in the general population are usually below LOQ (Annex 1, section 6.2.1), this proposal is in line with recommendations stated in ECHA Guidance (Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace, 2019): "In the absence of background exposure, or when background exposure is negligible, a BGV may be set at the limit of quantification, in which case the limit of detection should be as low as technically and practically possible".

RAC proposes to base a BGV on diisocyanate urinary metabolites (diamines), since, compared to other potential biomarkers (see Annex 1), diisocyanate urinary metabolites are more extensively studied and concentration ranges in an unexposed population are available for a majority of frequently used diisocyanate compounds. According to Budnik et al. (2011), the detection of isocyanate metabolites in hydrolysed urine by gas chromatography combined with mass spectrometric detection system appears to be the most suitable, reliable and sensitive method to monitor possible isocyanate uptake, and it allows the simultaneous screening of the urine metabolites of aromatic, aliphatic and cycloaliphatic isocyanates. Values exceeding the BGV in one or more workers at a specific workplace/task can trigger attention for improving risk management measures.[15]

General information on analytical methods for diisocyanate urinary metabolites (diamines) measurement, as well as diamines background levels in population not exposed to diisocyanates at the workplace, are presented in Annex 1 (sections 6.2.1, 6.2.3).

[15] This also includes recognising a poor occupational hygiene practice, such as hand-to-mouth exposure route, and dermal exposure.

RAC points out that biomonitoring cannot inform on peak exposures. Also, it is recommended that the timing of the urine collection in relationship to worker's exposure reflects excretion kinetics of relevant diisocyanates (Liu et al., 2004, Cocker, 2007, Gaines et al., 2010, Budnik et al., 2011; please see section 6.2.2 in Annex 1). For example, for diamines with very short half-lives such as HDI (around 2.5 h; Budnik et al., 2011), urine sampling should be performed at the end of exposure period, which is not necessarily the end of the work shift.[16] Also, it should be kept in mind that urinary samples taken before the beginning of the working shift could show non-occupational exposure to diisocyanates, and also reflect exposure to diisocyanates from previous working day(s) (in case of diamines with longer excretion time such as MDA, IPDA, or late second excretion peak, e.g. NDA). Predominant route of exposure could also play a role, since it influences diisocyanates toxicokinetics (e.g. Budnik et al., 2011, Hamada et al., 2018). In summary, for a majority of diisocyanates, if a predominant route of exposure is expected to be via the air, post-shift sample are generally considered adequately reliable. However, if it is likely that there is a significant dermal exposure, next morning sample could be more appropriate.

Notations

RAC proposes a skin notation and Notations for 'skin sensitisation' and 'respiratory sensitisation'.

A 'skin' notation is proposed in order to ensure prevention of systemic immunological effects (i.e. respiratory sensitisation) from dermal contact of diisocyanates. Namely, RAC considers that this notation is not limited only to substances for which the skin penetration is likely to make a significant contribution to the total body burden (SCOEL Methodology document, 2018), but points out that ECHA Guidance (Appendix to Chapter R.8: Guidance for preparing a scientific report for health-based exposure limits at the workplace, 2019) states that "the assessment whether a skin notation is required considers various types of information and is not necessarily quantitative", and that "it can include health effects observed in workers following skin exposure".

As discussed previously (section Biomonitoring of the Opinion), dermal absorption of diisocyanates is inadequately explored. Although it seems to be limited, several epidemiological studies indicate that dermal absorption seems a possible exposure route and needs to be further investigated (Scholten et al., 2020). Nevertheless, in the case of diisocyanate-related occupational asthma, the contribution of dermal route is actually not related to systemic uptake of diisocyanates as such via dermal exposure, but rather to systemic immunological effects following dermal contact. At the same time, it should be noted that "skin sensitisation" notation relates only to local immunological effects on skin (most frequently contact allergic dermatitis), and not to systemic immunological effects, such as respiratory sensitization. For further discussion please see Annex 1, section 8.3.

Health surveillance and other preventive measures

RAC considers that in the case of occupational exposure to diisocyanates, a specific health surveillance is appropriate, in line with Articles 6.3 and 10 of the Chemicals Agents Directive (Council Directive 98/24/EC). In line with Articles 10 of the Chemicals Agents Directive (Council Directive 98/24/EC), the Member States are recommended to introduce appropriate arrangements aiming to identify early signs and symptoms of respiratory sensitisation. These arrangements should be in accordance with national laws and/or practice, as well as in line with the principles and practices of occupational medicine. For further details please see Annex 1, section 8.4.

[16] E.g. if a task with diisocyanate exposure lasts for a very short time at the beginning of the working shift.

Also, adequate training of workers, such as described in the restriction proposal concerning diisocyanates, should minimise exposure, not only via inhalation (including peaks) but also via the dermal route and thus prevent diisocyanate induced health effects (ECHA 2017).

REFERENCES please see the Annex for all references

ANNEXES:

Annex 1 gives the scientific background for the opinion.

Annex 2 Comments received on the scientific report, response to comments provided by ECHA and RAC (excluding confidential information).